**Tetanic stimulus of ulnar nerve as a predictor of heart rate response to skin incision in propofol–remifentanil anaesthesia†**

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**Background.** To study adequate antinociception during general anaesthesia, tetanic stimuli of 5–10 s duration have been used previously as a standardized nociceptive stimulus. However, such stimuli have been found to correlate poorly with intraoperative nociception. We hypothesized that an electrical tetanic stimulus of the ulnar nerve, lasting 30 s, would provide a reliable experimental pain model.

**Methods.** Thirty-three patients, undergoing open abdominal surgery, were studied. Propofol and remifentanil were used for anaesthesia. Patients were randomized to receive remifentanil at three target-controlled infusion levels (1, 3, or 5 ng ml\(^{-1}\)) during short (5 s, Tet5) and a long-lasting (30 s, Tet30) tetanic (50 mA, 50 Hz) stimulus and skin incision. RR intervals (RRI) were obtained from the ECG and the mean RRI before each stimulus (Tet5, Tet30, incision) was compared with that after the stimulus.

**Results.** At remifentanil level 1 ng ml\(^{-1}\), the RRI responses to tetanic stimuli and skin incision were prominent but with higher concentrations (3 and 5 ng ml\(^{-1}\)), responses were very small. Tet30 (\(r^2=0.780\)) was the best predictor of the RRI response to skin incision when compared with Tet5 (\(r^2=0.611\)), remifentanil level (\(r^2=0.340\)), or propofol level (\(r^2=0.036\)).

**Conclusions.** Long-lasting tetanic stimulus of ulnar nerve may provide a better experimental pain model for surgical pain during general anaesthesia than shorter stimuli, which have been applied in earlier studies.


**Keywords:** anaesthetics i.v., propofol; analgesia; analgesics opioid, remifentanil; pain, experimental

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In clinical research, to evaluate the nociceptive–antinociceptive balance of an anaesthetized patient, an experimental pain test, which correlates sufficiently to analgesic medication and intensity of surgical stimuli, is needed.9 Such a test method should be non-invasive, harmless, specific to measure pain, sensitive, standardized, and repeatedly applicable.10 11 Experimental pain stimuli...
can be electrical, thermal, mechanical, ischaemic, or chemical. In the operating room, only the electrical pain model has potential clinical importance, because it is repeatable, non-invasive, and the strength of the stimulus is adjustable. Both single electrical stimulation and repeated electrical stimuli have been investigated. Most pain models usually reflect only surface pain, whereas surgical tissue damage also involves deep structures response. To describe those responses, electrical stimuli have to be sufficiently long lasting to activate both temporal and spatial nociceptive mechanisms. Such an experimental pain test may simulate skin incision as a noxious stimulus.

Tetanic stimulus of the ulnar nerve has been investigated as a standardized predictor of a patient’s responsiveness to nociceptive stimuli. Typically, stimuli lasting for 5–10 s have been used. However, it has been shown recently that a response to 5 s electrical tetanic stimulus has no predictive value in clinical surgical anaesthesia. In this study, we wanted to evaluate the physiological effects of short (5 s) and long-lasting (30 s) tetanic stimuli of the ulnar nerve.

We hypothesized that a long-lasting tetanic stimulus is better related to analgesic drug concentration and patient’s response to skin incision during propofol–remifentanil anaesthesia than a short tetanic stimulus.

Methods

The ethics committee of Tampere University Hospital approved the study, and written informed consent was obtained from each patient. Thirty-six patients (ASA I–II) were enrolled. Inclusion criteria were age between 18 and 65 yr and elective laparotomy under general anaesthesia. Exclusion criteria were known neurological disorders, history of head injury, any medication seriously affecting heart rate or the central nervous system, major cardiac problems, uncontrolled hypertension, disease of the thyroid, history of alcohol or drug abuse or BMI $>$ 30 kg m$^{-2}$.

All patients were premedicated with diazepam 5–10 mg orally 60 min before surgery. In the operating room, an i.v. catheter was inserted into a forearm vein and standard monitoring was started, including EEG spectral entropy (SE).

Anaesthesia was induced and maintained with target-controlled infusions (TCI Orchestra Primea®, Fresenius, France) of propofol and remifentanil. Tracheal intubation was facilitated with cisatracurium 0.15 mg kg$^{-1}$. Neuromuscular block was monitored every 20 s until a train-of-four (TOF) response below 4/4 was reached (Datex-Ohmeda S/5 Anaesthesia Monitor, GE Healthcare Finland Oy, Helsinki, Finland), and the trachea of the patient was intubated. After tracheal intubation, propofol TCI was adjusted to maintain SE level between 35 and 60, the target being at 50 (adequate surgical level of hypnosis). The lungs of patients were normoventilated with air–oxygen mixture ($F_{\text{IO}_2}$ 0.35).

