

Effects of nitrous oxide on Spectral Entropy of the EEG during surgery under balanced anaesthesia with sufentanil and sevoflurane

P. HANS, P. Y. DEWANDRE, J. F. BRICHANT and V. BONHOMME

Summary : *Background :* Spectral entropy of the electroencephalogram (EEG) has been proposed to monitor anaesthetic depth. We investigated the effect of nitrous oxide on response (RE) and state entropy (SE) of the EEG during lumbar disc surgery under anaesthesia with sufentanil and sevoflurane.

Methods : In an open study, anaesthesia was induced with propofol and sufentanil, and maintained with 2% end-tidal sevoflurane concentration in air/oxygen ($\text{FiO}_2 = 0.4$) in 25 patients. During surgery, nitrous oxide was randomly administered either at 0 or at 60% end-tidal concentration in 10 (control group) and 15 patients (nitrous oxide group), respectively. RE and SE were recorded at 2.5 min intervals for 10 min before randomization and for 25 min either continuously (control) or after achieving the target nitrous oxide concentration.

Results : Two patients who received nitrous oxide were excluded from statistical analysis because of protocol violation. Nitrous oxide provoked a significant decrease in RE and SE from 46.2 ± 11.1 and 44.3 ± 11.1 to a lowest value of 27.8 ± 8.3 and 27.1 ± 8.9 , respectively. The decrease in entropy persisted during the 25 min recording period.

Conclusions : Addition of nitrous oxide during balanced anaesthesia with sufentanil and sevoflurane provokes a decrease in response and state entropy of the EEG during lumbar disc surgery.

Key words : Monitoring : spectral entropy ; Anaesthetic agents : nitrous oxide.

Entropy of the electroencephalogram (EEG) quantifies the degree of chaos, complexity or irregularity of the EEG signal. This parameter is based on the Kolmogorov-Sinai principle providing a quantification of the amount of regularity in data, and was first applied to a power spectrum of a signal by Johnson and Shore in 1984 (7). It has been proposed to measure depth of anaesthesia, the initial hypothesis for developing this tool being that EEG activity would show more regularity in anaesthetized than in awake patients.

Several algorithms have been developed for entropy calculation. The approximate entropy quantifies the predictability of subsequent ampli-

tude values of data series (*e.g.*, the EEG) and has been shown to correlate with the end-tidal concentration of desflurane in surgical patients (5). The Shannon entropy is a standard measure for the order state of sequences which quantifies the degree of skew of the distribution of values. This parameter has also been correlated with end-tidal desflurane concentrations during surgery and suggested to be a useful EEG-derived measure of anaesthetic drug effect (4). The new Datex-Ohmeda™ S/5™ Entropy Module (M-Entropy™) provides two values of entropy, namely the state entropy (SE) and the response entropy (RE), calculated from specific ranges of frequencies and displayed on the monitor screen as numbers varying between 0 and 100. SE is computed over the frequency range from 0.8 Hz to 32 Hz that includes the EEG-dominant part of the spectrum and mainly reflects the cortical state of the patient. RE is computed over a frequency range from 0.8 to 47 Hz and includes both the EEG dominant and the electromyographic (EMG) dominant part of the spectrum. At this time, most validation of the entropy module has been performed in a controlled pharmacological setting. However, this device should still be validated in clinical practice.

Nitrous oxide is commonly used as an adjunct to anaesthetic agents because of its capacity to spare hypnotics, its potent analgesic properties and its low incidence of side effects. The interaction of nitrous oxide with volatile anaesthetics has already been investigated by measuring EEG-derived parameters such as the median power frequency, the spectral edge frequency and the bispectral index (3, 6, 10, 13). The purpose of this study was

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to evaluate the effect of nitrous oxide on RE and SE of the EEG during surgery under balanced anaesthesia with sufentanil and sevoflurane.

PATIENTS AND METHODS

In an open, prospective randomized fashion, we studied 25 patients, ASA status I or II, undergoing routine lumbar disc surgery under general anaesthesia, after informed consent and approval from the local Ethics Committee. Exclusion criteria included any neurological and psychiatric disease, pregnancy, consumption of illicit drugs and alcohol addiction.

