The Analgesic and Antihyperalgesic Effects of Transcranial Electrostimulation with Combined Direct and Alternating Current in Healthy Volunteers

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BACKGROUND: Transcranial electrostimulation (TES) has been reported to produce clinically significant analgesia, but randomized and double-blind studies are lacking. We investigated the analgesic and antihyperalgesic effects of TES in validated human experimental pain models.

METHODS: In 20 healthy male subjects we evaluated the analgesic and antihyperalgesic effects of TES_{60Hz} and TES_{100Hz} to heat and mechanical pain in experimentally induced ultraviolet B skin sunburns and in normal skin. Previous animal studies in our laboratory predicted that TES_{60Hz} would provide significant analgesia, and TES_{100Hz} was a suitable active control. The study was conducted in a double-blind, randomized, 2-way cross-over fashion. TES was administered for 35 minutes. Quantitative sensory testing evaluating heat and mechanical pain thresholds was conducted before TES, during TES, and 45 minutes after TES.

RESULTS: TES ($TES_{60Hz} > TES_{100Hz}$) evoked rapidly developing, significant thermal and mechanical antihyperalgesic effects in the ultraviolet B lesion, and attenuated thermal pain in unimpaired skin. No long-lasting analgesic and antihyperalgesic effects of a single TES treatment were demonstrated in this study.

CONCLUSIONS: TES produces significant, frequency-dependent antihyperalgesic and analgesic effects in humans. The characteristics of the TES effects indicate a high likelihood of its ability to modulate both peripheral sensitization of nociceptors and central hyperexcitability. (Anesth Analg 2010;111:1301–7)

Transcranial electrostimulation (TES) is a collective term for a variety of noninvasive, neuromodulating brain stimulation techniques, which use administration of the electrical current through the electrodes positioned on the skin of the subject's head.[1] In humans, TES has been reported to produce a plethora of electrotherapeutic effects, but of particular interest is its seeming ability to induce clinically significant, nonpharmacological analgesia.[2,3] Immediate analgesic effects of impressive magnitude have been reported in early preliminary TES human studies using an alternating current (AC) and a combined AC and direct current (DC:AC) stimulation. The potency of nitrous oxide was increased by approximately 40%,[4] intraoperative opioid requirements decreased by 30% during neuroleptanesthesia,[5] and use of the intraoperative opioids could even be completely avoided in up to 30% of cases.[2] However, a lack of randomization, adequate blinding, and controls has left the results of these studies inconclusive,[6] and the question of a true analgesic efficacy of TES remains open to speculation.

Recent double-blind and randomized TES studies in chronic pain patients using AC only,[7] DC only (tDC)[8,9] and microcurrent stimulation[10–12] have also produced controversial results. Although variable analgesic effects—as assessed by patients' self-reported improvements in pain and pain-related symptoms—could be demonstrated, the observed analgesia was typically of insidious onset, and concomitant reduction in pain medication requirements was either largely absent[8,9] or dubious at best.[7]

To address this controversy, recent attempts have been made to investigate TES-induced analgesia in experimental human pain models, which offer an ability to control the magnitude of the nociceptive stimulus, reliably quantify the behavioral and the neurophysiological responses,[13] and eliminate confounding factors related to psychological and cognitive aspects of the illness, such as anxiety, depression, and mood and sleep disturbances.[12,13] Using tDC stimulation, Boggio et al.[14] reported a modest 8%–10% increase in pain threshold to cutaneous electrical pain in healthy volunteers. Clinical interpretation of this finding, however, is limited. Electrically induced pain directly activates the entire population of nerve fibers, without preferential effect on primary nociceptors (Aδ- and C-fibers).[15]

We have shown that in rats, TES with combined DC and 60-Hz AC current (TES_{60Hz}) produces significant antinociceptive effects to heat-induced nociception,[1,16] suggesting a potential to elicit clinically relevant analgesia in humans.[17] Previous animal studies in our laboratory also predicted that TES_{100Hz} would be a suitable active control. We, therefore, embarked on the study to test the hypothesis that TES_{60Hz} would exert modality-specific analgesic and antihyperalgesic effects in humans. The subjects' responses to noxious heat and mechanical stimulation were evaluated in

