Opioid “Induced” Hyperalgesia (and Allodynia)

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Learning Objectives

- Define and describe the mechanisms of OIH
- Understand the methods of quantifying OIH
- Differentiate alternate explanations of hyperalgesia in chronic pain
Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes.

Conduct one or more studies to provide quantitative estimates of the serious risks of misuse, abuse, addiction, overdose, and death

Develop and validate measures of the following opioid-related adverse events: misuse, abuse, addiction, overdose and death

Conduct a study to validate coded medical terminologies (e.g. ICD10) used to identify the following opioid-related adverse events: misuse, abuse, addiction, overdose, and death

Conduct a study to define and validate “doctor/pharmacy shopping” as outcomes suggestive of misuse, abuse and/or addiction

Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following use of ER/LA opioid analgesics for at least one year to treat chronic pain.

We strongly encourage you to use the same trial to assess the development of tolerance following use of ER/LA opioid analgesics. Final Protocol Submission: 08/2014; Trial Completion: 08/2016; Final Report Submission: 02/2017.
Do Opioids “Induce” Hyperalgesia (and/or Allodynia)?

If you are a rat, yes. But in man…? 

See J. Mao, multiple refs
Animal Studies of OIH Like Phenomena

- Aley and Levine, 1995, 59 Rat ID DAMGO Mechanical
- Aley and Levine, 1997, 51 Rat ID DCP Mechanical AC
- Aley and Levine, 1995, 50 Rat ID DAMGO Mechanical PKC
- Aley and Levine, 1997, 52 Rat ID DAMGO Mechanical PKC
- Kim et al., 1990, 161 Rat IV Morphine Thermal
- Aley and Levine, 1997, 53 Rat ID DAMGO Mechanical
- Kim and Siegel, 2001, 162 Rat SC Morphine Thermal
- Arts et al., 1991, 54 Mouse ICV Morphine Thermal
- Kissin et al., 2000, 163 Rat IV Alfentanil Mechanical
- Lane et al., 2004, 164 Rat PAG Morphine Thermal
- Bie et al., 2003, 143 Rat IV Morphine Thermal
- Larcher et al., 1998, 165 Rat SC Heroin Mechanical
- Celerier et al., 1999, 38 Rat SC Heroin Mechanical
- Bie, 2003, 144 Rat IP Morphine Thermal
- Ludlum et al., 1999, 40 Rat SC Heroin Mechanical
- Li et al., 2001, 46 Mouse SCMorphine Thermal
- Celerier et al., 2001, 37 Rat SC Heroin Mechanical
- Li and Clark, 2002, 35 Mouse SC Morphine Thermal
- Liang et al., 2003, 73 Mouse SC Morphine Thermal
- Christensen and Kayser, 2000, 146 Rat SC Morphine Mechanical
- Colpaert et al., 2002, 147 Rat SC Morphine Mechanical
- Crain and Shen, 2004, 136 Rat SC Morphine Thermal
- Davies et al., 2003, 49 Mouse SC Morphine Mechanical
- Deen and Kriel, 1991, 148 Rat IP Morphine Thermal
- Dunbar and Pulai, 1998, 60 Rat IT Morphine Thermal
- Dunbar et al., 2000, 65 Rat IT Morphine Thermal
- Dunbar and Kieran, 2003, 100 Rat IT Morphine Thermal
- Eckert et al., 1993, 49 Rat II Morphine Thermal
- Galeotti et al., 2002, 150 Mouse Oral Morphine Thermal
- Gardell et al., 2002, 76 Rat SC Morphine Mechanical
- Grilly et al., 1981, 151 Rat SC Morphine Mechanical
- Harris et al., 2004, 153 Rat IP Morphine Thermal
- Heinzen and Palko, 2004, 154 Rat IV Morphine Electrical
- Hendrix, 1985, 137 Rat Oral Morphine Thermal
- Hendrix, 1989, 155 Mouse IP Morphine Thermal
- Hoffmann et al., 1998, 156 Rat SC Morphine Thermal
- Ikeda et al., 1997, 45 Rat IT Morphine Thermal
- Johnston et al., 2004, 66 Rat IT Morphine Thermal
- Kang et al., 2002, 137 Rat Fentanyl Thermal
- Kaplan and Fields, 1991, 150 Rat RVM Morphine Thermal
- Kayan and Mitchell, 1968, 159 Cat SC Morphine Mechanical
- Kayan et al., 1971, 32 Rat SC Morphine Thermal
- Kout et al., 2002, 160 Mouse SC Morphine Thermal
- Khedar et al., 1995, 55 Rat ID DAMGO Mechanical
- AC adenylate cyclase; DAMGO Tyr-D-Ala-Gly-(me) Phe-Gly-ol; EAA excitatory amino acids; HO heme oxygenase; ICV intracerebroventricular
Case Reports re: High-dose, Opioid-“induced” Allodynia/Hyperalgesia

