Acupuncture Decreases Somatosensory Evoked Potential Amplitudes to Noxious Stimuli in Anesthetized Volunteers

Winfried Meissner, MD*, Thomas Weiss, MD, PhD†, Ralf H. Trippe, PhD†, Holger Hecht†, Clemens Krapp, MD*, and Wolfgang H. Miltner, PhD†

Departments of *Anesthesiology and Intensive Care and †Biological and Clinical Psychology, Friedrich Schiller University Jena, Jena, Germany

The effect of acupuncture on pain perception is controversial. Because late amplitudes of somatosensory evoked potentials (SEPs) to noxious stimuli are thought to correlate with the subjective experience of pain intensity, we designed this study to detect changes of these SEPs before and after acupuncture in a double-blinded fashion. Sixteen volunteers were anesthetized by propofol and exposed to painful electric stimuli to the right forefinger. Then, blinded to the research team, the acupuncture group ($n = 8$) was treated with electric needle acupuncture over 15 min at analgesic points of the leg, whereas the sham group ($n = 8$) received no treatment. Thereafter, nociceptive stimulation was repeated. SEPs were recorded during each noxious stimulation from the vertex Cz, and latencies and amplitudes of the N150 and P260 components were analyzed by analysis of variance. P260 amplitudes decreased from 4.40 ± 2.76 μV (mean ± SD) before treatment to 1.67 ± 1.21 μV after treatment ($P < 0.05$), whereas amplitudes of the sham group remained unchanged (2.64 ± 0.94 μV before versus 2.54 ± 1.54 μV after treatment). In conclusion, this double-blinded study demonstrated that electric needle acupuncture, as compared with sham treatment, significantly decreased the magnitudes of late SEP amplitudes with electrical noxious stimulation in anesthetized subjects, suggesting a specific analgesic effect of acupuncture.

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Analgesic acupuncture has been used for thousands of years in different countries. Nevertheless, its effectiveness and its underlying mechanisms are still controversial. This is largely because perception of pain is subjective, and acupuncture is very difficult to blind to the patient and the investigator (1). Only a few studies have used any kind of blinded and controlled conditions, and these have reported contradictory results (2–4). One way to overcome these difficulties is to use anesthesia, which allows complete blinding of the studied subjects toward insertion of the acupuncture needles. In some of these studies, the requirement for anesthetics or postoperative analgesics was decreased (5–7); however, other studies have not been able to replicate these results (8–10).

Besides self-reported pain and observations of pain-related behaviors, analysis of somatosensory evoked potentials (SEPs) is a rapid measure of the information processing of noxious stimuli (11). Partial correlation analysis between amplitudes of late SEP components, physical stimulus intensity, and pain report confirmed that the size of these SEP measures is related not only to the physical intensity of stimulation (12–17) (for a summary see Ref. 18), but also to the subjective experience of pain (13). Because of this observation, it was suggested that these late SEP components to noxious stimuli primarily represent correlates of cognitive and evaluative stimulus processing (19).

Subsequently, many studies have indicated that measures of late SEP components can be useful in the evaluation of analgesic drugs. The amplitudes of these late SEPs are smaller when subjects are treated successfully by peripherally or centrally acting analgesics as compared with control conditions (20–22). Another field of investigation in which SEP measures can be applied is in acupuncture, which also reduces late SEP components (21,23–25). However, because subjects in these studies were not blinded and because psychological factors can also affect late SEP components

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Address correspondence and reprint requests to Winfried Meissner, MD, Department of Anesthesiology and Intensive Care, Friedrich-Schiller-University Jena, 07740 Jena, Germany. Address e-mail to meissner@med.uni-jena.de.

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(26), the analgesic effects observed in these studies cannot clearly be attributed to specific analgesic mechanisms of acupuncture.

In this study, we used general anesthesia together with SEP measures to evaluate the effect of acupuncture. Thus, the purpose of this double-blinded study was to evaluate the effectiveness of acupuncture by means of a measurable, electrophysiological correlate of pain.

Methods

The study protocol was approved by the IRB of the Friedrich Schiller University of Jena, Germany, and written, informed consent was obtained from all participants. Participants were included if their ASA physical status was I. They were excluded if they reported intake of analgesic or sedative drugs within the last 7 days, if they had not been fasting for at least 6 h before the start of anesthesia, or if there was any sign of acute or chronic respiratory infection.