Premedication consisted in alprazolam 0.5 mg and atropine 0.5 mg given orally 1 h before surgery. Upon arrival in the operating theatre, a peripheral venous catheter was sited. Non invasive blood-pressure monitoring, electrocardiography and pulse oximetry were instituted (Datex-Ohmeda™ S/5™, Helsinki, Finland). RE and SE were monitored with the Datex-Ohmeda™ S/5™ Entropy Module (M-Entropy™), using an Entropy Sensor (Datex-Ohmeda™, Helsinki, Finland) appropriately applied to the patient's forehead. In all patients, anaesthesia was induced with 1.5 mg.kg⁻¹ propofol and 0.15 mcg.kg⁻¹ sufentanil. Tracheal intubation was facilitated with 0.5 mg.kg⁻¹ rocuronium. Anaesthesia was maintained with sevoflurane 2% end-tidal concentration vaporized in air/oxygen (FiO₂= 0.4) and achieved at time of incision in all patients. After incision, and while surgery was fully on its way, namely about 15 minutes after induction of anaesthesia and sufentanil administration, RE, SE, heart rate (HR) and systolic (SBP), diastolic (DBP) and mean (MBP) blood pressure were recorded at 2.5 min intervals for 10 min as baseline values in all patients (Baseline). It had been previously decided to conduct the study in 25 patients and to consider 10 of them as control. Using a randomisation list generated with a computer, nitrous oxide was administered at 0 or 60% end-tidal concentration in 10 (control group) and 15 patients (nitrous oxide group), respectively, while keeping the same 2% end-tidal sevoflurane concentration. The above-mentioned parameters were then recorded at the same 2.5 min intervals for a 25 min evaluation period (EP1, EP2, ..., EP9, EP10), in a continuous way in the control group and after achieving the targeted 60% end-tidal nitrous oxide concentration in the nitrous oxide group. The four baseline values of HR, SBP, DBP, MBP, RE and SE were averaged to serve as a reference value for each

patient. Haemodynamic parameters were expressed as mean ± SD and compared during the recording periods (baseline and evaluation period) between groups and within groups, using a two-way mixed-design ANOVA. Tuckey's HSD tests were used for post-hoc comparisons. RE and SE were expressed as mean ± SD in both groups and analysed independently in each group using oneway within subjects ANOVA's. Values recorded during the evaluation period were compared to baseline values using two-tailed Dunnett's tests. Due to the interindividual baseline variability of RE and SE, those parameters were also expressed as percent of each individual baseline value ± SD. Comparisons between and within groups were then performed using a twoway mixed-design ANOVA and Tuckey's HSD for post-hoc comparisons. Normality of distributions was checked as required. A p value less than 0.05 was considered statistically significant.

RESULTS

Two patients in the nitrous oxide group had to be excluded from analysis because of protocol violation. Violation consisted in patient movement or sudden increase in blood pressure (MBP > 100 mmHg) during surgery, reflecting unstable conditions and requiring an additional sufentanil administration and/or an increase in sevoflurane concentration.

Both groups were similar in terms of age, weight, height, sex ratio and ASA status (Table 1). Individual baseline RE and SE values were highly variable in both groups (range 27.4-60.2 and 27.2-58.8, respectively). Nitrous oxide at a 60% end-tidal concentration provoked a significant 37.2 ± 10.3 and 36.9 ± 10.3% decrease in RE and SE, respectively. Absolute RE and SE values in the nitrous oxide group remained significantly lower than baseline throughout the 25 min evaluation period (Fig. 1A). On the contrary, RE and SE

Table 1
Demographic data of nitrous oxide group and control group

	Nitrous oxide group (n = 13)	Control group (n = 10)
Age (years, mean ± SD)	52.7 ± 12.2	45.4 ± 12.3
Height (cm, mean ± SD)	172.2 ± 6.7	168.7 ± 9.7
Weight (kg, mean ± SD)	77.6 ± 10.5	74.6 ± 13.4
ASA I/II	9/4	8/2
Gender (M/F)	8/5	4/6