- **104 M PO, IM, IV 60–300 mg/d PO; 150–960 mg/d IM; 20 g/d IV** Generalized allodynia, myocloni (1) n _ 4; cancer pain; substituting morphine with methadone, sufentanil, or ketobemidone reversed allodynia
- **105 M IV 175–200 mg/h** Generalized allodynia (5) aggravated neuralgia (3), myocloni (4) n _ 8; cancer pain (described in detail, n _ 2), dose escalation aggravated allodynia
- **106 M IT 37.5 mg/h** Spontaneous pain, allodynia not reported n _ 1; cancer pain, 50-fold reduction of IT morphine resolved pain aggravation
- **107 M IT 80 mg/d** Spontaneous pain and allodynia in dermatomes S5–T5 myocloni _ 1; cancer pain, primary pain T4–T7, dose reduction to 50 mg/d reduced allodynia
- **108 M IV 600 mg/h** Generalized allodynia, myocloni n _ 1; cancer pain, substituting morphine with methadone reversed allodynia
- **109 M PO, IT 400 mg/d IV; 48 mg/d IT** Generalized or lumbosacral segmental allodynia, myocloni(1)n _ 3; cancer and nonmalignant pain (described in detail, n _ 2), dose reduction or substituting morphine with sufentanil, fentanyl, or methadone reversed allodynia
- **110 M IV 105 mg/h** Generalized allodynia n _ 1; cancer pain in infant, reduction of morphine resolved allodynia
- **111 M IT 0.2 and 0.5 mg bolus** Allodynia in dermatomes T6–T7 n _ 1; central pain after spinal injury, administration of naloxone did not reverse hyperalgesia
- **112 M/MET IV/PO 200/75 mg/d; 90/90 mg/d** Generalized allodynia n _ 2; cancer pain, switching second patient to methadone did not reverse hyperalgesia
Hyperalgesia? Opioid Induced?

- OIH
- OIA
- Microwithdrawal hyperalgesia
- Opioid neurotoxicity
- ‘Natural’ pain and/or drug induced peripheral/central sensitization, augmentation
- Endocrinopathy induced sensitization (due to pain? Due to drugs?)
- Tolerance
What is the mechanism of hyperalgesia, either ‘natural’ (sensitization due to pain) or iatrogenic (eg, drug induced)?

- Peripheral sensitization
- Central sensitization/augmentation
- Disinhibition
- Sympathetically maintained
- etc
Peripheral Sensitization

Marchand F. et al. Nat. Rev. Neurosci. 6, 2005
Central Sensitization
The Tetrapartite Synapse in Nerve Injury

J.A. De Leo et al. / Pain 122 (2006) 17–21

After Nerve Injury

2- PRE-SYNAPTIC NEURON
• Depolarization
• Neurotransmitter release

3- ASTROCYTE
• Cytokine, chemokine release
• Glutamate & D-serine release
• Decreased GLT-1
• Ca²⁺ oscillations
• K⁺ channel dysregulation

1- MICROGLIA
• Cytokine, glutamate release
• Na⁺ channel activation
• TLR-4 expression
• K⁺/Ca²⁺ channel dysregulation

4- POST-SYNAPTIC NEURON
• Glutamate receptor activation
• Ectopic firing
Areas Active in CRPS
Decreased FA in CRPS, localized to a portion of the left callosal fibers (purple, shown in different orientations and magnifications; p < 0.05)
Hypothesis: CRPS maintained and reinforced by nested positive feed forward (afferent nociceptors) and feed back (efferent sympathetic nerves) loops
How do we measure/define hyperalgesia?

....and develop outcomes to address the FDA concerns about OIH
IASP ‘Glossary’ Definitions:

- **Allodynia**
  - Pain due to a stimulus that does not normally provoke pain.

- **Hyperalgesia**
  - Increased pain from a stimulus that normally provokes pain.

- **Hyperesthesia**
  - Increased sensitivity to stimulation, excluding the special senses.

- **Hyperpathia**
  - A painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as a decreased threshold.

- **Hypoalgesia**
  - Diminished pain in response to a normally painful stimulus.
Quantitative sensory testing: a comprehensive protocol for clinical trials

R. Rolke, W. Magerl, K. Andrews Campbell, C. Schalber, S. Caspari, F. Birklein, R.-D. Treede

Abstract

We have compiled a comprehensive QST protocol as part of the German Research Network on Neuropathic Pain (DFNS) using well established tests for nearly all aspects of somatosensation. This protocol encompasses thermal as well as mechanical testing procedures. Our rationale was to test for patterns of sensory loss (small and large nerve fiber functions) or gain (hyperalgesia, allodynia, hyperpathia), and to assess both cutaneous and deep pain sensitivity. The practicality of the QST protocol was tested in 18 healthy subjects, 21–58 years, half of them female. All subjects were tested bilaterally over face, hand and foot. We determined thermal detection and pain thresholds including a test for the presence of paradoxical heat sensations, mechanical detection thresholds to von Frey filaments and a 64-Hz tuning fork, mechanical pain thresholds to pinprick stimuli and blunt pressure, stimulus–response-functions for pinprick and dynamic mechanical allodynia (pain to light touch), and pain summation (wind-up ratio) using repetitive pinprick stimulation. 2005
Altered (thermal) quantitative sensory testing outcome in subjects with opioid therapy

