Comparison of different quantitative sensory testing methods during remifentanil infusion in volunteers†

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Background. The aim of this study was to compare thermal and current sensory testing stimuli with respect to opioid responsiveness.

Methods. Eighteen healthy volunteers were randomized in a placebo-controlled, double-blind crossover study to receive an infusion of remifentanil 0.08 μg kg⁻¹ min⁻¹ or saline for 40 min. Test procedures included determination of pain perception thresholds (PPT) and pain tolerance thresholds (PTT) to heat, cold, and current at 5, 250 and 2000 Hz, at baseline and at the end of the infusion.

Results. Both current at 5 Hz (PPT 3.69 (SD 2.48) mA vs 2.01 (1.52) mA; PTT 6.42 (2.79) mA vs 3.63 (2.31) mA; P<0.001) and 250 Hz (PPT 4.31 (2.42) mA vs 2.89 (1.57) mA; PTT 7.08 (2.68) mA vs 4.81 (2.42) mA; P<0.001) and heat (PPT 47.4 (2.7)°C vs 45.2 (3)°C; PTT 51.1 (1.8)°C vs 49.7 (1.8)°C; P<0.05) detected a significant analgesic effect of remifentanil compared with placebo. No analgesic effect was shown on cold or current at 2000 Hz. The magnitude of responsiveness of current stimuli at 5 Hz and 250 Hz was superior to heat stimuli.

Conclusion. Both current (5 and 250 Hz) and heat sensory testing detected a significant analgesic effect of a remifentanil infusion compared with saline. There was more response to current testing.

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The main outcome variables in clinical trials testing of analgesics are pain relief or pain reduction. Because of the high interindividual variability of subjective pain rating, several experimental approaches have been used in the early screening of new analgesics. Commonly, these tests measure subjective pain after pain stimuli. However, these approaches are limited mostly because of the poor standardization of subjective pain rating.1

An alternative for determining the effect of analgesics is quantitative sensory testing (QST). QST has the particular advantage of being a functional test that provides a quantitative pain stimulus and assesses the subject’s individual response to the stimulus.2,3 The repeatability of the visual analogue scale has been shown to be poor in a setting of human experimental heat pain compared with thermal QST.4 QST also provides a reliable assessment of changes in pain thresholds.

Both thermal and current sensory testing are currently used. Thermal QST (heat and cold) allows a distinction between predominantly C-fibre activity and Aδ-fibre activity. Current sensory testing by the means of the Neurometer® stimulator device offers the possibility of predominant stimulation of C, Aδ and Aβ fibres.5

The assessment of pain and pain tolerance thresholds is established in QST. However, there are conflicting data indicating which parameter is the more sensitive for the detection of analgesic effects.2 Also, the data on opioid sensitivity of thermal and current QST are conflicting. Recently we showed a dose-dependent increase in heat pain thresholds during a stepped remifentanil infusion in normal
skin of volunteers. In contrast, heat pain tolerance thresholds (PTT) during a stepped alfentanil infusion were not significantly different from saline, whereas electrical PTT showed a significant dose–response relationship. For QST, neither heat nor cold stimuli, or different electrical stimuli have been compared in relation to a defined opioid dose, nor has this been done for pain thresholds and pain tolerance thresholds in either model.

The aim of this study was to investigate the responsiveness of thermal and current QST to a constant dose of the μ-opioid receptor agonist remifentanil. We set out to compare heat and cold pain stimuli and to compare current sine-wave electrical stimuli at three different frequencies (5, 250 and 2000 Hz). We further compared pain perception thresholds (PPT) and PTT during each type of stimulation.

Methods
After obtaining approval of the Vienna University Institutional Review Board and written informed consent, 18 paid volunteers were included in this randomized, placebo-controlled, double-blind crossover study. Volunteers were ASA I men, aged 19–40 yr, with a BMI within the 15th and 85th percentiles. All subjects underwent a medical interview. Exclusion criteria were actual or chronic pain, use of analgesics within one week and a history of drug abuse. Subjects were not allowed any oral intake for 6 h before drug administration.