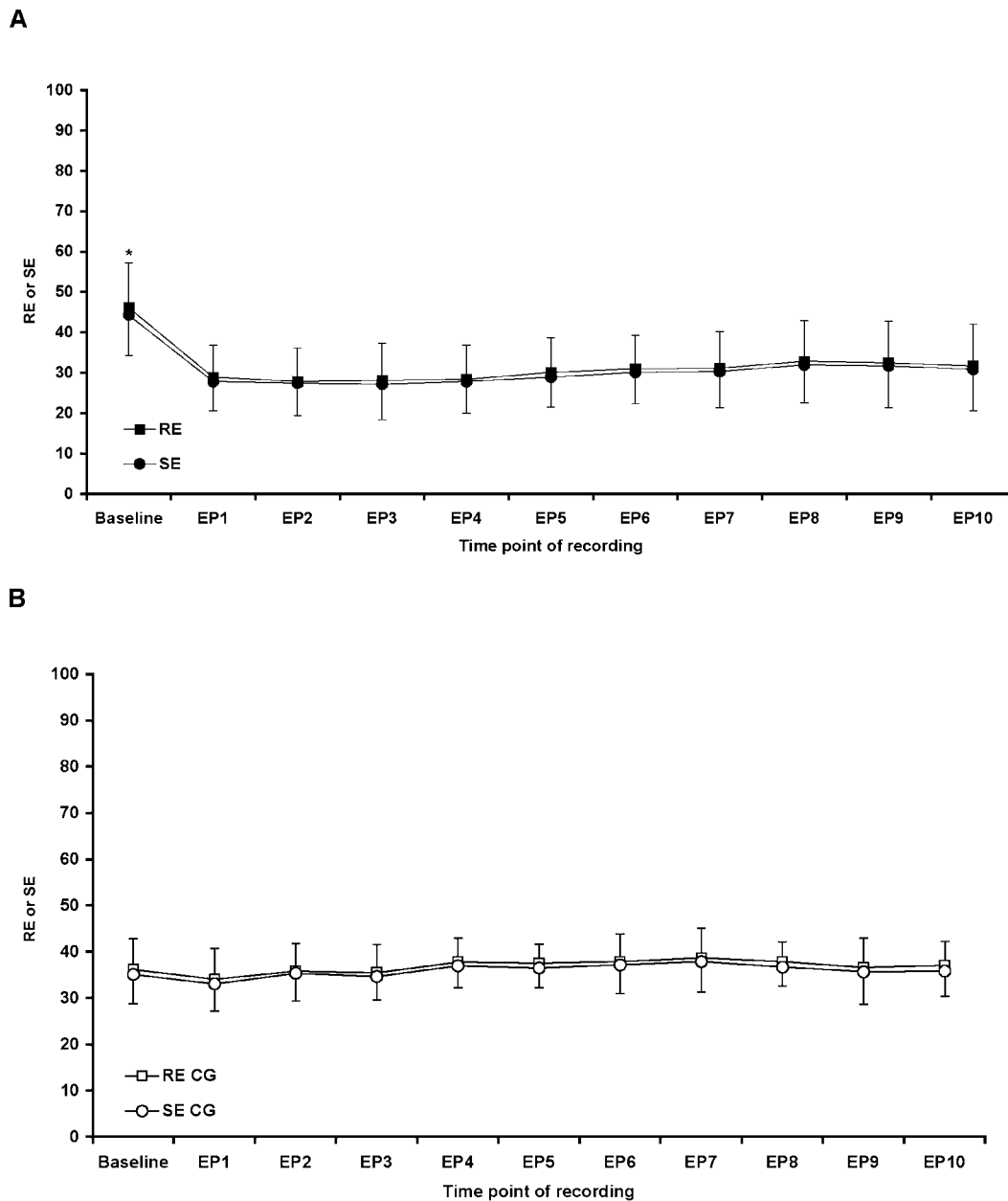


Fig. 1. — A : Absolute values of RE (squares) and SE (circles) recorded in nitrous oxide group during baseline and at the 10 evaluation points (EP1, EP2, ..., EP9, EP10), expressed as mean \pm SD. * = significantly higher than all other points of recording (RE : $F_{(10,120)} = 18.81$, $p < 0.001$, all Dunnett's $d_{(120,11)}$ values > 7 , $p < 0.01$; SE : $F_{(10,120)} = 15.91$, $p < 0.001$, all Dunnett's $d_{(120,11)}$ values > 7 , $p < 0.01$) ; B : Same as A but in control group (RE : $F_{(10,120)} = 2.66$, $p = 0.007$, all Dunnett's d values < 2 , non significant ; SE : $F_{(10,120)} = 2.41$, $p = 0.01$, all Dunnett's $d_{(120,11)}$ values < 2.3 , non significant).

remained remarkably stable during the whole evaluation period and no significant difference was observed with baseline (Fig. 1B). Relative values of RE and SE were significantly lower in the nitrous oxide than in the control group throughout the study, as shown in Figure 2. The difference between RE and SE values did not change significantly in both groups at any time.