Lucy Chen, Charlene Malarick, Lindsey Seefeld, Shuxing Wang, Mary Houghton, Jianren Mao

Abstract

Preclinical studies have suggested that opioid exposure may induce a paradoxical decrease in the nociceptive threshold, commonly referred as opioid-induced hyperalgesia (OIH). While OIH may have implications in acute and chronic pain management, its clinical features remain unclear. Using an office-based quantitative sensory testing (QST) method, we compared pain threshold, pain tolerance, and the degree of temporal summation of the second pain in response to thermal stimulation among three groups of subjects: those with neither pain nor opioid therapy (group 1), with chronic pain but without opioid therapy (group 2), and with both chronic pain and opioid therapy (group 3). We also examined the possible correlation between QST responses to thermal stimulation and opioid dose, opioid treatment duration, opioid analgesic type, pain duration, or gender in group 3 subjects. As compared with both group 1 (n = 41) and group 2 (n = 41) subjects, group 3 subjects (opioid n = 58) displayed a decreased heat pain threshold and exacerbated temporal summation of the second pain to thermal stimulation. In contrast, there were no differences in cold or warm sensation among three groups. Among clinical factors, daily opioid dose consistently correlated with the decreased heat pain threshold and exacerbated temporal summation of the second pain in group 3 subjects. These results indicate that decreased heat pain threshold and exacerbated temporal summation of the second pain may be characteristic QST changes in subjects with opioid therapy. The data suggest that QST may be a useful tool in the clinical assessment of OIH. 2009
Proposed tests to Assess for ‘Hyperalgesia’

Thermal QST:
- Warm Perception
- Cold Perception
- Heat Pain Perception
- Cold Pain Perception

Thermal Wind-up:
- Three series of five heat pulses is delivered using the same thermode ranging 39-49°C (2.4-second duration heat pulse) volar aspect
- A NRS is obtained after each pulse and an average of each of the three “taps” was analyzed.

Pinprick sensation testing:
- 256 mN weighted pin
- NRS is recorded with a single stimulation with the pin over the volar aspect of the non-dominant forearm
- This test is performed three times, and the average was analyzed.

Mechanical Wind-up:
- Subjects are stimulated with the same weighted pin at 1/second for 10 seconds, volar aspect
- NRS is recorded after the first, 5th and 10th stimuli.

Algometry
- Pressure pain threshold (kg/cm²), insertion of FDL
METHODS

- Chronic low back pain (any type)
- N=30 (20 in analysis)
  - 10 top half of those taking opioids
  - 10 taking no opioids
- A lab standard morphine milligram equivalency (MME) conversion was developed, averaging 5 available conversion tables
- Quantitative Sensory Testing was conducted
## Schedule of Study Procedures

<table>
<thead>
<tr>
<th>PROCEDURES</th>
<th>Visit 1one</th>
<th>Visit 2*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent</td>
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<td></td>
</tr>
<tr>
<td>Inclusion/Exclusion criteria</td>
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<td>X</td>
</tr>
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<td>Concomitant medication records</td>
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<td>X</td>
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<td><strong>Medical Evaluation</strong></td>
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<td>Personal health history</td>
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<td>X</td>
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<td>Physical exam</td>
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<td>X</td>
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<tr>
<td>Vital signs</td>
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<td><strong>Psychometric Testing</strong></td>
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<tr>
<td>SF-MPQ-2 Modified</td>
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<td>X</td>
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<tr>
<td>Pain Anxiety Symptoms Scale - 20</td>
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<td>Pain Disability Index</td>
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<td>CES-D 10</td>
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<td><strong>Psychophysical Testing</strong></td>
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<td>Thermal QST</td>
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<td>Thermal wind-up and after-sensation</td>
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<td>X</td>
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<tr>
<td>Pinprick wind-up and after-sensation</td>
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<td>X</td>
</tr>
<tr>
<td>Pinprick sensation testing</td>
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<td>X</td>
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<tr>
<td>Pressure pain threshold</td>
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<td>X</td>
</tr>
<tr>
<td>Vibration detection threshold</td>
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<td>X</td>
</tr>
<tr>
<td>Brush sensation test</td>
<td>X</td>
<td>X</td>
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<td><strong>Lab Tests</strong></td>
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<td>Free and total testosterone, DHT (men only)</td>
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<td>X</td>
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<tr>
<td>Estradiol (women only)</td>
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<td>X</td>
</tr>
<tr>
<td>LH (men and women)</td>
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<td>X</td>
</tr>
<tr>
<td>FSH (men and women)</td>
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# Morphine Milligram Equivalency (MME) Conversions