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normal and inflamed skin. For the latter, we used a validated experimental model of inflammatory cutaneous pain produced by ultraviolet B (UVB) irradiation (UVB, or sunburn lesion). The UVB lesion is characterized by induction of stable primary hyperalgesia (increased pain sensitivity within the inflamed area)[18–20] and reproduces many components of inflammatory response that accompanies acute tissue damage caused by trauma or surgery.[21–25] It also demonstrates high sensitivity to analgesic and antihyperalgesic effects of anti-inflammatory drugs[18,24,26] and opioids,[23,27,28] making it possible to compare the magnitude of TES-induced analgesic effects with those of benchmark pharmacological treatments.

METHODS

The study was approved by the Stanford University IRB, and the informed consent was signed by all the subjects. Twenty healthy Caucasian men, ages 20 to 49 years (mean 27.9 ± 9.2 SD), with normal weight and height, were enrolled in the study. The subjects were pain free, had an unremarkable medical history, did not take any prescription or over-the-counter medications, and agreed to abstain from alcohol and nicotine use for the duration of the study. The subjects were required to keep consistent bedtime and wake-up time for at least 3 days before each study day, and to get at least 7 hours of uninterrupted night sleep. The subjects were instructed to keep their normal pattern of food and caffeine consumption and to avoid any strenuous physical exercise on each study day. The subjects with a history of habitual alcohol and tobacco use, drug abuse, history of seizures, documented or suspected organic brain disease, eye disease, head or eye injury, history of surgery on the head or eye, skin lesions of the head, dental implants, and implanted medical devices were excluded from the study. The enrolled subjects did not participate in any other research protocols.

The study was conducted in a randomized, double-blind, 2-way cross-over fashion, with at least a 1-week washout period between the TES study sessions. A computer-generated randomization schedule assigned an equal number of subjects to receive TES_{60Hz} or TES_{100Hz} on the first study day and the alternative treatment on the second study day. The operator of the TES device, research subjects, research personnel assessing subjects' analgesic responses to TES, and the personnel collecting and entering the study data were blinded to the TES modality used. Heat pain thresholds (HPTh) and mechanical pain thresholds (MPTh) (see below) were assessed in normal skin and the UVB lesion at a baseline (before TES session), 15 minutes after the start of TES, and 45 minutes after TES was stopped. The subjects were adapted to all experimental procedures before the beginning of the study. Each study session was performed in a quiet room in the morning hours, and light snacks and noncaffeinated drinks were available to the subjects ad lib during the study days.

Induction of the UVB Lesion

Before induction of the UVB lesion, the minimal erythemal dose (MED) was determined for each subject, by simultaneously irradiating the subject's skin with 5 increasing doses (range from 40 to 100 mJ) of UVB light via a calibrated UVB source (Saalmann Multitester SBB LT 400, Saalmann GmbH, Herford, Germany). A small experimental UVB lesion (1.5 cm in diameter), located on the nontanned skin of the upper thigh, was induced with a dose equal to 2× MED 24 hours before each of the TES study days; the location of the sunburn was rotated between the thighs for different TES sessions. Experimental UVB inflammation is painless during and after induction, does not cause skin damage, is associated with small interindividual variability, and allows for the conducting of repeated and reproducible nociceptive testing.[18,23,26,29] The hyperalgesic nature of the UVB lesion was confirmed by a stable decrease in HPTh and MPTh at the site of inflammation before the beginning of each TES session.

Experimental Procedures

Using quantitative sensory testing (QST), we assessed the sensitivity to heat and mechanical pain consecutively in both, the UVB lesion and normal skin of the thigh, at sites 20 cm apart.