A twoway mixed-design ANOVA did not reveal any within or between groups significant

difference in MBP during the whole period of study (Fig. 3A). It revealed a significant main effect of time for HR, but neither main effect of group nor interaction between those two factors. Indeed, HR significantly decreased over time in the whole sample of patients. HR was significantly higher at baseline than at EP4, EP5, EP6, EP7, EP8, EP9 and EP10, and also significantly higher at EP1 than at EP4, EP5, EP6, EP7, EP8 and EP10 (Fig. 3B).

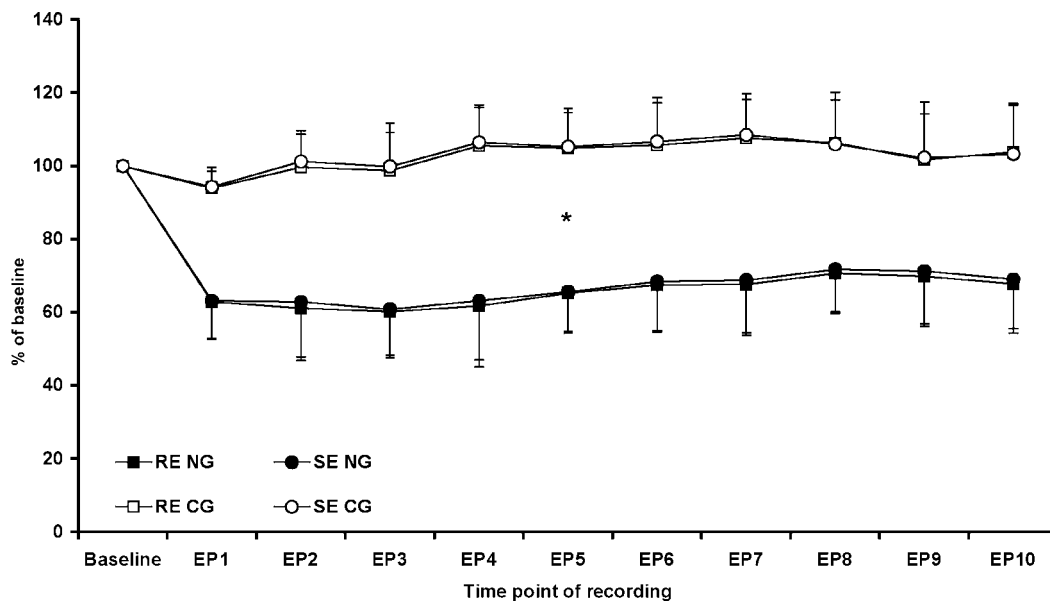


Fig. 2. — RE (squares) and SE (circles) expressed as % of baseline value in nitrous oxide group (closed) and control group (open) and at the 10 evaluation points of recording (EP1, EP2, ..., EP9 and EP10) (mean \pm SD). * = relative value of RE and SE was significantly higher in control group than in nitrous oxide group during the whole evaluation period (Interaction effect : $F_{(10, 210)} = 10.74$ for RE and 9.45 for SE, $p < 0.001$; simple main effects of group at time of recording : $F_{(1, 231)} > 42.03$ for RE and > 37.33 for SE at all time points, $p < 0.001$).

DISCUSSION

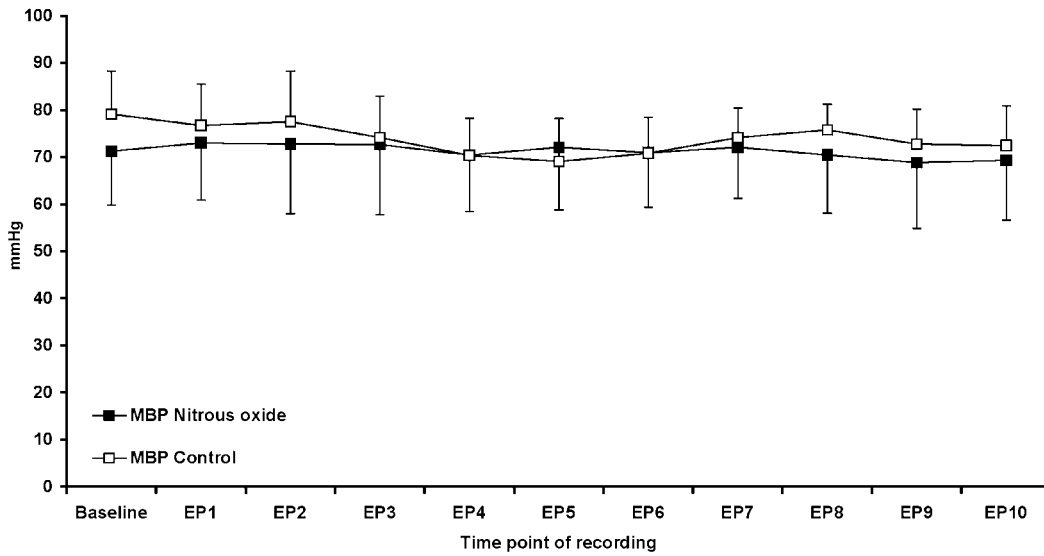
The results of this study show that under general anaesthesia induced with propofol and sufentanil, and maintained with sevoflurane at a constant end-tidal concentration, nitrous oxide administered at 60 volume % produced a significant decrease in Spectral entropy of the EEG without affecting the gradient between RE and SE.