Before the induction of propofol anesthesia was started, each subject's perception threshold and pain threshold were determined by using the method of limits. Subjects received intracutaneous electrical stimuli (12). An electrical current with an intensity between 10 and 1000 μA was applied intracutaneously to the tip of the forefinger of the right hand. The stimulation electrode consisted of an isolated golden pin with a diameter of 0.95 mm and a length of 1 mm. The pin was inserted into a small epidermal cavity of 1 mm diameter and about 1 mm depth and fixed with adhesive tape. The purpose of this preparation was to reduce the skin resistance and thus the amount of current necessary to elicit a pain sensation. A flexible stainless-steel electrode, fixed loosely around the first finger joint, served as a reference electrode. Subjects were grounded by using a broad, flexible, humid band electrode fixed around the wrist of the stimulated hand. All intracutaneous electrical alternating current stimuli were bipolar rectangular pulses of 20 ms duration. For threshold estimation, stimuli were applied with a randomized interstimulus interval of 8 $\pm$ 3 s. After each single-stimulus application, subjects were requested to rate the intensity of each stimulus by a standardized rating scale (27) ranging from 0 (no perception) to 6 (unbearably painful). One-hundred stimuli were applied in 2 runs of stimuli with stepwise increasing intensity up to 5 ("strongly painful") and decreasing down to 0. Pain sensation was defined as the intensity yielding a sensation described as a sharp painful pinprick, corresponding to a rating of 3. For the pre- and posttreatment stimulation during propofol anesthesia, the intensity of stimuli was fixed at an intensity rated as 5 ("strongly painful") during threshold estimation.

Thereafter, the volunteers were anesthetized with propofol and intubated by using a laryngeal mask airway. The volunteers' lungs were ventilated with a fraction of inspired oxygen of 0.3. Propofol was infused with the target-controlled infusion technique (28). Propofol levels were chosen according to the recommended target concentrations of propofol for non-premedicated patients (5–6 μg/mL). These levels were adjusted according to clinical signs of depth of anesthesia. Heart rate and arterial oxygen saturation were monitored continuously. Arterial blood pressure was measured noninvasively by using an oscillometric blood pressure monitor. The laryngeal mask was removed when volunteers responded to commands adequately. Subjects were observed for another 60–90 min and then were accompanied home by a responsible individual.

Forty-five minutes after the induction of propofol anesthesia, volunteers were exposed to 80 painful intracutaneous electrical stimuli at the right forefinger. Stimuli were delivered as described previously, with an interstimulus interval of 2.75 $\pm$ 0.25 s. SEPs were recorded as described below. Then, subjects were randomly allocated to an acupuncture ($n = 8$) or a sham ($n = 8$) group. Group assignment was kept in sealed envelopes. Acupuncture or sham treatment was performed. Five minutes after the end of treatment, the nociceptive stimulation with 80 electric stimuli and registration of SEP was repeated.

The acupuncture treatment consisted of electric needle acupuncture over 15 min at analgesic points on both legs (Sp 6 [Sanyinjiao], St 36 [Zusanli], and L 3 [Taichong]). The acupuncture points were located by using the traditional Chinese medicine system of "cun," where 1 cun is equal to the width of the thumb of the treated subject. Thus, the Sanyinjiao point was located 3 cun above the tip of the medial malleolus, on the posterior border of the tibia. The Zusanli point was located 3 cun below the lower border of the patella and 0.75 cun lateral from the anterior crest of the tibia. The Taichong point was located in the proximal angle of the first and second metatarsal bones. The needles (diameter, 0.3 mm; length, 50 mm; Seirin B-type No. 8, Seirin, Dreieich, Germany) were connected with a multichannel electric acupuncture device (AS Super 4; Pierenkemper, Ehringhausen, Germany) that delivered an electric current of 10 Hz and 10 mA for 15 min. Each of the three pairs of needles (Sp 6, St 36, and L 3) served as electrodes for an electric circuit connected with a separate channel. In the sham group, the device was switched on as well, but no needles were inserted into the volunteer. Acupuncture was performed by an experienced acupuncturist who was not involved in data acquisition, analysis, or delivering anesthesia. The site of acupuncture was covered from the research team and the anesthesiologist by curtains to double-blind the procedure.