Thermal (heat) pain testing.[24,30] A hand-held thermode (16 × 16 mm) connected to a sensory analyzer (TSA 2001, Medoc Advanced Medical Systems, Minneapolis, Minnesota) was brought into full contact with the skin. Starting from the adaptation temperature 35°C, the thermode temperature was increased at a rate of 1°C/s (cutoff 52°C). At the first perception of pain, the subject pushed a button on a hand-held device triggering a computerized recording of HPTh, and an immediate probe-cooling at a rate of 10°/s. This procedure was repeated 7 times with a stimulus interval of 30 seconds, and the average HPTh was computed for data analysis.

Mechanical pain testing.[24,30] MPTh was determined with the aid of custom-made, calibrated, punctuated pressure probes comprising stainless steel wires (240 μm diameter), mounted on copper rods of various weights (1, 2, 4, 8, 16, 32, 49, 64, and 81 g), and surrounded by a wider hand-held aluminum tube that allowed the wires to move freely inside. Starting with the lightest probe, we applied progressively stronger punctuated stimuli by positioning the steel wire tip perpendicular to the skin surface, so that the weight of the rod rested solely on the wire tip. Once the sensation of pain was elicited, consecutively lighter probes were used to record the transition from pain to no pain. A total of 7 data points were sought: 4 measurements reflecting a change from nonpainful to painful stimulation, and 3 measurements reflecting the opposite change. The average of these 7 data points was computed as a true MPTh, and was entered for data analysis.

TES procedure. The custom-made, constant-current TES apparatus includes controls for manual adjustment of pulse duration, DC:AC ratio, TES frequency, and current value, and is in compliance with the safety standards established by the Stanford Hospital Instrumentation and Electrical Safety Committee. The TES current value is continuously displayed on the front panel of the TES device. Subjects were positioned comfortably in a reclining chair. TES was administered through a cathode (10 × 5 cm), positioned on the forehead above the eyebrows, and paired retromastoid anodes (5 × 5 cm), all held in place by Velcro straps comfortably tightened around the subject's head. Each

