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A standard test of heat-pain responses using CASE IV

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Abstract

Heat-pain threshold and stimulus response characteristics can be evaluated with graduated heating pulses from a radiant heat source or a contact thermode. Results may be used to: (1) evaluate differences in sensation among anatomical sites, sides of the body, and with development and aging; and (2) provide an end-point for the study of the efficacy of drugs; or to follow the course of sensory alteration in disease (medical practice, epidemiologic studies, and controlled clinical trials). Because there is great variability in how tests of this kind are performed and scored, comparisons of results among medical centers are difficult. To meet this need, we have developed, and here describe, a standardized and validated test of heat-pain. We use both pyramidal and trapezoid-shaped stimuli. The range of stimulus magnitudes we recommend is sufficient to test heat-pain at a sensitive region (the face) of young people and an insensitive region (the foot) of healthy old people. From tests on healthy subjects and patients, we find that neither our previously published forced-choice or 4, 2, and 1 stepping algorithms are suitable for testing heat-pain sensation. We, therefore, introduce the Non-Repeating Ascending with Null Stimuli (NRA-NS) algorithm which performs satisfactorily. The graphed data points of responses to increasingly stronger heat pulses were made up of two components–the no pain (0) response line and the heat-pain response line (≥ 1 numerical scaling of the pain responses graded from 1 [least] to 10 [greatest]). For the pain responses, we found that usually a curve could be fit using a quadratic equation. Using this equation, or interpolation where necessary, it is possible to compute the heat-pain detection threshold (HPDT or HP:0.5), an intermediate heat-pain response (HP:5.0), and the difference between the two (HP:5.0–0.5). Our studies show that a certain time is needed between successive stimuli and tests to minimize changing basal skin temperature or threshold. We also demonstrated that low or high baseline skin temperatures can affect heat-pain responses, therefore, we advocate specific testing conditions. Based on a study of 25 healthy subjects, the reproducibility of the test falls within ± 1 stimulus steps 88% of the time for HP:5.0 and 76% of the time for HP:0.5. The precise approaches employed to make the test standard and reproducible are described. We illustrate that the algorithm-and testing system is able to document altered pain threshold with skin abrasion, with intradermal injection of nerve growth factor, and with diabetic polyneuropathy.

Keywords: Heat-pain sensation; Heat-pain detection threshold (HP:0.5); An intermediate heat-pain response (HP:5.0); Nerve growth factor; Skin abrasion; Diabetic neuropathy

1. Introduction

Quantitative sensory testing (QST) is increasingly used to assess thresholds of modalities of sensation in health (development, aging, side and anatomical part) and in disease of sensory receptors, nerve fibers, pathways, or cerebral association areas (Dyck et al., 1993a). In disease, it may be used to detect, characterize, and follow the course of sensory abnormality — in clinical practice, epidemiologic studies or controlled clinical trials. Systems using personal computers, electronic circuitry and transducers have become available, which can facilitate these evaluations (Dyck et al., 1993a, 1978; Arezzo et al., 1986; Jamal et al., 1985; Hansson and Lindblom, 1992; Verdugo and Ochoa, 1992). Using such systems, it is possible to deliver vibratory, touch-pressure, cooling and warming stimuli, having precisely defined and reproducible waveforms, with a magnitude which can be given at exact predetermined steps over a broad range of magnitudes, and in a predetermined sequence, interspersed with null stim-

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uli, and employing various algorithms of testing. Algorithms of testing and finding threshold have been developed to ensure sensitive, specific, quick and accurate estimates of normality, hypersensitivity, or hyposensitivity (Dyck et al., 1993a, 1978; O'Brien et al., 1989). Normal value tables, when available, can be programmed into the computer, so that it is possible to print out results for a patient being tested as a percentile specific for modality, site, age, gender, height, weight, body mass index, and body surface area (Dyck et al., 1995).

The authors of a recent consensus report on quantitative sensory testing from the Peripheral Neuropathy Association (PNA) emphasized that there was a need to develop and use tests employing standard stimuli, testing approaches, algorithms of testing, and finding threshold and calibration so that results from one medical center could be compared to that of another (Dyck, 1995). The stimulus waveform should be appropriate and quantitated, reproducible, and provided in exactly quantified steps over a broad range of magnitudes. The pre-conditions and environment of testing should be controlled. The algorithms of testing and finding threshold should be pre-specified step-by-step, and should have been validated (e.g., by computer simulation and in actual trials of healthy subjects and patients).

In previous studies of cooling (CDT), warming (WDT), or heat-pain (HP DT) detection threshold, we showed that the testing approach could markedly affect threshold (Dyck et al., 1993c). Increasing the temperature linearly or exponentially to the point at which the subject experiences cooling (or warming) and then depresses a response key, led to a great overestimate of the threshold, particularly when steep ramps were employed. Alternating the direction of thermal change and having the subjects respond when heating, then cooling was felt, and so on, was not a good strategy because thresholds of warming or cooling were overestimated and because thresholds for cooling, warming, and heat-pain were not discriminated. For testing cooling (CDT), warming (WDT) or heat-pain (HPDT), detection thresholds, pyramidal-shaped or flat-topped pyramidal-shaped (trapezoid) stimuli from skin temperature to 25 defined levels of intensity (steps) provided an excellent range of thermal pulses suitable for testing in forced-choice, (Dyck et al., 1993a, 1978) 4, 2, and 1 stepping (Dyck et al., 1993b), or open, algorithms.