During the experimental session, brain electrical activity was recorded by means of an electroencephalograph (EEG) (Nihon Kohden, Tokyo, Japan) from a Ag/AgCl electrode placed on the vertex (Cz) and referenced to linked ears (sampling rate, 500 Hz; bandpass, 1–100 Hz). Eye movements and blinks were recorded from 1 cm above and below the midline of the left eye with the same characteristics. All electrode impedances were kept <5 kΩ. Data were analyzed off-line. Segments of electroencephalogram (EEG) activity containing the SEPs were extracted from the continuous EEG recordings with segment boundaries 200 ms before and 1400 ms after each stimulus onset. After visual inspection of all 80 single EEG trials, trials with movement or technical artifacts were removed from the data; this was the case in 14 ± 8 trials. The remaining trials were digitally filtered (1–12 Hz), and ocular correction was calculated (29). EEG trials then were baseline-corrected by subtracting the average EEG activity within the 200 ms before stimulus onset from all activities after stimulus onset. Averages of SEP were received for each subject for the first and second period of noxious stimulation (i.e., before and after treatment). A peak extraction procedure was performed semiautomatically by a computer program (Vision Analyzer) for each SEP average. SEP amplitudes and latencies at electrode Cz were determined for N150 (100–210 ms) and P260 (210–360 ms).

Separate analyses of variance for repeated measures were calculated for the averaged peaks and latencies of SEP components comprising the between-subject factor group (acupuncture versus sham) and the within-subject factor treatment (pre- versus posttreatment). Averaged Sa_{O_2}, systolic and diastolic blood pressure, and heart rate were analyzed in a similar way by means of the between-subject factor group (acupuncture versus sham) and the within-subject factor time (preanesthesia versus anesthesia/pretreatment versus anesthesia/during treatment). Demographic and clinical differences between the groups were analyzed with Student's *t*-test. Data are expressed as means ± SD. $P \leq 0.05$ was considered significant.

Results

One female volunteer was excluded from the study because of high ventilation pressures after insertion of the laryngeal mask airway. There was no evidence of impairment of oxygenation or any other vital signs, and after anesthesia she recovered completely.

There were no significant differences between groups for demographic or clinical data (Table 1). Propofol dosage did not change in any volunteer during the experimental intervention (electrical stimulation and sham/acupuncture treatment). After the induction of anesthesia, there was a significant decrease of arterial oxygen saturation ($F_{1,13} = 4.02$; $P = 0.044$) and of systolic ($F_{1,13} = 8.87$; $P = 0.004$) and diastolic ($F_{1,13} = 21.75$; $P = 0.001$) blood pressure. However, analysis showed no main significant effect of the factor group and no time × group interaction effects. For heart rate, no significant effects of any of these analyses were observed (Table 2).

Regarding N150 magnitude and latency, because of a weak signal, we were unable to reliably identify the N150 amplitude during propofol anesthesia (five subjects in group 1 and four subjects in group 2 showed no component). Therefore, no statistical analysis of this variable is reported.

Regarding P260 magnitude (Table 3, Figs. 1 and 2), amplitudes of the acupuncture group decreased from 4.40 ± 2.76 μV (mean ± SD) before treatment to 1.67 ± 1.21 μV after treatment, whereas amplitudes of the sham group remained unchanged (2.64 ± 0.94 μV before versus 2.54 ± 1.54 μV after treatment). P260 decreases were observed in all 8 subjects of the acupuncture group ($P < 0.01$; sign test). There was a significant main effect of treatment ($F_{1,14} = 9.48$; $P = 0.008$), with significantly higher values of P260 before treatment (3.5 ± 2.2 μV) than after treatment (2.1 ± 1.4 μV). A group × treatment interaction ($F_{1,14} = 8.25$; $P = 0.012$) indicates a significant decrease of P260 magnitude from pre- to posttreatment in the acupuncture group, whereas no significant change of P260 magnitude was observed for the control group. We found no significant main effect for the factor group ($P > 0.1$). No significant main effects or interactions of P260 latency were observed.

Discussion

The results of this double-blinded study demonstrate a significant decrease of late SEP amplitudes after acupuncture compared with sham treatment during propofol anesthesia. This amplitude has repeatedly been shown to strongly correlate with the subjective experience of pain (13–16,21). Thus, our results suggest that the processing of noxious electrical stimuli was decreased by inserting stimulated electrical needles in certain points on the legs.

