Summary

Pain thresholds are determined by mechanical stimulation in patients with chronic pain syndromes of various etiologies and in a healthy control group. For this, 5 different cutaneous points on the hand and underarm were stimulated by means of a pressure algometer with interchangeable stamps. The pressure-pain thresholds showed good intraindividual reproducibility, but the interindividual variance is higher in comparison to heat stimulation. The threshold values are not dependent on age, sex or time of day. There are no significant differences between pain patients and the control group. The VAS score was higher in healthy controls as well as in those with a chronic pain syndrome, than for heat stimulation, and a reduction in skin temperature was shown as a sign of a higher sympathetic tonus. The lateralization tendency is less marked in pressure stimulation. The poor correlation between heat and pressure-pain thresholds, the lack of a threshold increase after mechanical stimulation in pain patients and a higher sympathetic tonus with pressure stimulation reveals a difference in central-level processing of both pain qualities.

Mechanical stimuli have thus far been generated by pinching skin folds or applying pressure against the skin found over the periosteum.

The purpose of this study is the standardization of an algesimetric method for evaluating threshold values in mechanical stimulation and subsequently verifying their validity on a control population. A pressure algometer with interchangeable stamps was used for mechanical stimulation. Of primary importance here is the use of a standard stimulus pattern for indicating pain and its verification for reproducibility in healthy patients and those with chronic pain syndromes.

METHODS AND TEST SUBJECTS

The test groups consisted of 24 (13 male; 11 female) persons between the ages of 21 - 46 years, who were neurologically and psychiatrically normal as well as 10 chronic pain patients (6 male; 4 female).

The stimulus apparatus works with an energy absorber for the value range of 0-20 N (overload capacity 30%). The construction is made from a copper-beryllium alloy, which carries four miniature wire strain gauges in full bridge circuitry. An output voltage of 137.5 µV is generated from a supply voltage of 25 V and an energy of 1 N. The circuit supplies 0.4 V/N. After mechanical release, the digital display shows the energy exerted with a precision of 0.1 N. The result can be recalled and registered via the analogue ports.

The contact surface for pressure stimulation can be varied with ten interchangeable stamps (radii r = 1-5 mm corresponding to surfaces A = 3.14-78.5 mm^2).

Five measuring points were chosen on the hand and underarm on both the left and right side, which were easily accessible and showed different tissue qualities: Finger pad dig. II, nail bed groove dig. III, middle phalanx dig. IV, hypothenar, medial elbow. Measurements were recorded via the analogue ports of the stimulation instruments after the online interpolation of an analogue/digital transformer in a personal computer. 100 data for every session were recalled according to categorized measuring points after terminating stimulation and subsequently transferred to a statistics program for evaluation.

The test subject, sitting at constant room temperature opposite the investigator, places his underarm on the table. The pressure algometer stamp is set to the appropriate measuring points, care being taken to keep the angle at 90° to the skin surface. Pressure is gradually increased in a linear manner with an energy increase of about 0.5 N/sec. Using a stamp with a 3.14 mm^2 contact surface, the pressure increase corresponds to 191 KPa/sec. The test subject indicates his "pain threshold" by pressing a button (instruction: Interruption of the stimulus when it becomes "just painful"). Subsequently, the stamp is placed on the next testing point. Each measuring point is stimulated ten times per session. Before and after every session, skin temperature is measured on the stimulated points as well as the finger pad of digits I and V as a reference.

Descriptive parameters, e.g. the arithmetic mean, standard deviation and variance, were intraindividually calculated for every session for each of the 10 measuring points. From the respective means of the individual test subject, the statistical values were calculated for interindividual comparison. For comparitive statistics (variance analysis, t-test, correlation, etc.), the appropriate program was used (e.g. ANOVA).