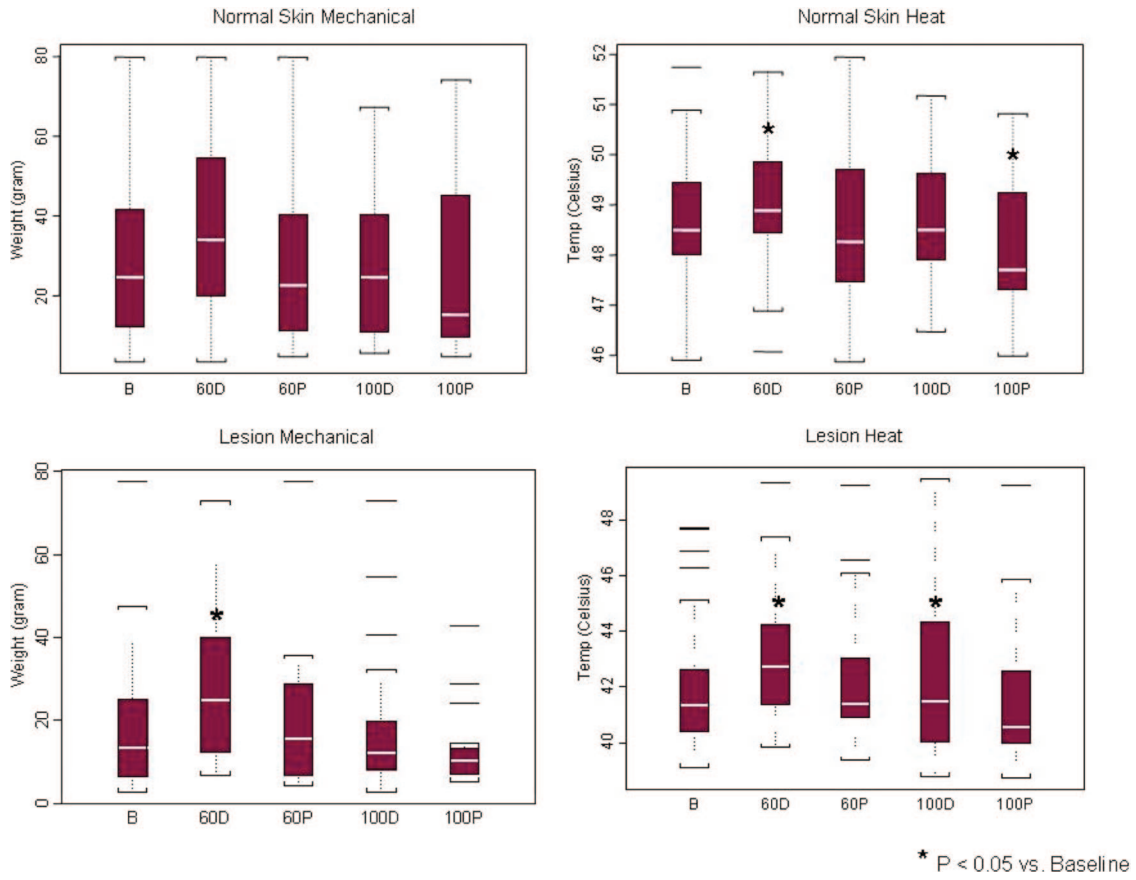

Figure 1. The effect of transcranial electrostimulation (TES) at 60 Hz and 100 Hz on heat and mechanical pain thresholds (HPTh and MPTh) in noninflamed and inflamed skin. Box plots show the change in HPTh and MPTh stratified by the TES treatment group and time. The white horizontal line inside each box is the median, and the height of the box represents the interquartile range, which is the difference between the third quartile and first quartile. The whiskers extend to a distance of 1.5 times the interquartile range; horizontal lines indicate outliers. An asterisk indicates a median value statistically different from baseline (*$P < 0.05$). B: baseline; 60D and 100D: HPTh and MPTh during TES_{60Hz} and TES_{100Hz}; 60P and 100P: HPTh and MPTh post TES_{60Hz} and TES_{100Hz}.

electrode consisted of a stainless steel plate and a flannel pad soaked in water, and was brought in direct contact with the subject's skin. To standardize stimulation intensity for both TES_{60Hz} (active treatment) and TES_{100Hz} (active control), the current was gradually adjusted by the operator to achieve a maximal tolerable, but comfortable (nonpainful) tingling sensation under the electrodes. Once the cutoff current value of 5 mA was reached (DC:AC current ratio was 2:1 [1, 16]), it was maintained at that level for the entire duration of TES procedure. The polarity of stimulation was manually switched by the operator every 10 minutes to prevent a DC charge transfer and to reduce the risk of electrolytic skin burns.[31] The total duration of the TES procedure was 35 minutes, upon which current was discontinued and the electrodes removed from the subject's head.

Statistical analysis. A power analysis indicated that studying 20 subjects would result in approximately 80% chance of obtaining statistical significance via repeated-measures analysis of variance (ANOVA), assuming a large effect size of 0.8.[32] Treatment effects were analyzed with a linear mixed-effects modeling approach, using the lme function of S-Plus (version 6.2, Insightful, Seattle, Washington). Mixed-effects models that account for correlation between repeated measures provide a more powerful and flexible tool for analyzing grouped data, in comparison with traditional statistics. Two levels of grouping were used: the factor subject and the factor date, indicating the day on which the experiment was conducted (random effects).[33] The contrasts option was used to estimate the effect of the treatment levels (TES_{60Hz} and TES_{100Hz} during and after TES application) on HPTh and MPTH in comparison with the baseline value (fixed effects). $P < 0.05$ was considered statistically significant.

RESULTS

The maximal current of 5 mA was reached for each study subject during each TES session, typically within the first 5 minutes of stimulation, and was maintained at that level throughout the entire TES procedure. A subjective tingling sensation under the electrodes was identical for both TES_{60Hz} and TES_{100Hz}, assuring appropriate blinding of the subjects. Overall, the subjects tolerated TES procedures well. One subject complained of a transient poststimulation headache, lasting 15 minutes.