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<tr>
<th>Opioid Medication</th>
<th>Average Parenteral MME Conversion</th>
<th>Average Oral MME Conversion</th>
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<tbody>
<tr>
<td>Morphine</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Buprenorphine Injection</td>
<td>30.95</td>
<td>75.00</td>
</tr>
<tr>
<td>Buprenorphine TD</td>
<td>1.33</td>
<td>--</td>
</tr>
<tr>
<td>Codeine</td>
<td>0.087</td>
<td>0.10</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.09</td>
<td>--</td>
</tr>
<tr>
<td>Fentanyl TD</td>
<td>0.20</td>
<td>--</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>--</td>
<td>0.90</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>6.67</td>
<td>3.70</td>
</tr>
<tr>
<td>Meperidine</td>
<td>0.12</td>
<td>0.10</td>
</tr>
<tr>
<td>Methadone</td>
<td>1.00</td>
<td>5.30</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>--</td>
<td>1.30</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>10.00</td>
<td>2.10</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>--</td>
<td>0.30</td>
</tr>
<tr>
<td>Tramadol</td>
<td>0.10</td>
<td>0.30</td>
</tr>
</tbody>
</table>
tQST
Severe cold allodynia, mod heat allodynia
Heat and Cold hypoesthesia
Cold Sensation and Cold Pain Thresholds

High Dose Opioids

No Opioids

F = .39; p = .54

F = .46; p = .51

Temperature (°C)

Cool Perception Cold Pain

High Dose Opioids

No Opioids
Warm Sensation and Heat Pain Thresholds

- Warm perception
- Hot pain perception

For warm sensation:
- High Dose Opioids: $F = .45; p = .51$
- No Opioids: $F = .08; p = .78$

For hot pain perception:
- High Dose Opioids: $F = .45; p = .51$
- No Opioids: $F = .08; p = .78$
Thermal detection and pain (tQST) by subject type and site. Data are mean °C (± sd) from 37 KOA subjects and 35 controls.

<table>
<thead>
<tr>
<th></th>
<th>Medial worst knee</th>
<th>Lateral worst knee</th>
<th>Contralateral elbow</th>
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<tbody>
<tr>
<td><strong>Thresholds</strong></td>
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<tr>
<td>(°C)</td>
<td>KOA</td>
<td>Control</td>
<td>KOA</td>
</tr>
<tr>
<td><strong>Detection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold</td>
<td>27.4 (2.8)*</td>
<td>28.9 (1.8)</td>
<td>24.1 (5.8)*</td>
</tr>
<tr>
<td>Warm</td>
<td>37.2 (3.0)</td>
<td>36.4 (2.7)</td>
<td>41.8 (4.6)</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold</td>
<td>10.5 (10.3)</td>
<td>9.2 (9.0)</td>
<td>4.2 (7.8)</td>
</tr>
<tr>
<td>Hot</td>
<td>45.5 (3.5)</td>
<td><strong>45.8 (2.9)</strong></td>
<td>47.9 (2.2)</td>
</tr>
</tbody>
</table>

* p < .01
# Thermal Wind-up methods

NRS pain report for 3 trains of 5 heat pulses using subject’s pain threshold.

<table>
<thead>
<tr>
<th>Train 1</th>
<th>Train 2</th>
<th>Train 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
</tbody>
</table>

Averages of all three trains were calculated for pulses 1, 3, and 5.
Pain During Thermal Wind Up

- **Tap 1**: 
  - High Opioid Dose: 5
  - No Opioids: 5
  - F = .03; p = .87

- **Tap 3**: 
  - High Opioid Dose: 5
  - No Opioids: 5
  - F = .04; p = .85

- **Tap 5**: 
  - High Opioid Dose: 5
  - No Opioids: 5
  - F = .28; p = .61
A Comparison of Two Wind-up Methodologies in Patients with Osteoarthritis Vs. Normal Controls

Gila I. Wallach, Ph.D.1, Christine M. Gagnon, Ph.D.1-2, R. Norman Harden, M.D.1-2

1Rehabilitation Institute of Chicago, Chicago, Illinois
2Northwestern University Feinberg School of Medicine - Department of Physical Medicine & Rehabilitation

Abstract:
This study explored the effectiveness of producing the thermal wind-up phenomenon comparing two methodologies. Participants included 37 subjects with osteoarthritis of the knee and 35 controls matched as to age, sex, and race. The study was conducted during a single session which included psychometric testing, history and physical, and psychophysical testing (quantitative sensory testing [QST] and wind-up). All testing was conducted at three sites; the medial and lateral joint lines of the most painful knee, and the elbow contralateral to the most painful knee. Participants received one of two wind-up procedures: windup temperatures determined by averages of heat pain threshold temperatures obtained during QST (range = 44.0° - 49.7°Celsius) or at a single super-threshold temperature of 49°C. All participants received three trials of 5 heat ‘taps’ at each location. The three trials were averaged and slopes were subsequently calculated for each location. Slopes were used to represent the magnitude of the windup effect. The implications of these finding to pain research will be discussed. This study was supported by a grant from GlaxoSmithKline.