Pain-related SEPs for measuring the analgesic potency of acupuncture have been used since the 1970s (25). In rats, Toda et al. (30) showed that acupuncture decreased the amplitude of P1 (latency, 11 ms) and N1 (latency, 20 ms) of dental pain SEPs compared with a control condition. Similar to our results, Chapman et al. (23) demonstrated that segmental and nonsegmental acupuncture in unblinded volunteers was followed by a reduction of pain intensity and a decrease in late SEP amplitudes. In the sham group, no such changes were observed. In a similar study, the same group compared the effects of electrical acupuncture, fentanyl, and nitrous oxide. When subjects were exposed to

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Table 1. Demographic and Clinical Data (Mean ± SD) of Participants in the Acupuncture and Sham Groups

Variable	Acupuncture (n = 8)	Sham (n = 8)
Age (yr)	25 ± 2.7	25 ± 4.3
Weight (kg)	66.0 ± 9.6	67.9 ± 10.8
Total propofol (mg/kg)	17.2 ± 2.8	16.1 ± 1.4
Target propofol serum concentration (μg/mL)	6.5 ± 0.4	6.6 ± 0.7
Anesthesia time (h)	1.1 ± 0.2	1.2 ± 0.1
Stimulus intensity for pain stimulation (mA)	0.8 ± 0.4	0.9 ± 0.2

Table 2. Hemodynamic Variables (Mean ± SD) of Participants in the Acupuncture and Sham Groups

Variable	Acupuncture group (n = 8)	Sham group (n = 8)
Systolic blood pressure (mm Hg)		
Before the induction of anesthesia	129 ± 9	124 ± 18
During anesthesia, before treatment	112 ± 13	115 ± 13
During anesthesia, during treatment	115 ± 15	120 ± 13
Diastolic blood pressure (mm Hg)		
Before the induction of anesthesia	79 ± 6	75 ± 9
During anesthesia, before treatment	66 ± 10	68 ± 8
During anesthesia, during treatment	69 ± 8	72 ± 12
Heart rate (bpm)		
Before the induction of anesthesia	79 ± 16	80 ± 17
During anesthesia, before treatment	75 ± 14	81 ± 9
During anesthesia, during treatment	77 ± 9	83 ± 9
Sao_2 (%)		
Before the induction of anesthesia	98 ± 1.4	97 ± 1.2
During anesthesia, before treatment	97 ± 0.7	96 ± 1.6
During anesthesia, during treatment	98 ± 1.5	97 ± 1.8

Table 3. Amplitudes and Latencies of the P260 Component of the Noxiously Evoked Potential

Subject	Treatment	Amplitude before treatment (μV)	Latency before treatment (ms)	Amplitude after treatment (μV)	Latency after treatment (ms)
1	Control	2.807	304	0.623	288
2	Acupuncture	8.792	288	3.235	270
3	Acupuncture	2.219	250	1.730	306
4	Control	2.893	264	1.389	246
5	Acupuncture	5.577	232	1.107	220
6	Control	3.546	252	2.667	318
7	Control	3.670	260	5.575	250
8	Control	3.470	308	1.487	302
9	Acupuncture	5.517	262	3.172	268
10	Control	1.386	274	2.417	290
11	Acupuncture	1.821	282	0.009	246
12	Control	1.803	284	3.633	246
13	Acupuncture	3.160	322	0.739	216
14	Acupuncture	7.076	322	2.594	304
15	Acupuncture	1.023	210	0.770	358
16	Control	1.527	214	2.553	226

acupuncture, subjective pain reports and amplitudes of P250 were significantly reduced, such as during fentanyl and nitrous oxide administration (21). In a third study, the effects of different levels of electrical acupuncture stimulation on dental pain-related SEP and subjective pain ratings were compared (24). Only at the highest stimulation of electrical acupuncture were pain reporting and the amplitudes of P100 and P250 components of dental SEPs significantly reduced. The authors addressed the possibility that the results might have been affected by changes of attention, judgment, and other cognitive activities. Because volunteers in these studies were awake, no blinding to acupuncture was included.