Study results are presented in Figure 1 and Table 1. Figure 1 shows the effect of different TES frequencies on HPTh and MPTh in normal skin and in the UVB lesion, during and after

Table 1. Model Estimates of the Effects of Different Transcranial Electrostimulation (TES) Frequencies on Heat and Mechanical Pain Thresholds (HPTh and MPTh) in Normal Skin and Ultraviolet B (UVB) Lesion

		Model parameters			
Normal skin mechanical		**Fixed effects**	**Estimate (g)**	**95% confidence interval**	
Versus baseline	*P* value	Baseline	30.6	22.0	39.1
60D	0.0919	60D	5.8†	−1.0	12.5
60P	0.4044	60P	−2.8†	−9.6	3.9
100D	0.7798	100D	−0.9†	−7.7	5.8
100P	0.5057	100P	−2.3†	−9.0	4.5
		Random effects‡	**SD**	**95% confidence interval**	
		Subject	15.2	9.6	24.1
		Day	10.9	6.8	17.5
		Model parameters			
Normal skin heat		**Fixed effects**	**Estimate (°C)**	**95% confidence interval**	
Versus baseline	*P* value	Baseline	48.7	48.1	49.2
60D	0.0389*	60D	0.3†	0.0	0.6
60P	0.0974	60P	−0.3†	−0.6	0.0
100D	0.5471	100D	0.1†	−0.2	0.4
100P	0.0114	100P	−0.4†	−0.7	−0.1
		Random effects‡	**SD**	**95% confidence interval**	
		Subject	1.1	0.7	1.6
		Day	0.6	0.4	0.9
		Model parameters			
UVB lesion mechanical		**Fixed effects**	**Estimate (g)**	**95% confidence interval**	
Versus baseline	*P* value	Baseline	19.0	12.5	25.5
60D	0.0004*	60D	8.5†	3.9	13.2
60P	0.8405	60P	−0.5†	−5.1	4.2
100D	0.5193	100D	1.5†	−3.1	6.1
100P	0.1805	100P	−3.1†	−7.8	1.5
		Random effects‡	**SD**	**95% confidence interval**	
		Subject	12.0	7.8	18.5
		Day	8.0	5.0	12.6
		Model parameters			
UVB lesion heat		**Fixed effects**	**Estimate (°C)**	**95% confidence interval**	
Versus baseline	*P* value	Baseline	41.9	40.8	43.0
60D	<.0001*	60D	1.2†	0.7	1.6
60P	0.1256	60P	0.3†	−0.1	0.8
100D	0.0368	100D	0.5†	0.0	0.9
100P	0.2329	100P	−0.3†	−0.7	0.2
		Random effects‡	**SD**	**95% confidence interval**	
		Subject	2.3	1.7	3.3
		Day	0.6	0.3	1.0

B = baseline; 60D and 100D = HPTh and MPTh during TES_{60Hz} and TES_{100Hz}; 60P and 100P = HPTh and MPTh post-TES_{60Hz} and post-TES_{100Hz}; SD = standard deviation.

* $P < 0.05$.

† Change from baseline.

‡ It is assumed that random effects have a mean of zero and follow a Gaussian distribution.

cessation of TES treatment, and Table 1 provides a model estimate of real population values. The development of thermal and mechanical hyperalgesia was confirmed in the UVB lesion, as was evidenced by decreased HPTh and MPTh at the site of inflammation in comparison with noninflamed skin (estimated HPTh decrease 6.8°C, 95% confidence interval [CI] 6.2° to 7.3°C; MPTh decrease 11.6 g, 95% CI 9.5 to 13.6 g). The administration of TES_{60Hz} significantly attenuated heat hyperalgesia in inflamed skin (estimated increase in HPTh: 1.2°C, 95% CI 0.7° to 1.6°C, $P < 0.0001$), and also provided significant analgesic effect to noxious heat in noninflamed skin (estimated increase in HPTh: 0.3°C, 95% CI 0.0° to 0.6°C, $P < 0.039$). In contrast, TES_{100Hz} had no effect on HPTh in normal skin, and was 2.5 times less effective than was TES_{60Hz} in reducing primary heat hyperalgesia in the UVB lesion (estimated increase in HPTh: 0.5°C, 95% CI 0.0° to 0.9°C, $P < 0.037$). TES_{60Hz} significantly reduced mechanical hyperalgesia in inflamed skin (estimated increase in MPTh: 8.5 g, 95% CI