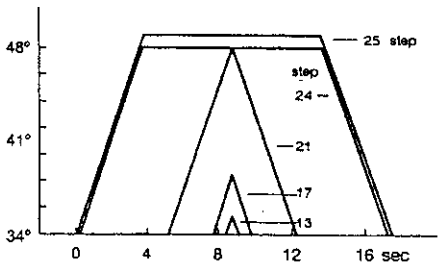

Fig. 1. Representative pyramidal and trapezoid heating stimuli used to assess warm and heat-pain thresholds using CASE IV. Different steps (stimuli) are overlaid to show the great variability of stimulus intensity that is available for testing. From steps 1 through 21, heating pulses are pyramidal shaped. The temperature at the face of the thermode changes from 34°C to its peak, and back to baseline with a change of 4°C per sond. At step 21, the highest temperature achieved is 48°C. At step 22, 48°C is achieved and held for 1.5 s; at step 23, 48°C is held for 5 s; at step 24, 48°C is held for 10 s, and at step 25, 49°C is held for 10 s. In healthy subjects, heat-pain detection threshold (HP: 0.5) is typically estimated at step levels 18–21 and an intermediate heat-pain response (HP: 5.0) at steps 21–23. Normal percentiles specific for site, age, gender, height, weight, body surface area, and body mass index have been estimated as Z score tables and have been published (Dyck et al., 1995).

Our goal for the present study was to: (1) develop a standard test of threshold and an estimated intermediate level of severity of heat-pain sensation; (2) test the influence on heat-pain responses of the time interval between stimuli and tests; (3) test the influence of low or high baseline temperature on heat-pain responses; and (4) test reproducibility.

2. Methods

2.1. The computer assisted sensory examination (CASE IV) system

The studies were performed using computer assisted sensory examination, system IV (CASE IV) (Dyck et al., 1993a, 1978). To summarize, the system consists of a personal computer, an electronic controller containing electronic circuitry to shape and control stimulus characteristics, and fail-safe mechanisms, vibratory and thermal transducers, a video screen for display of program instructions, testing options, error messages, and results, a printer, a visual cuing device, and a response key. The thermode has a stimulating area of 10 cm^2 and for these studies was programmed to provide pyramidal-shaped heating stimuli, with a straight line rise and fall of 4°C/s. Available for testing were pulses of heat increasing exponentially in magnitude from 1 to 25 based on our previous studies of just noticeable difference (Dyck et al., 1978). The great range in magnitude of thermal stimuli which can be given is illustrated in Fig. 1. From stimuli 1 through 21, the stimuli are pyramidal, reaching 48°C at step 21. At step 22, the maximal temperature at 48°C plateaus for 1.5 s; at step 23 for 5 s, and at step 24 for 10 s. At step 25 the temperature rises to 49°C and plateaus for 10 s. It should be appreciated that the surface of the thermode achieves these temperatures, whereas the skin at the level of nociceptors undergoes temperature changes which are derivatives of thermode temperature.

2.2. Algorithms of testing

Various algorithms of testing were employed: open (any step level by choice of the operator); step-wise increasing

with null stimuli (several versions); forced-choice; 4, 2, and 1 stepping (Dyck et al., 1993b), and non-repeating ascending with null stimuli (NRA-NS, described below).

2.3. The standard procedures using CASE IV

This section outlines the standard procedures we adopted for assessing heat-pain thresholds. The site to be tested is inspected, avoiding infected, calloused, or diseased skin. Excessively hairy skin is shaved. The initial skin temperature is taken with an infrared thermometer. If it is below 32°C, the limb is warmed in water. The thermode is snugly applied using a strap. The thermode (calibrated that morning for 34° and 50°C) is set at 34°C and allowed to accommodate the skin temperature. During accommodation, the following instructions are read to the subject or patient. The instructions are also displayed on a printed card placed on a stand before the patient.

"In this test, small pulses of warming heat are given during the display of the number 1. A yellow light precedes the display of the number 1 to alert you that a stimulus is about to be given. Many of the pulses of warming heat given are so small that they are not felt or are felt only as warm or hot, but without discomfort or pain. When you feel nothing or warm or hot but without any discomfort or pain, your response should be 0. This card (examiner points to the card shown in Fig. 1) lists what responses you should give, depending on what you feel. If you feel some degree of discomfort or pain, in addition to a warm or hot sensation (or without warm or hot) you must grade its severity from 1 to 10. Number 1 would correspond to the lowest level of discomfort or pain, number 10 would correspond to the most severe level of pain. To repeat, following every stimulus event as indicated by the number 1, choose 0 when you feel nothing or only warmth or heat. Choose a number from 1 to 10 if you experience any degree of discomfort or pain–number 1 is the least degree of discomfort or pain, whereas 10 is the most severe. Please note that we do not intend to hurt you, so we will be testing you only at the lower discomfort or pain levels. You should also tell me just as soon as you feel you would not like to be tested at a stronger stimulus. Do you want me to repeat the instructions? Any questions? Now I will give you a short demonstration."