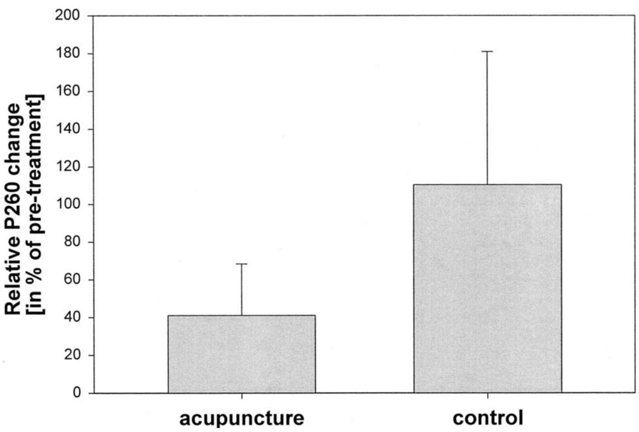

Figure 1. Relative changes of late somatosensory evoked potential amplitude with noxious stimulation after treatment in the acupuncture and sham groups, respectively.

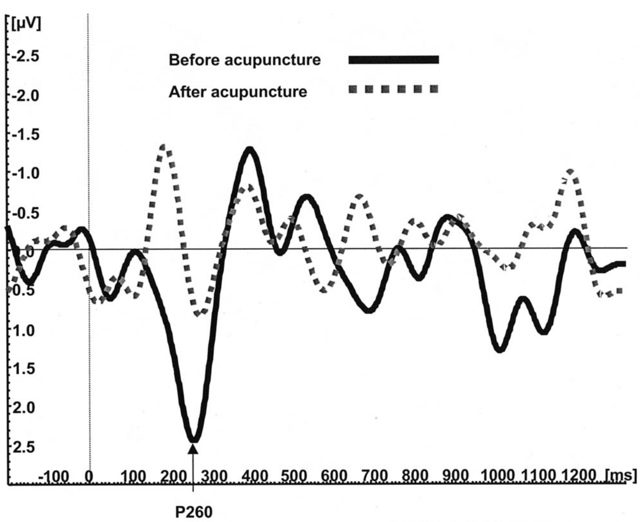

Figure 2. Somatosensory evoked potential components (grand average Cz) before and after acupuncture in the acupuncture group.

The fact that attention and other psychological concomitants might have contributed to the type of analgesic effect of the above-mentioned studies is further supported by a number of findings demonstrating decreased amplitudes of pain-related late SEPs when the subject's attention was distracted from painful stimulation (26). However, the study design of this investigation excluded such intervening variables by anesthetizing the participants. Thus, our findings support the hypothesis that acupuncture itself, and not accompanying factors, significantly affected the amplitudes of late pain-related SEPs. Another difference is that in the cited studies, electrical stimulation was continued during measurement of SEPs, whereas in our study, SEP recording took place after the acupuncture procedure was finished. Thereby, any kind of direct effect of the electrical needle stimulation on potential recording or concurrent stimulation effects on pain perception ("pain beats pain") (31) can also certainly be excluded.

Only very few studies have been completely blinded by combining acupuncture with general anesthesia. Results of these studies were not consistent: Christensen et al. (5) studied electroacupuncture starting at the end of surgery and continuing until termination of general anesthesia in women undergoing hysterectomy. The acupuncture group required half the amount of postoperative analgesics compared with the control group. In a second study from this group, however, these results could not be replicated. In contrast to their first experiment, electroacupuncture was started 20 minutes before skin incision and finished at the end of surgery (8). Kotani et al. (6) used intradermal needles at paravertebral points of the bladder meridian in patients undergoing upper and lower abdominal surgery. In the sham group, needles were not inserted, but only taped close to the acupuncture points. In the acupuncture group, postoperative morphine consumption was reduced by 50%. Another double-blinded study with volunteers demonstrated that electrical stimulation of auricular acupuncture points significantly reduced the amount of anesthetics required to prevent movement in response to noxious stimulation (7). However, in this experiment, subjects did not receive needle acupuncture, but some kind of transcutaneous electrical therapy. In a study using a similar outcome measurement, 3 points at the leg (Zusanli, Yanglingquan, and Kunlun) were needled and electrically stimulated with alternating frequencies of 2 and 100 Hz (10). The desflurane concentrations required to block motor responses to electrical pain stimuli did not differ between the groups.