Two ECG electrodes (Kendall ARBO H99SG, Tyco Healthcare Deutschland GmbH, Noustadt/Donau, Germany) were placed over the ulnar nerve on the left wrist. Patients were randomly allocated according to computer-generated random numbers (Excel 2000, Microsoft Corp., Redmond, WA, USA) to receive remifentanil at three different TCI levels: 1, 3, or 5 ng ml$^{-1}$ during intubation, tetanic testing, and skin incision. Patients were also randomized to receive first either a short tetanic stimulus (5 s, 50 mA, 50 Hz, square-wave, neurostimulator, Life Tech Inc., Houston, TX, USA) and thereafter the long-lasting tetanic stimulus (30 s, 50 mA, 50 Hz, square-wave), or vice versa. To ensure adequacy of the stimulus, neurostimulator pulse wave and current power were verified by a Tektronix A 6302 probe and Tektronix TM 502A Current probe amplifier (Tektronix Inc., Beaverton, Oregon, USA) before beginning the trial. Tetanic testing was started at steady-state anaesthesia after endotracheal intubation (minimum interval between intubation and testing was 10 min). The operating room was kept as quiet as possible and all external stimuli were minimized during the testing period. The time interval between each tetanic stimulus was 3 min. Surgery was allowed to start when 2 min elapsed after testing. Skin incision was annotated. The ECG was amplified and displayed on a Datex-Ohmeda S/5 monitor (GE Healthcare Finland Oy, Helsinki, Finland). Both ECG (sampling frequency 300 Hz) and tetanic stimuli annotations were recorded on a PC with S/5 Collect (software vers. 4.0) and analysed off-line.

The R-waves of the ECG signal were automatically detected and visually verified and corrected afterwards when necessary. A beat-to-beat R-to-R interval (RRI) signal was constructed as a series of time differences between the successive heart beats. The RRI-signal was analysed off-line in each separate individual using Matlab® software (Matlab, version 6.5, Release 13, The Mathworks Inc., MA, USA). The analysis period before each stimulus was 60 s, and the post-stimulation periods were 20 s for the short tetanic stimulus, 45 s for the long tetanic stimulus, and 60 s for the first skin incision. The length of the analysis period was determined based on the length of RRI responses. The mean RRI values within the analysed periods were computed and the post-stimulation values were divided by their pre-stimulus values. The investigator was not blinded during the data collection. However, the investigator who made all analyses off-line was blinded and was never present in the operating room.

The statistical analysis was performed with the SPSS® program (SPSS 12.0.1 for Windows, SPSS Inc., Chicago, IL, USA). The general linear model for repeated measures was applied for studying the effect of remifentanil on RRI responses produced by different stimuli (Tet30, Tet5, and incision). One-way ANOVA and paired-sample t-test were used for post hoc analyses. Linear regression analysis was performed to study the correlation of responses with propofol and remifentanil concentrations.
used to predict the RRI response to the skin incision by pre-incision variables, that is, RRI responses to tetanic stimuli and drug (remifentanil and propofol) levels. Data are shown as mean (sd) or range, unless otherwise indicated. P-values of <0.05 (two-tailed) were considered statistically significant.

Results
Thirty-three patients (22 women and 11 men) were studied. Their mean age was 48 (12.3) yr (range 18–64 yr) and BMI 26 (3.4) kg m\(^{-2}\). Three patients were excluded due to technical problems in the data collection.

Tetanic stimuli and skin incision induced prominent RRI responses at remifentanil level of 1 ng ml\(^{-1}\) (Fig. 1A). Post/pre RRI ratios were 0.97 (0.04), 0.91 (0.07), and 0.90 (0.09) for Tet5, Tet30, and skin incision, respectively (P<0.01 between Tet5 and others; P=0.407 between Tet30 and skin incision, Table 1). At 3 and 5 ng ml\(^{-1}\) remifentanil levels, all stimuli types were associated with very small RRI responses (Fig. 1B and C).

The RRI response to Tet30 was the best predictor of the RRI response to the skin incision (\(r^2=0.780\)) of all the measured variables (\(r^2\) for remifentanil level 0.340, for propofol level 0.036, and for the Tet5 0.611) (Fig. 2). When all the variables were combined, the model predicted the RRI response to skin incision only slightly better (\(r^2=0.811\)) than the RRI response to Tet30 alone.

SE levels during tetanic testing and skin incision remained stable and unaltered. Significant hypotension did not occur and no vasoactive drugs were needed. The intensity of neuromuscular block was similar in all patients (fewer than 4/4 responses for TOF stimulation) throughout the study period.

Discussion
Our results show that RRI response to 30 s tetanic stimulus predicted the RRI response to skin incision. However, these findings were seen at the lowest remifentanil level only. With higher remifentanil concentrations, RRI remained unresponsive to all stimuli including skin incision. In this study, the responsiveness of RRI to stimuli correlated with the level of analgesic medication.