A step-by-step interactive demonstration of a test is then given to ensure that the subject or patient appreciates that some stimuli may not be felt (too small to be felt or null stimuli), whereas others are warm or hot but without pain. When the subject appreciates how the test is given, the formal test is given using the NRA-NS algorithm.

2.4. Safety features

A series of software and hardware features were built into the system to recognize faulty operation conditions or excessive temperatures and to shut down the system if aberrant conditions occurred. It was decided that the sensory technician or a physician must remain adjacent to the subject or patient during heat-pain testing to recognize tissue damaging stimulation. In addition, the subject or patient was told to report excessive thermal stimuli.

We have now performed this heat-pain test in ~ 1000 subjects and patients. As described elsewhere, erythema is regularly produced but not blistering or injury of the skin. Early in the development of the system, due to a faulty electrical connection and excessive temperature of the thermode, a skin burn was produced.

2.5. Healthy subjects

Healthy volunteers, without neurologic disease or diseases predisposing to neuropathy, men and women, both young and old, from Rochester, Minnesota, were recruited for our studies.

2.6. Calibration and stimulus conditions

The design of the thermode and the controlling electronic circuitry have been described in previous publications (Dyck et al., 1993a, 1978). To calibrate the thermocouple (TC 1) mounted on the backside of the thermoelectric unit in contact with the skin (TEU 1), the electrically inactivated thermode was suspended in fluid and calibrated against a high quality mercury thermometer (National Bureau of Standards) through a range of temperatures from 0° to 50°C. Then using the read-out from TC 1 and providing current to TEU 1 as needed, it was possible to fashion the pyramidal or trapezoid heat pulses from baseline to different temperatures (steps of stimuli) desired. The use of the other components of the thermode in controlling temperature and dealing with excessive heat have been described in previous publications.

To confirm that the desired thermal waveforms were being reproduced at the surface of the thermode in contact with a realistic heat-sink load comparable to flesh, a standardized external heat-sink and monitoring approach was devised. A copper constantan junction was taped to the surface of TEU 1. This thermocouple had been calibrated (as described above) for temperatures between 0 and 50°C. Strips of copper, with thickness chosen to approximate the thermal mass of flesh were laid over the stimulating surface of the thermode. Recording from TC 1 and from this external thermocouple, it was shown that the ramp of thermal change (4°C/s) was reproduced even with the copper plates in place. As described previously, a small lag, at onset and end of the thermal ramps occurred.

To calibrate the thermode for use (done each morning) the thermode is placed on a styrofoam block overlaid by a 0.13 mm copper constantan junction, calibrated for temperatures between 0° and 50°. By keyboard, the controller is instructed to maintain the surface temperature of the thermode at 30°C. To meet calibration, the temperature

should be at 29.9° to 30.1°C at 5 min. Then the thermode is set at 45°C. At 5 min, it should be at 44.9°C to 45.1°C. In practice, the controlling system and thermode reproducibly achieves these temperatures, giving the operator confidence that the unit is calibrated. If it does not, the potentiometers of the amplifiers have to be adjusted so that calibration is achieved.

3. Results

3.1. Choosing the stimulus waveform and range of stimulus magnitudes (steps)

These studies using the open algorithm were performed on various anatomical sites of eight healthy subjects. Typically, when a single stimulus of low magnitude (step) was presented, nothing was felt. With a stronger stimulus, a pulse or surge of warmth or heat was experienced. With an even stronger stimulus, a pricking pain or burning was superimposed at the peak of the heat pulse. In some persons or at some sites (e.g., the foot), the first sensation experienced, in testing serially from small to large magnitude stimuli was not warmth or heat, but pain. At such sites, warm receptors are probably not present (Dyck et al., 1993a). In all cases, sensation was experienced only with the first direction of thermal change from baseline temperatures to peak and not with return of temperature to baseline. Usually, heat-pain sensation was first experienced at stimulus steps 19–21. As greater steps of thermal intensity were tested, no difference in the quality of the sensation was experienced except that the stimulus was more intense and longer in duration. Occasionally, a cooling sensation was experienced between stimuli, at a time when the thermode was actively cooling the skin to achieve baseline (34°C) skin temperature.

In choosing the stimulus waveform and range of stimulus steps, our first goal was to choose a range of stimulus magnitudes sufficient to test both a sensitive part (the face of a young person) and an insensitive part (the foot of an old person). The largest stimuli should produce erythema without causing blistering or epidermal injury. Based on trials of healthy subjects, we focused on two stimulus waveforms: 1) pyramidal-shaped stimuli (a uniform waveform throughout the range of stimulus magnitudes) with a maximal temperature to 55–60°C, and 2) pyramidal and trapezoid-shaped stimuli to 49°C. We chose the second approach because we did not want to use temperatures to 55–60°C, because it is well above the temperature (~ 43.5°C), which when maintained for a prolonged period of time, induces pain and skin damage. The margin of safety is less at the higher temperature than it is at lower temperatures and, were the higher temperature to be used, more critical fail-safe approaches would be needed. We found that the magnitude of pain experience could be increased by changing a pyramidal to a trapezoid-shaped stimulus. The heat-pain experience was not altered by going from a pyramidal to a trapezoid-shaped stimulus except that it was more intense and lasted for a longer time. Testing at step 25 usually produced erythema but no blistering or frank injury. However, repeated stimulation at this intensity level was avoided.