Measurements
PPT and PTT were assessed by both thermal and current quantitative sensory testing. Thermal sensory testing was done using a commercially available thermal sensory testing device (TSA-2001, Medoc, Ramat Yishai, Israel). The Peltier thermode, size 18×18 mm, was attached to the left volar forearm. Skin adaptation temperature was 32°C, and the rate of temperature change was 0.8°C s⁻¹, with a return rate of 4°C s⁻¹. Stimulator temperature range was 32–53°C and 1°C. Thresholds were measured by the method of limits as described previously. Subjects were initially trained in the use of the device in a standardized manner. They were instructed to stop the decrease or increase in temperature at the first perception of unpleasant cold (cold pain perception threshold, CPPT) and heat (heat pain perception threshold, HPPT) by means of a switch. Pain thresholds were measured in triplicate and averaged. Interstimulus intervals were 30 s. Afterwards the volunteers were instructed to stop the decrease and increase of temperature at the perception of unbearable cold (cold pain tolerance threshold, CPTT) and heat (heat pain tolerance threshold, HPTT). This was performed twice and averaged. Interstimulus intervals were 60 s.

Current sensory testing was performed by means of the neuroselective stimulator device Neurometer® (CPT, Neurotron, Baltimore, USA) through the method of limits at three frequencies: 2000, 250 and 5 Hz. Current PTT (EPPT) and PTT (EPTT) were assessed in a similar manner to the thermal sensory testing. They were performed at the tip of the left index finger in triplicate and twice, respectively, for each frequency, and averaged. Interstimulus intervals were 15 s and 60 s, respectively.

Measurements were made at baseline (before drug infusion) and then repeated at 25 min (TSA) and 35 min (Neurometer) after the start of the drug infusion.

Study sessions were performed in a quiet, unstressful environment in the same air-conditioned location, always at the same time in the afternoon, and with the volunteer in a sitting position. The same trained observer supervised all tests.

From the beginning of the study, subjects were continuously monitored for heart rate, ventilatory frequency, oxygen saturation and non-invasive arterial pressure (right arm). During the application of the study drugs, a sedation score (0=awake, 1=tired, 2=asleep but arousable, 3=non-arousable) was assessed every 10 min. All side effects were noted.

Subjects were randomly assigned by computer to two groups receiving consecutively either remifentanil (group 1) (Ultiva® GlaxoWellcome, Austria) or saline (group 2) in a crossover fashion. The order of applications was randomized between the groups. Each subject was studied in two sessions at least 5 days apart.

Before each session, a study nurse not otherwise participating in the study prepared an indistinguishable infusion syringe containing remifentanil or saline. The syringes were attached to a continuous syringe pump and administered as though each contained active drug.

After insertion of an i.v. catheter (20G) at the left cubital vein, a continuous infusion of remifentanil 0.08 μg kg⁻¹ min⁻¹ or saline was applied for 40 min. Based on our previous study, this dose significantly increased HPPT without inducing side-effects.

During each session glucose 5% 150 ml was infused continuously and oxygen 2 litre min⁻¹ was administered nasally. The infusion was stopped in the event of a drop in ventilatory frequency to less than 7 bpm, peripheral oxygen saturation less than 85%, heart rate less than 40 beats min⁻¹, mean blood pressure less than 60 mm Hg, sedation preventing adequate handling of the switch (sedation score ≥2), or at the volunteer’s request.

Statistical analysis
The intention was to detect a 50% difference between pain threshold values, an effect level of 0.75, with an α error of 5%. Using a two-tailed Student’s t-test, the study population was calculated to be 18 participants to reach a minimum power of 85% (nQuery software for Windows, Statistical Solutions, Boston, MA, USA).

Raw data were corrected to baseline values. Assessment of the non-linear association between CPPT, CPTT, HPPT,
HPTT, EPPT and EPTT values and probability of pain reception was accomplished by the means of the binary logistic regression procedure of the SPSS software, version 10.0 for Macintosh (SPSS inc., Chicago, IL, USA).