The decrease in entropy globally suggests a deeper level of anaesthesia. It may reflect either a direct increase in the hypnotic depth, or an improvement of analgesia that may secondarily affect the hypnotic component of anaesthesia. Due to its sparing property on hypnotics, nitrous oxide combined to the same end tidal concentration could provoke a deepening in hypnosis reflected by a decrease in entropy. Previous studies performed in volunteers have shown that neither entropy nor BIS is affected by nitrous oxide in the absence of painful stimulations. Anderson and Jakobson reported no modification of entropy at loss of response to verbal commands during induction of anaesthesia with nitrous oxide (1). In another study, 10-50% nitrous oxide had no major sedative effect and affected neither the bispectral index (BIS) nor the spectral edge frequency (10). Finally, inhalation of 70% nitrous oxide has been shown to induce loss of consciousness without any change in BIS (3). However in those studies, nitrous oxide was used

as the sole anaesthetic agent. As emphasized by Sleigh and Barnard, BIS and spectral entropy are primarily indicators of cerebral activity and must be considered to reflect cortical activity rather than level of consciousness (15). According to Kaneda *et al.*, nitrous oxide administration during sevoflurane anaesthesia provokes some deceleration in EEG activity (8). Such a deceleration in EEG activity could be accounted for a decrease in spectral entropy but this hypothesis deserves further investigation. On the other hand, the hypnotic component of anaesthesia may be affected by noxious surgical stimulations that trigger arousal reactions. Indeed, in addition to autonomic and somatic reactions, noxious surgical stimulations may induce some degree of arousal. They have been shown to cause a rightward shift of the EEG concentration-response relationship of desflurane (12). Therefore, under general anaesthesia, surgical stimulations likely modify entropy in the same way that they affect the level of cortical electrical activity measured by the spectral edge frequency, the median frequency and the BIS (12).

In our patients, nitrous oxide did not affect the gradient between RE and SE which remained very low in both groups throughout the study period. It has been hypothesized that in case of insufficient analgesia in non-paralysed patients, EMG facial activity would increase before any change in EEG activity, leading first to an increase in RE and