We next made decisions about how the test should be administered and scored based on study of healthy subjects. The goal was to estimate the heat pulse (step) needed to induce heat-pain threshold, an intermediate level of severity of heat-pain, and the difference between threshold and this intermediate pain level (Hardy et al., 1953; Beecher, 1959; Huskisson, 1974; Joyce et al., 1975; Levine et al., 1982; Ohnhaus and Adlev, 1975; Dubner et al., 1974; Price et al., 1983, 1992; Feine et al., 1991; LaMotte, 1983). Following presentation of a thermal stimulus or a null stimulus (indicated by display of the number 1 to coincide with the stimulus event), subjects or patients were asked to grade their response after looking at a sign placed before them (Fig. 2). Subjects or patients were asked to grade their response as 0 (no discomfort or pain–warmth or heat might be experienced), or as a number between 1 (the least degree) and 10 (the greatest degree) of discomfort or pain. The heat-pain detection threshold (HPDT) is the thermal step level at which the stimulus is felt as painful 50% of the time. For reasons given below, we limit testing in the nociceptive range and so do not actually determine the step level which is just painful 50% of the time. Instead, we estimate the 0.5 (HP:0.5) and 5.0 (HP:5.0) pain response level by testing all steps between the two response levels. At some insensitive sites, HP:5.0 cannot be estimated. In such cases, the next highest level is estimated, e.g., HP:4.0, 3.0, 2.0, or 1.0. The difference in steps between HP:5.0 and HP: 0.5 is HP 5–0.5. We have now estimated HP:0.5, HP:5.0, and HP:5.0–0.5 of the dorsal foot, lateral leg, anterior thigh, dorsal hand, volar

No Discomfort or Pain (nothing, warm or hot)	Any Degree of Discomfort or Pain (hot + discomfort or pain)
0	1 2 3 4 5 6 7 8 9 10

Fig. 2. The visual display which is placed before the patient during the heat-pain test. The specific instructions read to the patient before onset of the test are given in the text.

forearm, and lateral shoulder in more than 275 healthy subjects between 18 and 74 years of age and have determined percentile values considering site, age, gender, and such physical variables as height, weight, surface area, and body mass index. These results will be presented in detail elsewhere. For most anatomical sites tested, it was possible to estimate both HP:0.5 and HP:5.0 except for HP:5.0 for dorsal foot of elderly persons. In these persons, it was usually possible to identify a lower level e.g., HP:4.0, HP:3,0, HP:2.0, or HP:1.0.

3.2. The minimal time interval needed between successive stimuli

From the known characteristics of nociceptors, we assumed that a minimum pause should be allowed between successive stimuli in the nociceptive range. Two criteria were used to assess this question: 1) the least time interval without threshold change; and 2) the least time interval for the skin temperature not to rise. Three different intervals of time were compared. For algorithm 1, the only pause was the time taken by the subject to respond, the response to be entered by keyboard, and the warning light for the next stimulus to be given (~ 5–10 s). For algorithm 2, the times between successive stimuli varied from 3 s at step 22–30 s at step 25 (in addition to the operational time referred to above). For algorithm 3, the comparable pauses were 15 and 90 s. Testing the same mid-volar forearm site of ten healthy subjects, we determined the average pain response from successive pairs of stimuli of equal magnitude but with different pauses between stimuli (the three algorithms). Testing was begun below pain threshold (HP:0.5) and extended beyond the HP:5 level. This allowed us to compare average pain thresholds for the same steps of stimulus intensity. In Table 1, we show the mean pain response for the first and second pairs of stimuli using three different pauses between successive stimuli. Only in algorithm 1 (the no pause algorithm) did the pain response increase significantly with presentation of the record stimulus.

In two healthy subjects we used an infra red thermometer to measure the temperature of the volar forearm skin between successive stimuli given with a very short pause (~ 2 s) in the nociceptive range. An unequivocal rise in baseline temperature was demonstrated. Even a short pause, e.g., 10–20 s between successive stimuli, prevented this rise in temperature.

Table 1
Comparison of the average pain responses (1 = least, 10 = greatest) for pairs of heat stimuli of equal intensity (volar forearm, 10 healthy subjects)

	Mean response 1	Mean response 2	S.D.	P-value
Algorithm 1 [a]	3.4163	3.7616	0.3651	0.0152
Algorithm 2 [a]	3.5137	3.4813	0.4659	0.8304
Algorithm 3 [a]	3.4375	3.5591	0.5124	0.4720

[a] The variable time allowed between successive stimuli is outlined in text.