Introduction:
Wind-up is a known correlate of central sensitization. There been many methods of evaluating wind-up in patients with chronic pain conditions. Many methods of temperature wind-up utilize a protocol of heating the patient’s skin to a supra-threshold temperature that causes discomfort or pain in most people. However, because this method relies on a temperature that everyone finds uncomfortable, there is a risk of finding a ceiling effect in the patient’s response to the wind-up protocol. Additionally, wind-up is usually looked at in terms of an innocuous stimulus that becomes uncomfortable or painful with repeated stimulation, it is logical to attempt to find a method of thermal wind-up that is less severe.

Participants:
Participants in this study were 37 participant with osteoarthritis of either knee (OA) and 35 age, race, and sex matched controls (CON). Demographic information for participants can be viewed in Table 1. Participants were included in the OA group if they had chronic (lasting more than six months) osteoarthritic pain in either knee as defined by the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association (cited). The control group consisted of subjects with no knee pain of any kind and no history of knee injury.

Methods:
Participants for this study were recruited as part of a larger study exploring correlate of OA knee. For this section of the study thermal stimuli was delivered using the Medoc Thermal Sensory Analyzer (TSA-2000; Ramat Yishai, Israel) Peltier element based stimulator. The basic protocol was similar to that used in previous studies. The Peltier device delivered three trains of five heat pulses each. Participants were asked to rate the intensity of the second pain sensation on a Numeric Rating Scale (0-10). The participant were grouped in one of two groups. In the control group, the peak heat pulse during wind-up trains temperature correlated to their individual threshold temperature as established with previous testing. In the supra-threshold group, participants experienced peak heat pulses of 49°Celsius regardless of their established pain threshold. After sensations were obtained at 10 second intervals until either the participant returned to baseline or 0 levels of reported pain, or three minutes had elapsed. Each participant underwent the Wind-up protocol on three areas, the medial and lateral joint lines of the most painful knee, and the joint line of the elbow on the arm contralateral to the most painful knee.

Results:
A 2x2x3 (participants x windup methodology x location) mixed-model repeated measures ANOVA was used to analyze the data. Location served as the within subjects factor and participants and methodology were the between subjects factors. Windup did not differ significantly by location (F = 2.850, p = .075). OA participants produced significantly greater mean windup slopes than did the control participants (F = 10.340, p = .002) and the super-threshold windup procedure yielded significantly greater mean slopes compared to the pain threshold windup procedure (F = 9.189, p = .004). There was a significant participant by windup methodology effect (F = 6.202, p = .015). There was a greater magnitude of windup in the OA participants, especially when using the super-threshold temperature.

Discussion:
In undertaking this study, we attempted to determine whether the patient’s own threshold for pain was enough to determine a temperature that could adequately be used to show wind-up. We found that patient threshold was inadequate to produce the desired wind-up effect in both participants with OA and controls. However, in super-threshold conditions wind-up was observed in participants. This finding was evident particularly in participants with OA. This indicates that more accurate wind-up information may be obtained using super-threshold temperatures for participants in studies using wind-up as a measure for central sensitization. That the wind-up phenomenon was more prevalent in participants with OA suggests that central sensitization is indeed in effect in OA and that it is not only a peripheral phenomenon. These findings suggest further investigation into the correlates of central sensitization and osteoarthritis. However, when using thermal wind-up techniques to determine the existence of the phenomenon, super-threshold temperatures yield more accurate results.

Citations:

Table 1: Sample characteristics by subject type

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n = 35)</th>
<th>Osteoarthritis (n = 37)</th>
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</thead>
<tbody>
<tr>
<td>Age (mean ± SD years)</td>
<td>62.06 (9.52)</td>
<td>64.76 (11.75)</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>62.9</td>
<td>75.7</td>
</tr>
<tr>
<td>Race/ethnicity (%)</td>
<td></td>
<td></td>
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<tr>
<td>White non-Hispanic</td>
<td>82.9</td>
<td>64.9</td>
</tr>
<tr>
<td>African-American</td>
<td>11.4</td>
<td>29.7</td>
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<tr>
<td>Hispanic</td>
<td>2.9</td>
<td>2.7</td>
</tr>
<tr>
<td>Other</td>
<td>2.9</td>
<td>2.7</td>
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<tr>
<td>Marital Status (%)</td>
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<tr>
<td>Married</td>
<td>54.3</td>
<td>37.8</td>
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<tr>
<td>Single</td>
<td>22.9</td>
<td>13.5</td>
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<tr>
<td>Divorced</td>
<td>14.3</td>
<td>32.4</td>
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<tr>
<td>Other</td>
<td>8.6</td>
<td>16.2</td>
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<tr>
<td>Educational level (%)</td>
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<tr>
<td>Less than High School</td>
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<td>2.70</td>
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<td>High School</td>
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<td>Some College</td>
<td>20.00</td>
<td>29.73</td>
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<tr>
<td>Associates Degree</td>
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</tr>
<tr>
<td>Bachelor's Degree</td>
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<tr>
<td>Master's Degree</td>
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<tr>
<td>Professional Degree</td>
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<td>2.70</td>
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<table>
<thead>
<tr>
<th>Chart 1: Windup Means: 49 degrees, OA Subjects and Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>LateralOA</td>
</tr>
<tr>
<td>Pain NRS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chart 2: Windup Means: Threshold, OA Subjects and Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>LateralOA</td>
</tr>
<tr>
<td>Pain NRS</td>
</tr>
</tbody>
</table>