A



B

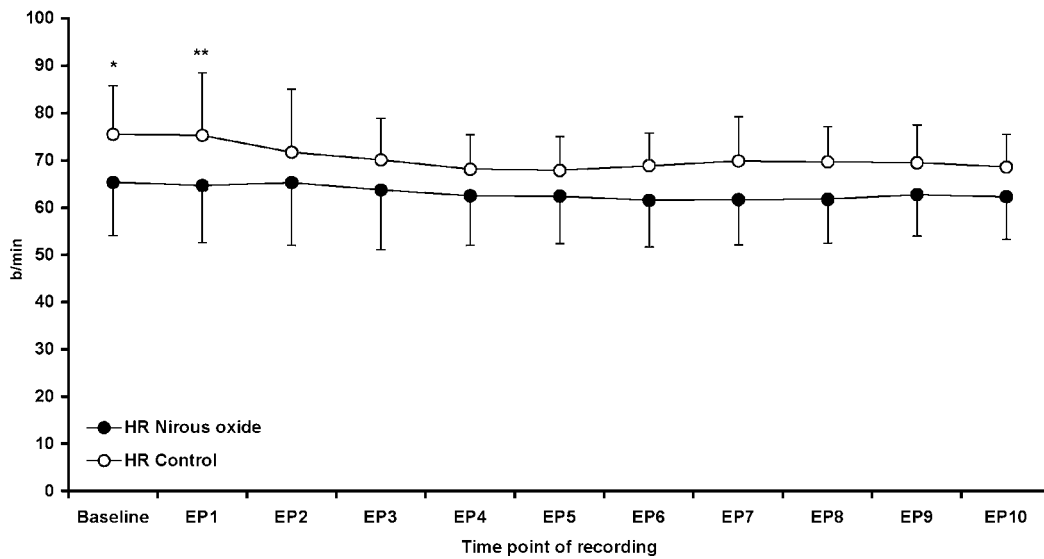


Fig. 3. — MBP (A) and HR (B) recorded in both groups during baseline (Group means \pm SD of the averaged four individual values recorded at 2.5 min intervals) and during the 25 min evaluation period (EP1, EP2, ..., EP9 and EP10, group means \pm SD of individual values recorded at 2.5 min intervals). * = significantly higher than EP4, EP5, EP6, EP7, EP8, EP9 and EP10 when considering all subjects together. ** = significantly higher than EP4, EP5, EP6, EP7, EP8 and EP10, when considering all subjects together (Main effect of time : $F_{(10, 210)} = 5.16$, $p < 0.001$; Tuckey's HSD : $q_{(210)}$ always > 5.01 for each of the above-mentioned significant difference, p at least < 0.05).

consequently in the RE-SE gradient before any change in SE. Should that hypothesis proven correct by appropriate studies, our results would not support a substantial improvement of the analgesic state to explain the effect of nitrous oxide on entropy since no significant difference between RE and SE was observed. However, such an effect of

painful stimulations on RE might be of short duration and not easily detectable in our patients, according to the study design.

The high interindividual variability in baseline entropy value observed in our patients is in agreement with the study of Vanluchene et al. who reported a wide range of RE and SE values versus

propofol effect-site concentration (16). It incited us to consider individual trends rather than absolute values for evaluating the adequacy of depth of anaesthesia.

The pharmacodynamic interaction of nitrous oxide with different volatile anaesthetics has already been investigated in surgical patients by measuring the EEG median power frequency and using isobolographic analysis (13). Considering the EEG median power frequency as the target end-point, it was reported to be compatible with additivity (13). In our patients, addition of nitrous oxide at 60 volume % to 2% end-tidal sevoflurane concentration roughly yielded a 60% increase in MAC-incision (from 1 to 1.6). As a result of that effect, the mean decrease in entropy amounted \approx 40%. However such a comparison must be considered as inaccurate. Indeed, the MAC concept relies on the suppression of movement after painful stimuli, which is an anaesthetic action localized in the spinal cord and independent from anaesthetic action in the brain (2, 9, 11). Hence from that viewpoint, entropy should behave like the BIS or other EEG parameters and be devoid of any predictability regarding patient movement in response to noxious stimulations. In this regard, the two patients who were excluded from the study exhibited a sudden and unexpected important increase in entropy during surgery that was resolved by deepening the level of anaesthesia. Therefore, caution should be paid when extreme values are observed and prediction of future events should not be expected from the use of spectral entropy, as it has already been stated for other currently available monitors (14).

In this study, baseline values were recorded simultaneously during surgery in all patients. According to randomization, the recording was then continued without interruption in the control group but delayed by approximately 15 minutes in the nitrous oxide group until the 60% end tidal concentration was achieved. Hence, we acknowledge a potential limitation that includes a different timing of measurement in the two groups during the evaluation period. The registration delay in the study group introduces a bias and could affect the data regarding the effects of premedication, medications used at induction (propofol, sufentanil and rocuronium) and surgical stimulation. This methodological flaw cannot be ignored, nor the study limitation ruled out. However, the premedication consisting in alprazolam 0.5 mg was very weak. Patients from both groups were perfectly conscious at admission in the operating room and had comparable entropy values before induction of anaesthesia, compatible

with a fully awake state (i.e. higher than 90). The most critical concern lies in the balance between the residual effect of sufentanil and the degree of surgical stimulation. No difference was observed in MBP and HR between groups, which could have reflected a difference in the balance between depth of anaesthesia and painful surgical stimulation. In addition, the profile of entropy values differed in the two groups during the evaluation period. Compared to baseline, RE and SE values decreased and remained significantly lower in the nitrous oxide group while they did not change over time in the control group. Finally, lumbar disc surgery is commonly considered as a weak painful procedure without any particular period of intense stimulation.

In conclusion, addition of nitrous oxide to balanced anaesthesia with sufentanil and sevoflurane significantly reduced spectral entropy of the EEG in lumbar disc surgery patients. Further investigations are still required to define if entropy could be used to monitor the interaction between nitrous oxide and sevoflurane at different times, using other drug combinations or in other patient conditions.

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