Table 2
Average heat-pain thresholds (steps) of volar forearm of 10 healthy subjects comparing different intervals of time between heat-pain assessments (volar forearm, 10 healthy subjects)

	Mean response 1	Mean response 2	*P* value
HP: 0.5, Δ 45 min	20.23	20.32	0.63
HP: 5.0, Δ 45 min	23.28	22.88	0.08
HP Δ: 5.0–0.5, Δ 45 min	3.04	2.56	0.08
HP: 0.5, Δ 90 min	19.82	19.58	0.48
HP: 5.0, Δ 90 min	22.82	22.62	0.25
HP Δ: 5.0–0.5, Δ 90 min	3.00	3.05	0.90
HP: 0.5, Δ 4 h	19.27	19.30	0.93
HP: 5.0, Δ 4 h	22.71	22.60	0.50
HP Δ: 5.0–0.5, Δ 4 h	3.54	3.31	0.53
HP: 0.5, Δ 24 h	19.56	19.54	0.96
HP: 5.0, Δ 24 h	22.45	22.60	0.49
HP Δ: 5.0–0.5, Δ 24 h	2.82	3.07	0.52

3.3. Setting the shortest time between successive tests

Another requirement in designing a standard heat-pain test is determining the shortest interval of time that should be allowed before the heat-pain test can be repeated. To answer this question, we compared heat-pain responses (HP:0.5, HP:5.0, and HP 5.0–0.5 with pauses of 45 min, 90 min, 4 h, and 24 h in ten healthy subjects. A statistically significant difference was not found (Table 2).

In these healthy subjects, we observed the physical condition of the skin after a test. Erythema was evident in all cases but persisted for a variable period of time (5–25 min). In no cases was blistering or greater injury of the skin encountered.

3.4. Choice of the non-repeating ascending with null stimuli algorithm (NRA-NS)

We considered use of our previously published forced-choice and 4, 2, and 1 stepping algorithms for heat-pain sensation assessment. Based on studies on ourselves and healthy subjects, we found that these algorithms were unsuitable for three reasons: (1) too many excessively painful stimuli are given – objectionable to subjects, possibly causing local tissue alterations, and possibly altering threshold; (2) too much time is needed – long pauses between stimuli might be needed for the strong stimuli which would be included; and (3) the HP:5.0 is not estimated with these algorithms. To overcome these problems, we designed the Non-Repeating Ascending with Null Stimuli (NRA-NS) algorithm.

The NRA-NS algorithm begins testing at a level unequivocally below HP:0.5 (step 13), increases by steps of 2 until step 21 or a ≥ 1 pain response, and then increases by

single steps until ≥ HP:5.0 is attained or step 25 has been tested (whichever comes first). Only a single heat pulse is given for each stimulus step between pain responses 1 and ≥ 5. After each stimulus event, the subject is asked to report whether the stimulus was not felt, was felt as warm or hot, but was without pain (0 response) or was associated with discomfort or pain (judged as 1 [least] to 10 [greatest]. If a response ≥ 1 is reported for any of the steps 13, 15, 17, 19, or 21, the step immediately smaller, if not previously tested, is then tested and single stepping to successively higher steps is used thereafter. In each sequence of three stimuli, one is randomly selected to be a null stimulus. If the subject gives an answer between 1–10 for a null stimulus, the test is declared invalid, the instructions and demonstration is repeated, and the test is given again.

The algorithm has now been employed in approximately 1000 different healthy subjects and patients. The approach is easily explained and is well accepted. With set-up time, explanation, and administration of the test, it is completed in from 8–15 min. The use of the warning light and number 1 for both the stimulus and null stimulus events prevents the subject from knowing the identity of the stimulus.

3.5. Graphing responses

Visual inspection of graphed data points of the stimulus responses indicated that the graph was made up of two components – the no pain response and the pain response. It seemed reasonable, therefore, to fit a line to each of these components. The no pain response line is at 0. For fitting a line to the stimuli with pain responses, an operational definition was needed for which stimulus response levels should be included. Let the highest step tested = n. Sequentially consider the responses from testing at steps n, $n-1$, and $n-2$, next from steps $n-1$, $n-2$, and $n-3$, then from $n-2$, $n-3$, and $n-4$, and so on, in groups of three steps of decreasing stimulus magnitude. In the estimation algorithm, we will consider only steps that are included in a group which has at least 2 (of the 3) responses ≥ 1. Using quadratic least squares regression, regress response against step number. From the models (linear, logistic, and quadratic regression) tested on representative data sets, the quadratic regression appeared to perform satisfactorily. In less than 5% of cases, the quadratic equation did not perform well, e.g., only-one response > 0. In these cases, linear interpolation/extrapolation was used to obtain estimates.

Estimation of HP:0.5, HP:5.0 and HP 5.0–0.5 and graphical displays are performed by computer and printed out.

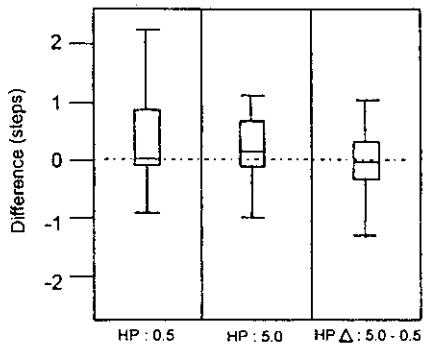

Fig. 4. Box and whisker figures to show the difference (first minus second) in stimulus steps to achieve heat-pain detection threshold (HP: 0.5), intermediate heat-pain response (HP: 5.0), and HP 5.0–0.5. Heat-pain threshold was estimated on the volar forearm of 25 healthy subjects as described in text. The extremes of the whiskers represent the range, the ends of the boxes, the 25th and 75th percentiles and the line in the box, the 50th percentile. For HP: 0.5, the results fall within ±0.25 steps 48% of the time; for ±0.5 steps 64%; for ±1 step 76% and for ±2 steps 96% of time. For HP: 5.0, comparable percentages were 32%, 56%, 88%, and 100%. (For HP: 5.0-0.5, comparable percentages were 32%, 60%, 84%, and 100%).