RESULTS

1. Healthy test subjects

Inter- and intraindividual observations. The results of the threshold measurements in 24 test subjects (13 male; 11 female) between the ages of 21–45 years (x = 26.6, SD = 4.3 years) are shown in Fig. 1. The most sensitive point for pressure pain is the elbow; however, together with the hypothenar, it has the most variations, the latter also possessing the highest threshold. With the exception of the finger pad dig. II and the middle phalanx dig. IV with $p = 0.6392$, all measuring points significantly differed from each other ($p \leq 0.05$). There were no sex-dependent differences in cross-section values found: X_{male} = 1.89 MPa ± 0.17; X_{female} = 1.92 MPa ± 0.33; $p = 0.77$. Differences between morning and afternoon measurements of pain thresholds were not significant [$p = 0.7431$; $X_{morning}$ = 1.84 MPa ± 0.13; $X_{afternoon}$ = 1.89 MPa ± 0.33]. Different session intervals did not significantly differ: X_{short} = 1.89 MPa ± 0.33; X_{long} = 1.90 MPa ± 0.2; $p = 0.9308$]. Age dependence could not be determined. The correlation (age/cross-section value) was $r = -0.34$.

The temporal course of the stimulation (see Fig. 2) shows a slight habituation beginning with the 3rd measurement row for regions with soft tissue (finger pad, elbow and hypothenar), while points with good bone contact (middle phalanx, nail bed groove) tend to be more sensitive. Between the three sessions, significant differences were registered at the 95% level in 2 persons and a maximum of 3 out of 10 respective measuring points.

The finger pads II showed the lowest intraindividual scattering, while the hypothenar also had the highest variance here (Fig. 3). Female test subjects showed a significantly higher standard deviation ($p \leq 0.05$) with the middle phalanx. No significant influence could be determined in the time of day, between morning and afternoon measurements [$p = 0.9213$; $X_{morning} = 0.201$ MPa ± 0.025; $X_{afternoon} = 0.198$ MPa ± 0.038]. Significant differences were not found for the various session intervals: $p = 0.886$; $X_{short} = 0.198$ MPa ± 0.038; $X_{long} = 0.204$ MPa ± 0.025. The variance of the measurements is also independent of age. The correlation (Age/cross-section value of SD) is $r = -0.34$ ($p \geq 0.05$).

Subjective pain evaluation. Test subject entries for pain intensity ranged from 2 to 7 ($x = 4.47$, $SD = 1.41$). Sex differences were not determined here: $X_{male} = 4.59 \pm 1.41$; $X_{female} = 4.31 \pm 1.49$; $p = 0.68$. Furthermore, the thresholds obtained in pressure pain were independent of the subjectively estimated score. The correlation (score VAS / cross-section value of pain threshold) is $r=0.21$. No age dependency for pain classification was determined ($r = -0.31$). The p-values of the coefficients are ≥ 0.05 each.

The following ranking list expresses how the quality of pressure pain was experienced by the test subjects: crushing (11), stabbing (7), flashing (2), short and intensive (2).

Skin temperature before and after stimulation (Tab. 1). The cross-section values of the non-stimulated skin points showed that female test subjects had a significantly lower difference in temperature [$X_{male} = -0.44°$ C ± 1.12; $X_{female} = -1.23°$ C ± 0.65, p

= 0.04] (Fig. 4), whereas this observation was not made on the stimulated area [X_{male} = 0.2° C ± 0.50; X_{female} = 0.05° C ± 0.83; p = 0.63]. The cross-section values (delta T) of the stimulated skin surfaces as compared to the non-stimulated ones are significantly higher by 0.91° C ($p \leq 0.0001$). The temperature differences measured are independent of the corresponding pain thresholds obtained. The correlation (cross-section value of the pain threshold / cross-section value delta T) is $r_{stimulated}$ = 0.03 for stimulated areas and $r_{non-stimulated}$ = -0.05 for non-stimulated ones.

The subjective pain assessment of the test subjects does not provide a correlation for the observed differences in skin temperature. The correlation (scale value VAS /cross-section value delta T) is $r_{stimulated}$ = 0.01 for stimulated points and $r_{non-stimulated}$ = -0.22 for the reference points.