Discussion:
In undertaking this study, we attempted to determine whether the patient’s own threshold for pain was enough to determine a temperature that could adequately be used to show wind-up. We found that patient threshold was inadequate to produce the desired wind-up effect in both participants with OA and controls. However, in super-threshold conditions wind-up was observed in participants. This finding was evident particularly in participants with OA. This indicates that more accurate wind-up information may be obtained using super-threshold temperatures for participants in studies using wind-up as a measure for central sensitization. That the wind-up phenomenon was more prevalent in participants with OA suggests that central sensitization is indeed in effect in OA and that it is not only a peripheral phenomenon. These findings suggest further investigation into the correlates of central sensitization and osteoarthritis. However, when using thermal wind-up techniques to determine the existence of the phenomenon, super-threshold temperatures yield more accurate results.

Citations:
Pin Prick testing

5.46 von Frey hair
1 train of 10 taps
Taps 1, 5, and 10 used in the analyses

*Or 256 mN weighted pin
Pain During Pinprick Mechanical Wind Up

- **1st** trial: $F = 1.17; p = .29$
- **5th** trial: $F = 2.25; p = .15$
- **10th** trial: $F = 2.22; p = .64$

Categories:
- **High Opioid Dose**
- **No Opioids**
Pressure Algometry

1 cm² surface area contact provides most replicable measurements
Pressure Pain Threshold

- Right Arm: High Dose Opioids vs. NO Opioids
  - ANOVA: F = .00; p = .99

- Left Arm: High Dose Opioids vs. NO Opioids
  - ANOVA: F = .22; p = .64

**Pressure Pain Threshold (Kg/in²)**

- Right Arm: 2 kg/in²
- Left Arm: 1.5 kg/in²
Algometer

lat, p = .000
med, p = .000
elbow, p = .006
Sympathetic Reactivity to the Cold Pressor Challenge in Amputees: Comparison of Residual Limbs to Contralateral Unaffected Limbs

Kiran Vadada, MD, R. Norman Harden*, MD, Christine M. Gagnon*, PhD, Michael A. Gallizzi, MS, and Nelson Arnold, MD
The Center for Pain Studies at the Rehabilitation Institute of Chicago

*Affiliates of the Northwestern University Feinberg School of Medicine - Department of Physical Medicine & Rehabilitation

Abstract

Figure 1: Pre (left) and Post (right) Cold Pressor IRT Images

Methods

Each participant was studied during a single session consisting of dichotomous testing, quantification of their testing and infrared thermography. This discussion will focus on the thermography portion of our study.

Preparation: The first step was to equilibrate our subjects with the ambient room temperature. For this we were impressed to sit comfortably in the testing room for 15 minutes. Subjects were given specific activity restrictions up to 4 hours before the testing appointment in order to help standardize the temperature measurement.

Positioning: An important task was to ensure that the amputated limb was positioned symmetrically to its contralateral normal limb. This was especially difficult with the lower extremity amputees that naturally shifted their weight to direct their center of gravity over their normal leg. To eliminate this tendency a support structure was built to allow them to use their arms for weight bearing without obstructing the camera’s view. The camera was positioned as close as possible to the subject while retaining a complete view of both stumps being studied (either upper or lower). It was also important to angle the camera perpendicular to the surface being tested.

Thermography: Baseline and post-cold pressor challenge thermographic images were taken with the patient standing in front of a homogenous background away from any identified sources of heat in the room.

Cold Pressor Challenge: For the challenge, the non-involved extremities were immersed in an ice-water bath for the greater of two minutes or the point of maximum tolerance. Upper extremity amputees immersed their feet, while lower extremity amputees immersed their hands.

Table 1: IRT Measurements

Discussion

The Cold Pressor Challenge proved to be an adequate sympathetic stressor; however its efficacy is questionable in the amputee population. For the lower extremity subjects, having to immerse their hands in ice water while balancing on their only leg and also attempting to maintain symmetrical posture was cumbersome and caused them unnecessary stress. It can even be argued that this stress causes variations in the degree of the evoked sympathetic response we are measuring.

Infrared Thermography (IRT) is a well established method of measuring physiological temperature changes. It works by recording infrared energy (heat) that is emitted from a surface and processing that data to create digital images with temperature measurements.

Results/Statistics

The Cold Pressor Challenge proved to be an adequate sympathetic stressor; however its efficacy is questionable in the amputee population. For the lower extremity subjects, having to immerse their hands in ice water while balancing on their only leg and also attempting to maintain symmetrical posture was cumbersome and caused them unnecessary stress. It can even be argued that this stress causes variations in the degree of the evoked sympathetic response we are measuring.