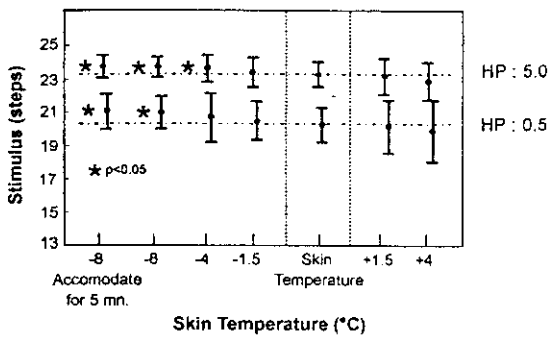

Fig. 3. Heat-pain responses were estimated on the volar forearm of 10 healthy subjects using accommodating temperatures below (−1.5, −4, −8 and −8°C [accommodated for 5 min]) and above skin temperature (+1.5 and +4°C). Results are given as the mean and 1 SD. Note that on average it takes a higher stimulus intensity to obtain the intermediate heat-pain response (HP: 5.0)when accommodating temperatures of −4°C or −8°C are used. Likewise, for heat-pain detection threshold (HP: 0.5) higher stimuli steps are needed for −8°C accommodating temperature. This difference was not overcome by a longer (5 min) accommodating time at −8°C. At these low accommodating temperatures, it takes a stronger heat pulse to bring dermal nociceptors to the temperature at which pain is perceived than to change their temperature to this point when accommodating temperatures are at skin temperature (e.g., 34°C).

3.6. Initial skin temperature and heat-pain thresholds

This was tested on the volar forearm of 10 healthy subjects. We found that the accommodating baseline temperature influenced heat-pain thresholds (Fig. 3). When accommodating temperatures were below skin temperatures, higher steps of stimulus intensity were needed to achieve HP:0.5 and HP:5.0 (with several reaching statistical significance). With higher accommodating temperatures, lower steps of stimulus intensity were needed to achieve these thresholds (but without reaching statistical significance).

3.7. Comparison of left versus right

Heat-pain thresholds were tested on 10 volar forearms of healthy subjects. No statistically significant differences were found between sides.

3.8. Reproducibility

This was tested for the volar forearms of 25 healthy subjects with a mean (SD and range) age of 48.5 years (14.3, 22–74 years). The tests were performed at marked (with indelible ink) sites of the volar forearm. The test was repeated no sooner than 24 h and no longer than two weeks after the initial evaluation. In Fig. 4, we show the low variability of the differences (first minus second).

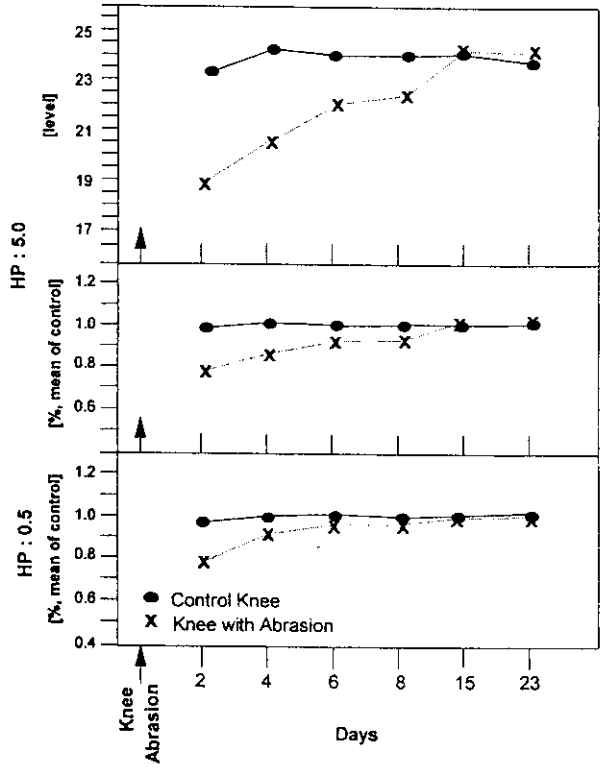

Fig. 5. Two days after an abrasion injury of the right knee in a bicycle accident, a 66-year-old man had estimates made of heat-pain responses of abraded skin of the right knee and of an homologous region from the contralateral knee. In the top panel, we show the step value at which HP: 5.0 was experienced on the injured side. In the middle panel, this is shown relative to the mean value of the control side. In the lower panel, we show the step value at HP: 0.5 on the injured side relative to the control side. The figure illustrates two important points. The first point is the relative stability of the thresholds for the healthy knee over time. The second point is that the heat-pain test can reliably demonstrate the lowered heat-pain responses which develops consequent to skin abrasion. At two days, heat-pain responses were about 25% lower than normal and only returned to normal by two weeks at a time when the abraded skin was epithelialized.