In right-handers: 50% of the skin areas are neutral; 45% obtained higher values on the right and only 5% on the left; see Fig. 5. Individual examination shows that at the points finger pad (66.7%), nail bed groove (50%) and middle phalanx (75%), are lateralized above-average on the right (Fig. 6). The hypothenar and the elbow with 66.7% or 83.3% are mainly neutral. The sex differences are slight (p = 0.87). The ambidextrous and left-handed subjects showed only a slight lateralization tendency with 73.3% or 80% of neutral points (Tab. 2).

In the variance analysis (ANOVA) of individual measuring points for right-handers, the elbow and the wrist as "proximal" areas with regard to pain lateralization significantly differed from the middle phalanx and finger pad ($p \leq 0.0352$), and only tendencially from the nail bed groove ($p = 0.275$). The measuring points in ambidextrous ($p \geq 0.4475$) and left-handed subjects ($p \geq 0.3409$) did not differ significantly.

2. Chronic pain patients

Inter- und intraindividual observations. In 12 patients (7 male; 5 female) with a chronic pain syndrome between the ages of 29 - 69 years ($x = 47.6$, $SD = 6.8$ years), the mean cross-section value of the pain thresholds of 1.88 MPa is only insignficantly lower than the value for the control group ($p=0.8044$); see Tab. 1. The individual measuring points also showed no significant differences.

The mean cross-section value of the standard deviation is significantly higher by 0.057 MPa in the patient group as compared to the controls ($p \leq 0.0001$). The individual measuring points, with the exception of the hypothenar ($p = 0.08$), each reached a 95% level of significance.

Subjective pain assessment. Chronic pain patients did not significantly differ in their entries on the VAS from the healthy group: $X_{pain\ pat.} = 4.73 \pm 1.32$ ($p = 0.74$), while female patients clearly tended toward a higher score ($X_{female} = 5.21$ vs. $X_{male} = 4.15$; $p = 0.0832$). There is also a high correlation here between the clinical and experimental assessment of pain ($r = 0.93$).
The verbal assessment is as follows: stabbing (7), crushing (6), sharp (2), flashing (1).

Skin temperature before and after stimulation. The cross-section values of the temperature differences (delta T) did not signficantly differ from the healthy subjects either in stimulated or non-stimulated areas ($p_{stim.} = 0.1875$; $p_{n-stim.} = 0.7345$); Tab 4. The temperature range (delta T_{stim} - delta $T_{n-stim.}$) is, indeed, wider in pain patients than in healthy subjects (1.22° C vs. 0.91° C), but a significance level was also not reached in this case ($p = 0.3258$).

Pain lateralization. In comparison to the control group, there was no significant difference in lateralization ($p = 0.6235$).

DISCUSSION

1. Healthy test subjects

Mechanical stimulation of pain is usually induced by direct pressure with a stamp against the skin or by pinching skin folds. Kohllöffel et al. [15] developed an apparatus with an area of 28.3 mm2 and a cylinder with a length of 12 mm (weight 330 mg) which practically hits the skin in "free flight". The flight speed may be varied from 7.5 - 22.5 m/sec. A pain sensation with a mean pressure of 46.1 KPa is obtained with this technique which is also called "bumping".

The correlation between pain threshold and stimulation site is much more pronounced in mechanical than in heat stimulation. The most important influence parameters are variation of density of the mechanosensitive nociceptors as well as structure of the subcutaneous tissue (e.g. immediate periosteal contact, pronounced muscular layer, etc.). The pain-sensation threshold values reported in the literature vary widely. A compilation of these values is given in Survey 1.