The Cold Pressor Challenge proved to be an adequate sympathetic stressor; however its efficacy is questionable in the amputee population. For the lower extremity subjects, having to immerse their hands in ice water while balancing on their only leg and also attempting to maintain symmetrical posture was cumbersome and caused them unnecessary stress. It can even be argued that this stress causes variations in the degree of the evoked sympathetic response we are measuring.

Table 1: IRT Measurements

References

Aftersensation by site, subject type, wind-up parameter, and time. Data are n (%) of 37 KOA subjects and 35 controls who reported NRS > 0 at 10, 30, 60 and 180 sec following termination of the TWU and MWU protocols.

<table>
<thead>
<tr>
<th>Site</th>
<th>Subject</th>
<th>10 sec</th>
<th>30 sec</th>
<th>60 sec</th>
<th>180 sec</th>
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<tr>
<td></td>
<td>Thermal Aftersensation</td>
<td>Mechanical Aftersensation</td>
<td>Thermal Aftersensation</td>
<td>Mechanical Aftersensation</td>
<td>Thermal Aftersensation</td>
</tr>
<tr>
<td>Medial knee</td>
<td>KOA</td>
<td>10 (27)</td>
<td>10 (27)</td>
<td>8 (22)</td>
<td>8 (22)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>4 (11)</td>
<td>3 (8)</td>
<td>1 (3)</td>
<td>2 (6)</td>
</tr>
<tr>
<td></td>
<td>p-value*</td>
<td>.167</td>
<td>.124</td>
<td>.080</td>
<td>.034</td>
</tr>
<tr>
<td>Lateral knee</td>
<td>KOA</td>
<td>12 (32)</td>
<td>12 (32)</td>
<td>4 (11)</td>
<td>6 (16)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>4 (11)</td>
<td>2 (6)</td>
<td>1 (3)</td>
<td>2 (6)</td>
</tr>
<tr>
<td></td>
<td>p-value*</td>
<td>.060</td>
<td>.066</td>
<td>.008</td>
<td>.392</td>
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<tr>
<td>Contralateral elbow</td>
<td>KOA</td>
<td>10 (27)</td>
<td>7 (19)</td>
<td>4 (11)</td>
<td>5 (14)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>5 (14)</td>
<td>3 (8)</td>
<td>0</td>
<td>1 (3)</td>
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<tr>
<td></td>
<td>p-value*</td>
<td>.298</td>
<td>.476</td>
<td>.354</td>
<td>.128</td>
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*Two-sided Fisher’s exact test p-values
Endocrinopathy in Pain

- Cortisol
- ACTH
- TSH
- Pregnenolone
- DHEA
- FSH
- LH
- Estrogen, Progesterone
- Testosterone free and bound
Is Post Amputation Pain a Sympathetically Maintained Pain?

Nicholas H. Weber, BS1, R. Norman Harden, MD1,2, Christine Gagnon, PhD1,2
1Rehabilitation Institute of Chicago, Chicago, Illinois
2Northwestern University Feinberg School of Medicine - Department of Physical Medicine & Rehabilitation

Introduction

The term sympathetically maintained pain (SMP) refers broadly to all pain syndromes that can be characterized by past physical trauma to the painful area, continuous burning pain and mechanical hyperalgesia, allodynia and relief of pain by sympathetic blockade. As many as 80% of patients who undergo amputation report experiencing pain in the missing body part. The objective of this study is to evaluate the mechanism of sympathetically maintained pain as a possible cause of post-amputation pain.

Hypotheses:
1. Pain anxiety will show a relationship with electrophysiological tests of pain and sensory threshold, as well as differences in limb temperature, and physical findings.
2. Pain anxiety will correlate with presence of typical symptoms of sympathetically maintained pain.
3. Electrophysiological tests of pain threshold, sensory threshold, and limb temperature will correlate with the presence of typical symptoms of sympathetically maintained pain.

Methods:

• Data were collected from amputee patients at the Rehabilitation Institute of Chicago who responded to solicitations for participation in a three-hour laboratory study at the Center for Pain Studies.
• Subjects were asked to assess their current status of pain and then completed a health history, physical exam and several psychometric questionnaires.
• Main Outcome Measures: Infrared telethermography (IRT), thermal quantitative sensory testing (tQST), physical observations of SMP symptoms, PASS-20, MPQ-SF. See Figure 1 for an example of a captured thermographic image from a study participant.