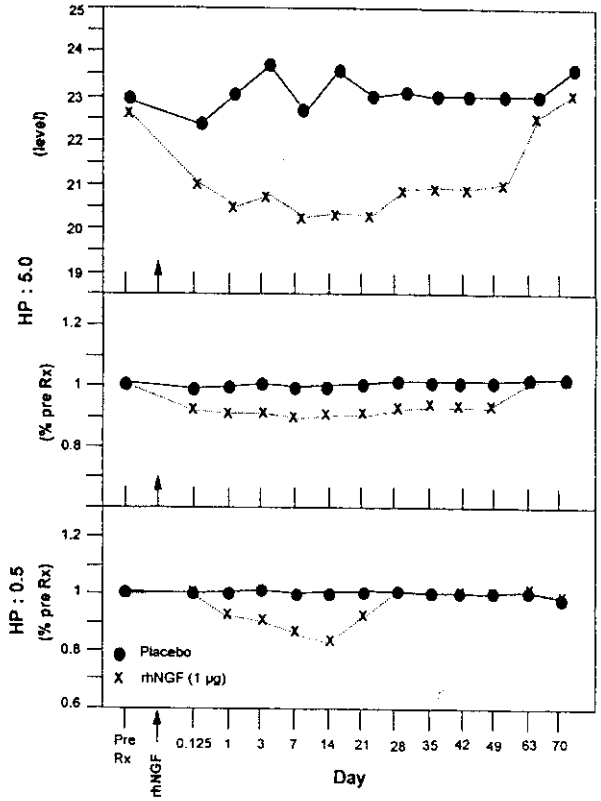

Fig. 6. Sequential heat-pain responses from a healthy subject (M, 66 years) who received 1 μg of recombinant human nerve growth factor (rhNGF; Genentech, Inc.) intradermally into the volar forearm on one side and a similar volume of saline into the other. In the upper panel, we show serial values of the HP: 5.0 (by stimulus steps needed to induce this degree of pain). Notice the similarity of threshold prior to NGF injection at onset, the normal variability of the HP: 5.0 of the saline injected side over the duration of the experiment, and the dramatic lowering of the HP: 5.0 on the rhNGF injected side which persisted for many weeks. In the middle panel, we show these results plotted as a percent of baseline values. In the lower panel, we show the HP: 0.5 changes with time plotted as a percent of baseline. The outcome of this study has been confirmed in a study of 16 healthy subjects using dosages of 1 and 3 μg of rhNGF (in preparation for publication). In addition to showing how stable threshold measures of heat-pain can be over long time periods, it provides evidence that NGF can lower heat-pain thresholds in man, a result anticipated from tests in the rat model using the tail-flick test.

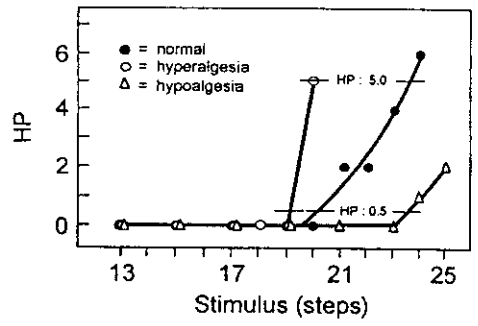

Fig. 7. A superimposition of the plotted values of three diabetic patients illustrating a normal response, one with hyperalgesia and one with hypoalgesia. Note that it is possible to estimate the HP: 0.5 and the HP: 5.0 for the first two but only the HP: 0.5 for the third. In the third case, it is possible (and useful for percentile estimation) to estimate the HP: 2. See text for further discussion of what these differences imply.

3.9. Responses in health and disease

To illustrate the use of the heat-pain test, we demonstrate the lowered HP:0.5 and HP:5.0 following skin abrasion (Fig. 5), and injection of intradermal nerve growth factor (Fig. 6) and raised thresholds which may occur in diabetic polyneuropathy (Fig. 7). The steeper than normal stimulus-response line is indicative of hyperalgesia, and the less steep line of hypoalgesia (Fig. 7).

4. Discussion

There is considerable information about the underlying neurobiologic basis of stimulus-induced heat-pain sensation (Light and Perl, 1993; Bessou and Perl, 1969; van Hees and Gybels, 1972; Torebjörk and Hallin, 1974; Torebjörk, 1974). Pricking (first or epicritic) pain is mediated by A δ (small myelinated fibers) whereas burning (second or protopathic) pain is mediated by C fibers (Head, 1920; Collins et al., 1960; Kugelberg, 1948; Lewis and Pochin, 1938; Price, 1972). Electrical, chemical, mechanical injury, heat or cold may be used to illicit pain (Light and Perl, 1993).

Heat-pain threshold probably relates more to tissue temperature (and presumably its duration) than it does to rate of thermal change (Hardy et al., 1953). The lowest prolonged temperature which induces heat-pain is the same as the sustained minimal temperature which induces skin injury, and is about 43.5°C (Hardy et al., 1953). Pulses of heat from contact thermodes provide a good way of assessing stimulus induced pain because the skin can be accommodated to a baseline temperature and precisely quantitated, shaped and graded stimuli can be superimposed. Extensive studies in health and disease of thresholds (detection (e.g., prickling pain) and also of differences in magnitude) were performed by Hardy, Wolf and Goodell (Hardy et al., 1953). With thermoelectric technology, it is possible to maintain skin temperature at defined baseline temperatures and to superimpose defined magnitudes of cooling or heating waveforms. Using such approaches we, and others, have designed systems for experimental and clinical use (Dyck et al., 1978; Arezzo et al., 1986; Jamal et al., 1985; Hansson and Lindblom, 1992; Verdugo and Ochoa, 1992).