The same stimulation surface and stimulation rate yield a difference of 188 KPa in the pain threshold of finger pad dig. V and toe pad dig. II. Jensen R. [13] reports a threshold increase by 57 KPa for a 6.76 KPa/sec increase in stimulation rate. The most important factor, however, is the application surface. Jensen R. [13], for example, obtained a pain-threshold increase by the factor 2.3 by reducing the stimulation surface by one fourth with a constant pressure increase per time unit . This explains why Hardy [25] obtains a pain sensation at 55 KPa for a stimulated 0.78 cm^2 area of the forehead whereas Peters [20], applying 180 times the pressure on 1/46th of the surface, achieves the test subjects' pain threshold only after a mean of 33 seconds.

The pain thresholds in our test series are most similar to those obtained by Brennum [2], who reports values of 695 KPa for the finger pad of digit II and 647 KPA for the middle phalanx of the 5th finger. Although these threshold values corresponded to only 1/3 of the values obtained by our study group, the stimulated area was larger by a factor of 9. Göbel [8], who used slightly smaller stimulation areas of 2.56 mm^2, reports pain sensations after 4 seconds with a constant pressure application of 2.64 MPa.

As a rule, skin points over adjacent osseous structures (e.g. nail bed grooves) have a lower pain threshold than primarily soft tissue (e.g. hypothenar). These observations are confirmed by Kohllöffel et al.[15].

In mechanical stimulation also, it is necessary to mention the variability of the nociceptor density in addition to the locally dependent tissue quality to explain the different pain thresholds at each measuring point. A reduction of the stimulated area results in a disproportional threshold increase (see survey 1 and our preliminary tests).

Our experiments demonstrate the importance of selecting a rather low pressure application rate in order not to overestimate the pain threshold on the basis of the test subject's reaction time. High stimulation rates also make it difficult, on the basis of the answer-back signal of the pilot light, to keep the pressure increase really constant with the stamp . The results obtained by Jensen R. [13] and Kohllöffel [15] show higher threshold values for larger stimulation rates.

Most authors found significantly lower pain thresholds in female than in male test subjects [2,3,5,14,18,19]. Our results and those obtained by Jensen R. [13] revealed no sex differences ($p = 0.77$).

There are no reports in the literature about a circadian dependency of pressure pain. Our measurements show no significant difference between morning and afternoon sessions.

Previous studies report no significant differences in various sessions [12,19]. Our results with session intervals of 2 weeks or two months revealed no significance.

Some studies report an age dependency of pain thresholds: threshold values increase with age [14], but there are no significant differences according to sex. Such a dependency [2,13] was not observed in our or in other groups, since the study was designed to consider only a very narrow age range.

Because of the difference in threshold values and number of measurements, the comparability of standard deviations in various

studies is strongly limited due to the specification of absolute values. Some authors therefore take the relative variation coefficient as measurement for intraindividual scattering. Values ranging from 14% [2,13] to 25% [13,18] are reported in the literature. Our results show coefficients of approximately 6%.
A mild sensibilization (discrete reduction of pain thresholds from measuring rows 1 to 10), particularly at the measuring points with immediate bone contact, was observed during pressure stimulation. Reeh et al. also report no adaptation of mechanical pain stimuli [23].
Thus far, there have been few investigations on subjective pain assessment based on a VAS of pain-pressure thresholds. In a study by Peters [20], healthy test subjects assess their threshold values at 54.4% (SD = 27.2%). These figures are higher than the average VAS values (44.7 ± 14.1%) obtained by us. The values are independent of sex and age. The limited vocabulary of the test subjects for a verbal description of pain is indicative of the monotonous pain quality of pressure stimulation.
The comparative measurements of skin temperature before and after pressure stimulation reveal a discrete warming at stimulated skin points (delta T = 0.14°C), compared to a significant cooling (delta T = 0.77°C; p µ 0.0001) at unstimulated reference points, with female test subjects exhibiting significantly lower temperatures. The latter must be interpreted as a sympathicotonic reaction in the form of a vascular reflex with skin vessel constriction and subsequent reduced circulation and thus lower skin temperature. The slight temperature change in the stimulated skin areas could be interpreted to be the result of a