3.9 to 13.2 g, $P < 0.0004$); there was also a strong trend towards a reduction of MPTh in noninflamed skin (estimated increase in MPTh: 5.8 g, 95% CI −1.0 to 12.5 g, $P < 0.09$). TES_{100Hz} had no effect on mechanical pain in inflamed and noninflamed skin. Neither TES_{60Hz} nor TES_{100Hz} resulted in significant analgesic or antihyperalgesic aftereffects. On the contrary, hypersensitivity to heat-induced pain was observed in inflamed skin 45 minutes after the cessation of TES_{100Hz} administration (estimated decrease in HPTh: −0.4°C, 95% CI −0.1° to 0.7°C, $P < 0.011$).

DISCUSSION

Our study is the first to demonstrate that TES with DC:AC current produces significant frequency-dependent analgesic and antihyperalgesic effects in validated human experimental pain models, which mimic important aspects of clinical pain.[13,15,23,27,34] In particular, the UVB sunburn lesion features many components of the peripheral inflammatory response associated with surgery, tissue injury, and inflammatory diseases, including sensitization of peripheral nociceptors and induction of a primary hyperalgesic state.[18–25] Both analgesic and antihyperalgesic effects of TES with DC:AC current develop rapidly, as opposed to such modalities as TES with AC only[3,7,35] or microcurrent stimulation,[11,12] which may take several hours or treatment sessions to develop. These findings suggest that TES with DC:AC current may be a valuable, nonpharmacological analgesic intervention for a wide variety of painful conditions and disorders.

In this study, TES_{60Hz} significantly reduced primary thermal and mechanical hyperalgesia in the UVB lesion, revealing its ability to modulate the activity of primary nociceptors. The C fiber polymodal nociceptors are predominantly responsible for mediating thermal pain.[36] They are also highly sensitive to opioid compounds in QST,[27,29] allowing preliminary comparison between the traditional opioid and TES DC:AC–induced analgesia, which is also believed to be mediated by μ-opioid receptor-selective ligands, albeit of endogenous character (β-endorphin).[2,3,35,37,38] When tested under similar experimental conditions, TES_{60Hz} appears to be 2.5 times less potent than is remifentanil (0.05 mcg $\cdot$ kg^{-1} $\cdot$ min^{-1}) in alleviating thermal pain in unimpaired skin (0.3°C vs. mean ~0.75°C),[27] and twice less potent than is remifentanil (0.08 mcg $\cdot$ kg^{-1} $\cdot$ min^{-1}) in attenuating primary thermal hyperalgesia in UVB lesion (1.2°C vs. mean 2.5°C).[23] Nevertheless, TES-induced analgesia seems to be clinically relevant. The estimated steady-state blood concentrations of remifentanil required to produce the respective analgesic (1.3 ng $\cdot$ mL^{-1}) and antihyperalgesic (2 ng $\cdot$ mL^{-1}) effects[39,40] are substantial, correlating with those required to reduce the minimum alveolar concentration (MAC) of isoflurane by 50%[39] and block the sympathetic responses to skin incision in 50% of patients (EC_{50}) receiving target-controlled propofol anesthetic.[41,42]