Subjects:
43 unilateral amputees patients of the Rehabilitation Institute of Chicago - 20.9% upper limb, 79.1% lower limb
Gender: 16 females (37.2%), 27 males (62.8%)
Ages: 25 to 75 with a mean age of 49.21 years (SD = 12.19)
Race and ethnicity: 51.2% Caucasian (22), 39.5% African American (17), 7% Hispanic or Latino (3)
Level of education: 2 did not complete high school (4.7%), 9 high school diploma (20.5%), 2 GED (4.7%), 12 some college (27.9%), 1 Associate’s degree (2.3%), 13 Bachelor’s degree (30.2%) 4 Master’s degrees (9.3%)
Amputation etiology: 26 traumatic (60.5%), 2 embolic or acute arterial occlusion (4.7%), 5 peripheral vascular disease (11.6%), 6 other etiologies (cancer, infection, etc.), 3 mixed causes

Results:

Table 1. Summary of descriptive statistics for physical characteristics of SMP.

<table>
<thead>
<tr>
<th>PHYSICAL FINDING</th>
<th>YES</th>
<th>NO</th>
</tr>
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<tbody>
<tr>
<td>Temperature change? (n=42)</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>Skin change? (n=42)</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td>Jerking limbs? (n=42)</td>
<td>24</td>
<td>18</td>
</tr>
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</table>

Table 1. Summary of descriptive statistics for physical characteristics of SMP.

Results (continued):

<table>
<thead>
<tr>
<th></th>
<th>Temperature</th>
<th>Color</th>
<th>Jerking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>Changes</td>
<td>Changes</td>
<td>Movements</td>
</tr>
<tr>
<td></td>
<td>(rpb)</td>
<td>(rpb)</td>
<td>(rpb)</td>
</tr>
<tr>
<td>McGill Pain Questionnaire</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MPQ VAS Now</td>
<td>40</td>
<td>.318*</td>
<td>.301</td>
</tr>
<tr>
<td>MPQ Total</td>
<td>33</td>
<td>.446**</td>
<td>.461**</td>
</tr>
<tr>
<td>MPQ Sensory</td>
<td>33</td>
<td>.462**</td>
<td>.459**</td>
</tr>
<tr>
<td>MPQ Affective</td>
<td>39</td>
<td>.254</td>
<td>.366*</td>
</tr>
</tbody>
</table>

Discussion:

• The presence of SMP symptoms (temperature/color change, edema, trophic skin, hair, nail growth abnormalities, impaired motor function, hyperalgesia/allodynia, sudomotor changes) was evident in half or more than half of subjects.
• A hypothesized relationship between pain anxiety and the electrophysiological tests was not supported (H1). Neither limb temperature nor sensory thresholds were related to a patient's self-report of pain related anxiety. Therefore, it seems that the assumed sympathetic mechanism causing pain anxiety is not the same mechanism which produces vasomotor changes.
• There was nearly complete concordance between the presenting symptoms of SMP and pain anxiety measures (H2).
• The relationship between SMP symptoms and electrophysiological tests (H3) was partially supported. The extent to which SMP traits and thermographic differences relate to each other is unclear because only two associations between these variables were significant.

Conclusion:

• Results suggest that an association between physical characteristics of SMP and pain anxiety psychometric measures is important for possible determination of SMP in post-amputee pain, whereas the connection between vasomotor function (limb temperature difference) and psychometrics is not central to this model.
• There are many signs, symptoms and tests in PAP that would suggest that at least a subset of these subjects may have SMP.

References:

Pain Ratings for OA subjects Before and After Stair Climb (Natural mech. wind-up)

\[ t(33) = 4.880, p = 0.000 \]
## Relationship between psychometrics and wind-up ratios of the patients

<table>
<thead>
<tr>
<th></th>
<th>VAS</th>
<th>MPQ.SF-T</th>
<th>WOMAC-T</th>
<th>PDI</th>
<th>BDI-T</th>
<th>PASS-20-T</th>
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<td><strong>Medial Knee</strong></td>
<td></td>
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<tr>
<td>Thermal wind-up ratio</td>
<td>-0.179</td>
<td>r=-0.330* p=0.050</td>
<td>-0.214</td>
<td>-0.106</td>
<td>-0.014</td>
<td>-0.242</td>
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<td>0.023</td>
<td>-0.120</td>
<td>0.166</td>
<td>-0.277</td>
<td>-0.292</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thermal wind-up ratio</td>
<td>-0.040</td>
<td>0.024</td>
<td>-0.048</td>
<td>-0.012</td>
<td>0.038</td>
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<tr>
<td>Mechanical wind-up ratio</td>
<td>-0.093</td>
<td>-0.111</td>
<td>-0.222</td>
<td>-0.275</td>
<td>-0.218</td>
<td>-0.107</td>
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<tr>
<td><strong>Contralateral elbow</strong></td>
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<tr>
<td>Thermal wind-up ratio</td>
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<td>r=-0.351* p=0.049</td>
<td>-0.252</td>
<td>-0.102</td>
<td>-0.101</td>
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<tr>
<td>Mechanical wind-up ratio</td>
<td>-0.368</td>
<td>0.047</td>
<td>-0.134</td>
<td>-0.156</td>
<td>-0.068</td>
<td>-0.111</td>
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Plenty of ways to quantitate pain but need to select
Psychometrics sensitive to “iatrogenic” flavors of the pain experience

Chapman JR et al Spine 2011
Papaver Sominiferum