Significance of the coefficient estimate was calculated using the Wald test, and a model fit to the observed data was performed by the Hosmer and Lemeshow goodness-of-fit test. The prediction probability was also calculated for each variable. To identify possible best combinations of testing procedures, procedures showing a significant association with pain perception were then entered into a stepwise logistic regression model and non-significant variables were eliminated.

The area under the receiver operating characteristic (ROC) curve was used to summarize the accuracy of threshold values. The ROC curve for each index plots sensitivity (fraction of responsive volunteers who are correctly predicted to be responsive) against 1–specificity (fraction of unresponsive volunteers who are correctly identified) and reflects the discriminating power of the index. The area under the ROC curve was determined non-parametrically together with SE and 95% confidence interval (CI).

Values can be between 0 and 1. A value of 0.5 indicates that the screening measure is not better than chance, whereas a value of 1 implies perfect performance.

### Results

All 18 subjects completed the study. Both groups were comparable with respect to their characteristics (Table 1). No relevant cardiovascular or respiratory side-effects were seen during the whole study. In all volunteers, ventilatory frequency was at least 10 bpm and oxygen saturation did not decrease to 92% in any subject during the whole infusion. Mild sedation was seen in some subjects, but never exceeded sedation score 1. The raw baseline data showed no significant differences between the two groups in either the thermal or current measurements. Raw data at the end of infusion are summarized in Table 2.

ROC curves simultaneously show sensitivity and 1–specificity for the individual threshold values of the different test procedures (Figs 1–5). The corresponding statistical data such as area under the curve, SE and 95% CI are given in Table 3. Briefly, the current tests at 5 Hz and 250 Hz – both PTT and PPT – showed the best area-under-the-curve values, followed by heat testing. Current testing at 2000 Hz resulted in non-satisfactory values.

When building logistic regression models, EPTT5 (P<0.001), EPPT5 (P<0.001), EPTT250 (P<0.001) and EPPT5 (P<0.01) were very good predictors, HPPT and HPTT showed good prediction (P<0.05), EPTT2000 was borderline significant (P=0.042) and EPPT2000 and cold sensory testing showed no significance. The details such as β0, β1 are given in Table 4.

The results of the stepwise logistic regression model demonstrated that the combination of HPTT + EPTT250 + EPTT5 gives an increase of test efficiency to 88.9.

### Discussion

Data from the current study demonstrate that both methods of QST (current and thermal sensory testing) detect the...
analgesic effect of remifentanil. However, current at 5 and 250 Hz showed a superior responsiveness to heat. No analgesic effect was shown on cold and current at 2000 Hz.

QST is well established in the assessment of nociception in man. Both thermal and current threshold testing provide standardized and quantitative results. However, the inter-individual variability of pain perception is high. We therefore performed a crossover trial, allowing intra-individual comparisons with placebo. Sensitivity to opioid analgesia has separately been shown for both methods. The direct quantitative comparison of two different measurement methods like heat and current is not possible. We therefore chose an approach of calculating the ROC curves.