These systems have been used to study detection and magnitude estimates of the heat-pain response (Price et al., 1992). There are topographical differences in heat-pain threshold and thermode area may affect threshold (spatial summation) (Price et al., 1992). Heat-pain threshold appears to be less variable over the surface of the body than is vibratory or cooling detection threshold (Dyck et al., 1993a, c, 1978; Price et al., 1992). Whereas vibratory threshold, especially of acral limbs, is markedly influenced by age and cooling, heat-pain thresholds are thought to be less affected.

CASE IV and our 10 cm^2 thermode provides the necessary broad range of thermal stimuli suitable for testing heat-pain in health or in disease. The system is standardized and provides stimuli reproducibly in whatever array is specified. In algorithms which sequentially test all steps to 25, only erythema without blistering or tissue injury is produced. From our experience, if properly calibrated and used, injury of insensitive skin should not occur. To ensure that it does not occur, examining personnel must adhere to use of the standardized test and be in attendance at all times.

How should the test be administered? Our previously described forced-choice and 4, 2, and 1 stepping algorithms seemed unsuitable for evaluation of heat-pain sensation. Both of these algorithms employ more than the desirable number of nociceptive stimuli. The Non-Repeating Ascending Algorithm with Null Stimuli (NRA-NS) introduced here appears to perform well. In this algorithm, we proceed only from small to large stimuli and do not repeat testing at any step in the nociceptive range. The algorithm uses short pauses between stimuli based on present studies. Use of excessively short pauses raises skin temperature and spuriously increases heat-pain responses. Although the increased heat-pain responses which resulted from use of short pauses between successive stimuli could be from sensitization of nociceptors, it probably resulted simply from raising skin temperature. With a rise in accommodating temperature, the same step stimulus can raise the temperature in skin to a higher temperature resulting in a slightly greater pain response. In addition to emphasizing that the pause between stimuli be sufficiently long, our results also indicate that it is most important to use a standard accommodating temperature, e.g., 34°C. With its use, the thermal steps used in testing will be alike among patients from one cutaneous site to another and among medical centers.

Herein we provide evidence that excessively low accommodating temperature can affect heat-pain thresholds. With accommodating temperatures of -4°C and -8°C (below skin temperature) greater stimuli were needed to illicit HP:0.5 or HP:5.0. Although this could be explained by a difference in receptor function (LaMotte, 1983), it is more likely to be due simply to a temperature effect at the level of the nociceptors – it needs a bigger thermal pulse to bring them to the temperature at which nociceptors discharge impulses. The use of null stimuli permits detection of persons who respond erroneously to stimulus events rather than to the stimulus itself.

We also recommend use of the standardized approach, developed here, to estimate detection threshold (HP:0.5), the stimulus needed to elicit an intermediate level of pain (HP:5.0 [or 4.0, 3.0, 2.0 or 1.0 if 5.0 cannot be elicited]), and the difference in steps between the two (HP 5.0–0.5). The rules adopted can be programmed into computer memory so that these values can be automatically determined and compared to normal results, plotted, and printed.

So that standardized tests can be used to estimate percentile responses specific for site, age, gender, and various physical characteristics and then to express results using these percentiles we have described the standard stimuli and approaches in great detail. All aspects of stimulus waveform and magnitude, calibration, pause between stimuli and tests, accommodating temperature and algorithm of testing, and finding threshold have been described. If precisely the same approaches are used at another medical center, and even by a different hardware system, it should be possible to get identical test results among different medical centers. The need to use standard and common testing approaches is evident so that test results can be compared among medical centers.

Having developed a standard test of heat-pain sensation, it has been possible to estimate normal limits on a representative healthy subject cohort considering anatomical site, age, gender, and other physical variables (Dyck et al., 1995). In a patient, it is now possible to print out specific percentile responses for a given site in a patient. The uses for the test are several. We anticipate being able to characterize heat-pain loss distribution and change over time in various neurologic diseases, and applying this ability to both clinical practice and clinical trials. In epidemiologic studies, it should be possible to report the incidence and prevalence of pain loss with disease and assess the contribution of pain loss to such clinical phenomena as distal mutilating acropathy (plantar ulcer and Charcot joints). The test also allows one to study hypersensitivity phenomena (Hansson and Lindblom, 1992; Price et al., 1987; Verdugo et al., 1994) and whether pharmacologic agents change threshold or hypersensitivity.

The uses made of a heat-pain test (as the one developed here) were illustrated by study of newly abraded skin, intradermal injection of nerve growth factor, and diseases of nerves. In both abraded skin and intradermal injection of NGF, the heat-pain responses were at strikingly lower stimulus intensities as compared to the control contralateral side. Demonstrated also, was a low variability of heat-pain threshold in serial evaluations over several weeks and in reproducibility studies of 25 healthy subjects.

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