Our results support the findings that showed positive effects of acupuncture administered during anesthesia. Different results between the studies might be explained by different timing or loci of acupuncture or by different outcome variables. For example, the inconsistency between the two studies of Christensen et al. (5,8) might be due to the different time course of acupuncture in these trials. The negative results of the volunteer study of Morioka et al. (10) might be caused by the choice of acupoints. The authors themselves reported successful needling at other loci (auricular points) with the same methodology. Moreover, in contrast to propofol, desflurane is thought to have not only hypnotic, but also analgesic, properties, which might have interfered with the analgesic effects of acupuncture in their study.

Another possible explanation of these inconsistent findings is that the analgesic effects of most acupuncture techniques are rather small, short-lasting, or both, so they are detectable only very briefly or with sensitive outcome measurements. This effects would indeed limit the clinical importance of acupuncture. Clinical relevance aside, our study was designed to demonstrate acupuncture effects different from sham treatment when using a strictly blinded protocol and an objective and sensitive measurement of analgesia.

Some limitations of our study need to be acknowledged. The fact that N150 components were not detectable in most of our subjects might be attributed to the influence of propofol. Although propofol acts mainly as a hypnotic drug, it has also been acknowledged that it influences SEP amplitudes to painful stimuli (32). Nevertheless, because propofol's influence on SEP is small compared with other anesthetics (33) and because late components were detectable, propofol might not be the only explanation for this phenomenon.

Also, amplitudes of late SEP component P260 tended to be higher in the acupuncture group than the control group before treatment, though this difference was not statistically significant. Although propofol target concentrations did not differ between the groups, they may have suppressed SEP amplitudes in the sham group more than in the acupuncture group. It is important to note, however, that because propofol dosage was kept constant during the experimental intervention, hemodynamic variables did not change significantly between the pretreatment and the treatment phase, and there were no group differences in these variables. Thus, any such propofol effect could hardly explain the marked reduction in P260 amplitude after treatment in the acupuncture but not in the sham group. Another, more likely, explanation for the pretreatment variability is physical differences between subjects; e.g., despite strict randomization, the individuals in the two groups may have differed with respect to their electrophysiologic reaction to painful stimuli. However, because these differences influence both pre- and posttreatment measurements, they cannot explain the observed decrease in SEP amplitudes in the acupuncture group to levels that were even below the amplitude of the sham subjects. The same holds true for any other factor constituted in our subjects, which also should have influenced all SEP amplitudes in the same direction. Nevertheless, it would be interesting to see these results replicated in a study design that guaranteed equal pretreatment SEP values.

Although any confounding effect of cognitive variables can be largely excluded, it is unclear whether the observed decrease of late SEP amplitudes really indicates a reduction of subjective pain. Because of propofol treatment, subjects were unable to supply subjective pain ratings during the procedure. Thus, the hypothesis that acupuncture has any effect on the processing of pain is based on the assumption that changes in SEP validly reflect such phenomena. As mentioned previously, studies performed in awake subjects showed a remarkable agreement between subjective ratings of pain and reduction of late SEP amplitudes in response to noxious stimulation.

In conclusion, this double-blinded study demonstrates that acupuncture, as compared with sham treatment, significantly decreases the magnitudes of late SEP amplitudes after electrical noxious stimulation in anesthetized subjects.

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Erratum

In the September 2003 issue, in the case report by Paul et al., "Failure to Detect an Unusual Obstruction in a Reinforced Endotracheal Tube with Fiberoptic Examination" (Anesth Analg 2003;97:909–10), the abstract was omitted. The publisher regrets the error. The abstract is reproduced below:

Obstruction of an endotracheal tube (ETT) is a potentially life-threatening event. We report an unusual obstruction of a reinforced ETT. The valve-like obstruction was caused by a partial detachment of the inner coating from the embedded spiral of the ETT. It led to an increase in inspiratory airway pressure, failure to detect end-expiratory CO_2, and generated a wheezing sound in forced expiration. Fiberoptic inspection, which is a recommended procedure for a suspected ETT-obstruction, failed to identify this detachment. Exchanging the defective ETT immediately resolved the critical clinical situation. The detachment was most likely caused by re-autoclavation of the ETT, which was a specified single-use product.

(Anesth Analg 2003;97:909–10)