Our study is the first to find significant opioid sensitivity of both heat and current sensory testing methods at a given dose of opioid. In contrast Luginbühl and colleagues using
Table 3 Sensitivity, specificity, test efficiency and prediction probability of cold and heat pain perception threshold (CPPT, HPTT), and current pain perception threshold (EPPT) and pain tolerance threshold (EPTT) at 2000 Hz, 250 Hz and 5 Hz (subscript numbers) (n = 207)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Test efficiency (%)</th>
<th>Prediction probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPPT</td>
<td>83.3</td>
<td>38.9</td>
<td>61.1</td>
<td>0.65</td>
</tr>
<tr>
<td>CPTT</td>
<td>94.4</td>
<td>16.7</td>
<td>55.6</td>
<td>0.53</td>
</tr>
<tr>
<td>HPPT</td>
<td>77.8</td>
<td>66.7</td>
<td>72.2</td>
<td>0.76</td>
</tr>
<tr>
<td>HPTT</td>
<td>61.1</td>
<td>72.2</td>
<td>66.7</td>
<td>0.74</td>
</tr>
<tr>
<td>EPTT2000</td>
<td>50.0</td>
<td>66.7</td>
<td>58.3</td>
<td>0.63</td>
</tr>
<tr>
<td>EPTT250</td>
<td>66.7</td>
<td>72.2</td>
<td>69.4</td>
<td>0.76</td>
</tr>
<tr>
<td>EPTT5</td>
<td>72.2</td>
<td>83.3</td>
<td>77.8</td>
<td>0.87</td>
</tr>
<tr>
<td>EPTT250</td>
<td>44.4</td>
<td>83.3</td>
<td>63.9</td>
<td>0.70</td>
</tr>
<tr>
<td>EPTT2000</td>
<td>83.3</td>
<td>88.9</td>
<td>86.1</td>
<td>0.92</td>
</tr>
<tr>
<td>EPTT5</td>
<td>77.8</td>
<td>94.4</td>
<td>86.1</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Table 4 Results of the logistic regression models: $\beta_0$, constant; $P (\beta_0)$, significance of constant; $\beta_1$, estimate of the coefficient of the independent variable; $P (\beta_1)$, significance of coefficient; $P (LHT)$, significance of the Hosmer and Lemeshow goodness-of-fit test; C/H/E PPT, cold/heat/current pain perception threshold; C/H/E PTT, cold/heat/current pain tolerance threshold; subscript numbers refer to the current

<table>
<thead>
<tr>
<th>$\beta_0$</th>
<th>$P (\beta_0)$</th>
<th>$\beta_1$</th>
<th>$P (\beta_1)$</th>
<th>$P (LHT)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPPT</td>
<td>-0.011</td>
<td>0.199</td>
<td>1.109</td>
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<tr>
<td>CPTT</td>
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<td>0.468</td>
<td>-0.648</td>
<td>0.491</td>
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<tr>
<td>HPPT</td>
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<td>0.030</td>
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</tr>
<tr>
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<td>-40.581</td>
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</tr>
<tr>
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<td>0.140</td>
<td>-3.532</td>
<td>0.142</td>
</tr>
<tr>
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<td>0.041</td>
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<tr>
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<tr>
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<td>0.003</td>
</tr>
<tr>
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<td>-6.960</td>
<td>0.002</td>
</tr>
<tr>
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<td>0.059</td>
<td>0.002</td>
<td>-7.362</td>
<td>0.001</td>
</tr>
</tbody>
</table>

a similar methodology failed to demonstrate a significant analgesic effect of alfentanil on electrical and heat PTT compared with placebo. With the same 5-Hz current stimulus used in our study, Liu and colleagues demonstrated a 50% increase in pain perception at fentanyl i.v.

Moreover, we found a clear tendency towards a more pronounced opioid responsiveness of current compared with heat. These findings add pharmacological evidence to neurophysiological findings that electrical nociception is different from heat nociception and should be considered separately.

The observation that remifentanil increased pain thresholds at 5 and 250 Hz, but not at 2000 Hz is consistent with the hypothesis that pain evoked by 5 and 250 Hz is mediated predominantly by nociception of C and Aδ fibres and that opioids inhibit dorsal horn activity evoked by small unmyelinated C fibres. 17–19

We did not show an analgesic effect of remifentanil on cold pain stimuli. The negative result could be because of the small size of our probe. However, for heat, we demonstrated highly significant effects with the same thermode. To our knowledge, this is the first study that shows, for thermal sensory testing, a lack of opioid-induced analgesia for cold pain at a significant analgesic dose for heat pain. The absence of cold analgesia is in agreement with findings that cold stimulation of normal skin induces activity in small myelinated fibres, whereas opioid activity is predominately on C fibres. Thus, the exclusive opioid responsiveness to heat pain stimuli is consistent with the fibre selectivity of thermal QST as described by Yarnitsky and colleagues in untreated volunteers. Taken together these findings support further pharmacological approaches to characterize pain mechanisms and may lead to better understanding of controversial opioid responsiveness in hyperalgesia. 21

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References