"competition" between central vasoconstrictive influences and local vasodilatation mechanisms at the smooth vessel muscles [11]. Most authors describe higher threshold values on the right, i.e. the dominant side of the body, while Göbel [8] reports a strong lateralization tendency in left-handed women. Jensen R. [14] found significantly higher threshold values on the right side of the body in right-handers, otherwise, there were no significant differences in the groups investigated (right-handed, left-handed or ambidextrous individuals). Other investigators found no <u>differences in sides</u> for pressure-pain sensibility [5,13,16,22]. Our results reveal an indifference most frequently found in right-handers, followed by the highest values on the right side of the body. Ambidextrous and left-handed individuals lateralize very little with 73.3% and 80% and otherwise reach higher pain thresholds on the left. Looking at the various measuring points in the case of right-handers, it was significant that the more distal locations (finger pads, nail bed groove, midddle phalanx) exhibited the highest threshold values most frequently on the right, whereas the elbow and the hypothenar only demonstrated a slight lateralization tendency. One might now assume that skin points with a larger cortical representation (distal locations) possess a more pronounced lateralization tendency. However, there are thus far no conclusive research results.

2.2. Chronic pain patients

Langemark [16] and Schoenen [26] report on significantly lower pressure pain thresholds in patients with tension headaches. Also, in a study by Ohrbach [19], significantly lower threshold

values were achieved by patients with myogenic temperomandibular neuralgia ($p = 0.03$), as well as in patients with rheumatoid arthritis found in a study by Gerecz-Simon [5]. Peters et al.[20] described a distinctively higher pain threshold in back pain patients as compared to a control group ($p = 0.12$). However, with repetitive stimulation, they showed a reduced pain tolerance ($p = 0.085$). Merskey [18] found significantly higher pressure pain thresholds in patients with organically originating pain, compared to patients with psychogenic pain and healthy test subjects. Alo, patients with Bekhterev's or osteoarthritis each achieve significantly higher threshold values [5]. Our results show only a slight difference in the cross-section values of pain thresholds between pain patients and healthy subjects ($p = 0.8044$). The individual measuring points also did not differ significantly.
The intraindividual variance is significantly higher on the average compared to healthy test subjects ($p \leq 0.0001$). This may be explained by a reduced attention level or a reduced perception ability for identical nociceptive stimuli in those pain patients.
The entries on the VAS with regard to threshold values are only slightly higher with 47.3% than the controls (44.7%). In a study by Peters [20], back-pain patients even evaluated their pain thresholds after mechanical stimulation with 52.4% (SD = 25.5%).
Only a limited vocabulary was used to describe the pain quality of the stimuli which does not differ from the control group.
The differences in skin temperature before and after pressure stimulation show no variance in either stimulated or non-stimulated measuring points compared to healthy subjects.
Consequently, the significant cooling (delta $T = -0.55°C$) on the non-stimulated skin areas also has to be interpreted as a

vasocontriction due to a sympathicotonic reaction. The sympathetic nervous system influences the skin pain threshold by means of fast and slow mechanisms, e.g. by vasomotoric changes (permeability of microvessels, tissue resistance, secretion of vasoactive substances), direct modulation of sensory receptors and control of enzymatic reactions [21]. The autonomous nervous system shows the same reaction in both test groups. In contrast to this are the results obtained by Ekenvall [4], where patients with vibration-induced Raynaud syndrome showed no or only weak vasoconstriction to mechanical or thermic pain stimuli. Therefore, in these patients as well as in those with sympathetic reflex dystrophy, a reduced response of the vasoconstrictive system to nociceptive stimuli as well as an impairment of the thermoregulatory function of this system was observed, and a central disorder of the sympathetic nervous system was postulated [9]. Moreover, Hankemeier et al. [10] reported that the activation of various sympathetic effectors (vasomotricity, sweat secretion, hair position) may be influenced by chronic disorders (e.g. on a central nervous level).

There are no significant differences in pain lateralization between right-handers and controls ($p = 0.6235$).