In previous trials, rather short-lasting (5 or 10 s) tetanic stimuli have been used as an experimental non-invasive

![Fig 1](https://academic.oup.com/bja/article-abstract/99/4/509/304011/10.1093/bja/99.4.509?download=true)
test stimulus to cause nociception during general anaesthesia.

Our study supports the previous finding that a short tetanic stimulus relatively poorly reflects the physiological response caused by a surgical stimulus. It has been presumed that short electrical stimulation elicits mainly cutaneous pain mechanisms, whereas surgical tissue damage also contains deeper components. Petersen-Felix and Arendt-Nielsen have suggested that a stimulus has to be long lasting or repeated to activate temporal or spatial summation mechanisms and, hence, to elicit intense pain sensation. A long-lasting electrical stimulus activates various afferent pathways, because C-fibres have a higher activation threshold than A-fibres.

In a previous study, Luginbühl and colleagues concluded that pulse plethysmography (PPG) response to a short-lasting (5 s) tetanic stimulus does not predict the responsiveness to endotracheal intubation at different levels of analgesia and anaesthesia, and thus the PPG response to a short-lasting tetanic stimulus does not reflect the analgesic state accurately. This conflicts somewhat with our finding where RRI responses to tetanic stimuli (both 30 and 5 s, though the former with significantly better correlation) were significant predictors to RRI responses to skin incision—clearly better predictors than the drug levels alone, which were the best predictors in a study by Luginbühl and colleagues. We hypothesize that this difference may be at least partially related to the different nature of skin incision and tracheal intubation as a stimulus. The intubation causes a strong direct autonomic stimulus (e.g. through direct stimulation of baroreceptors), which is combined with the nociceptive stimulus, whereas in skin incision, the direct nociceptive stimulus dominates and no direct autonomic stimuli occur. Hence, at least part of the response to intubation may be related to the direct autonomic stimulus rather than pure nociception, making its prediction by use of experimental pain models less probable. In addition, though skin incision in different types of surgery is certainly neither a well-controlled nor a standardized clinical stimulus, intubation is even more prone to inter-individual variance in magnitude and duration of stimulation. Thus, we hypothesize that the use of skin incision as a reference of clinical pain has a better potential to give an accurate association between an experimental and clinical stimulus, and autonomic responses to skin incision better reflect the real nociceptive–antinociceptive balance than those responses to tracheal intubation.

Our results confirm a clear association between a long-lasting tetanic stimulus and abdominal skin incision during propofol–remifentanil anaesthesia. We did not study the later phases of surgery. The reliability of a tetanic stimulus to predict reflections caused by visceral manipulation or other nociceptive events remains to be evaluated.

All patients were paralysed with cisatracurium, leading to significantly attenuated motor responses for tetanic stimuli. Theoretically, omitting the use of cisatracurium and consequent vigorous muscle contractions during tetanic testing would have led to stronger heart rate responses. However, we aimed at standardized study circumstances for both tetanic testing and skin incision. Our goal was not to study the effect of muscle relaxation on heart rate but to elucidate the association between the length of the tetanic stimulus and skin incision, without unnecessary confounding factors. Moreover, a long abdominal skin incision without neuromuscular block was considered potentially problematic and was therefore discarded.

No harmful side-effects occurred in our study. Patients were interviewed later on by a trained research nurse for theoretically possible damage caused by tetanic stimuli. No tetanic stimulation associated symptoms or signs of ulnar nerve damage were noted.

In conclusion, the RRI response to the long-lasting electrical tetanic (30 s, 50 mA, 50 Hz) was a better predictor of the RRI response to skin incision than a short tetanic

### Table 1

<table>
<thead>
<tr>
<th>Remifentanil level (ng ml⁻¹)</th>
<th>Remifentanil (1 ng ml⁻¹)</th>
<th>Remifentanil (3 ng ml⁻¹)</th>
<th>Remifentanil (5 ng ml⁻¹)</th>
<th>P-value²</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRI Tet30</td>
<td>0.912 (0.072)†</td>
<td>1.01 (0.027)*</td>
<td>0.999 (0.022)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RRI Tet5</td>
<td>0.968 (0.037)†</td>
<td>0.999 (0.011)***</td>
<td>0.990 (0.012)</td>
<td>0.013</td>
</tr>
<tr>
<td>RRI incision</td>
<td>0.900 (0.091)‡</td>
<td>0.993 (0.026)‡</td>
<td>1.00 (0.035)**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P-value¹</td>
<td>0.001</td>
<td>0.296</td>
<td>0.310</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Fig 2** A scatter plot of the mean post/pre-stimulus RRI ratios: skin incision vs 30 s tetanic stimulus at different remifentanil levels.
stimulus or drug (remifentanil and propofol) level. We suggest a tetanic stimulus lasting 30 s as a standardized, non-invasive, repeatable test method, which simulates the RRI response to skin incision in healthy individuals during propofol–remifentanil anaesthesia.

References
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