In our study, the thermal antihyperalgesic effect of TES_{60Hz} in the UVB lesion was significantly more pronounced than was its analgesic effect to heat in intact skin (1.2°C vs. 0.3°C; Table 1). This contrasts strongly with the similar analgesic and antihyperalgesic activity observed for opioids,[23,27] suggesting that nonopioidergic mechanisms may be equally involved in mediating TES-induced analgesia. This speculation is further supported by the capacity of TES_{60Hz} to attenuate primary mechanical hyperalgesia in the UVB lesion (8.5 g; Table 1). There is substantial evidence to suggest that the generation of primary punctuate mechanical hyperalgesia in different types of inflammation, including UVB, may be largely attributed to the activation of silent, high threshold mechano-insensitive A δ and C afferents, and particularly silent C nociceptors (28,43–45), which are not as potently affected by opioids as are C-nociceptors responsible for thermal pain and hyperalgesia.[29] Furthermore, the fact that silent C-nociceptors are strongly implicated in the development of central sensitization[28,34,43,44] highlights the possible beneficial role of TES in reducing central hyperexcitability. Absence of poststimulation analgesia in our study does not necessarily diminish the significance of this finding. Prolonged or repetitive TES application may be required to achieve sustained clinically significant effects,[3,8,9,12] possibly reflecting gradual development of neuroplastic changes in extensive neural networks.

The TES_{60Hz} antihyperalgesic effect on heat and mechanical pain in the UVB lesion was nearly identical to that observed after oral administration of a single 800-mg dose of ibuprofen.[24,26] Although this corresponds to a similar antihyperalgesic effectiveness, the underlying mechanisms are likely different. The main mechanism of ibuprofen's antihyperalgesic action involves blocking the peripheral cyclooxygenase-dependent sensitization of cutaneous nociceptors,[18,24,26] which is reflected by its lack of analgesic activity in unimpaired skin.[18,24,26]

The demonstrated superior analgesic and antihyperalgesic effect of TES_{60Hz} over TES_{100Hz} confirms the results of our animal study, identifying TES_{60Hz} as the preferred antinociceptive frequency,[1] and further validates our rat model of cutaneously administered TES as an accurate experimental paradigm for future exploration of TES antinociceptive effects and mechanisms of action.

In conclusion, we have demonstrated that TES evokes significant, rapidly developing, frequency-dependent ($TES_{60Hz} > TES_{100Hz}$) antihyperalgesic and analgesic effects. Preliminary QST comparison places TES half as effective as remifentanil (0.05 mcg $\cdot$ kg^{-1} $\cdot$ min^{-1}, steady-state concentration 1.3 ng $\cdot$ mL^{-1}) in achieving 50% MAC reduction of isoflurane. A seeming ability of TES to effectively modulate altered central processing of nociceptive input, presumably by nonopioidergic mechanism(s), constitutes one of the most conspicuous findings of our study, suggesting the potential role of TES in clinical pain management. The future of this technique will rest on the confirmation studies directly elucidating the mechanism(s) of TES_{60Hz} action, exploring its effects in experimental human pain models of secondary hyperalgesia and allodynia, and demonstrating the presence of the analgesic and antihyperalgesic aftereffects of prolonged or repetitive TES application.

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Ischemic Preconditioning Attenuates Pulmonary Dysfunction After Unilateral Thigh Tourniquet-Induced Ischemia–Reperfusion: Erratum

In the article that appeared on page 539 in the August 2010 issue of volume 111 of *Anesthesia & Analgesia*, in Table 2 on page 541, one of the footnotes was incorrect:

"T2–4 = 2 hours, 6 hours, and 24 hours after tourniquet deflation" was incorrect.

The correct footnote should be: "T2–5 = 0.5 hours, 2 hours, 6 hours, and 24 hours after tourniquet deflation"

This error has been noted in the online version of the article, which is available at www.anesthesia-analgesia.org.

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Lin L, Wang L, Wang W, Jin L, Zhao X, Zheng L, Jin L, Jiang L, Xiong X. A randomized trial of the traditional sitting position versus the hamstring stretch position for labor epidural needle placement. Anesth Analg 2010;111:539–43