Entropy of the electroencephalogram as applied in the M-Entropy S/5™ Module (GE Healthcare) during increases in nitrous oxide and constant sevoflurane concentrations

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Keywords: monitoring; depth of anaesthesia; monitoring; electroencephalography; monitoring; entropy; anaesthetics volatile; sevoflurane; anaesthetic gases; nitrous oxide

Abstract

Background: It has been suggested that spectral entropy of the electroencephalogram as applied in the M-Entropy S/5™ Module (GE Healthcare) does not detect the effects of nitrous oxide (N₂O). The aim of this study was to investigate the effect on entropy by graded increases in N₂O concentrations in the presence of a constant concentration of sevoflurane, in the absence of surgical stimulation.

Method: This single-blind, randomised study was conducted at an altitude of approximately 1 400 m. Patients received sevoflurane 2% (1.7% at sea level) and N₂O, at end-tidal concentrations of 0%, 10%, 20%, 30%, 40%, 50%, 60% or 70% (equivalent to 8.5%, 17%, 25.5%, 34%, 42.6%, 51.1% and 59.6% at sea level). Entropy was measured before, during and after N₂O administration. The absolute changes and ratios of entropy relative to the baseline were calculated. Between- and within-group comparisons were made using analysis of variance and covariance.

Results: None of the entropy variables differed significantly within and between groups before and after N₂O administration. Within-group analysis revealed that entropy during N₂O administration was significantly lower than before or after N₂O administration (P < 0.007). While a minor clinical but statistically significant linear relationship was observed between increasing N₂O concentration and decreasing entropy from N₂O 0% to 60%, a steeper and clinically important decrease (relative change > 20%) was noted at N₂O > 60% (> 51% at sea level).

Conclusions: The M-Entropy Module S/5TM responds to increasing concentrations of N₂O in the presence of 2% (1.7% at sea level) sevoflurane, in the absence of surgical stimulation. There is a linear relationship between increasing N₂O concentrations and decreasing entropy with a steep and clinically important decrease at N₂O > 60% (> 51% at sea level). The influence of ambient pressure on the partial pressures, which determine the effects of anaesthetic agents, must be taken into account.

Introduction

Spectral entropy of the electroencephalogram (EEG) as applied by the M-Entropy S/5™ Module (GE Healthcare, Instrumentarium, Helsinki, Finland) is one of several electrophysiologic monitors that have been promoted to assess the level of consciousness during sedation and anaesthesia.1,2 Anaesthetic drugs exert certain group-specific effects on the EEG, the diversity of which may influence the ability of various EEG-based monitors to evaluate consciousness, particularly when drugs with differing EEG effects are administered concurrently.

The EEG changes that are associated with nitrous oxide (N₂O) include decreases in frequency and amplitude in the alpha waveband and increases in the high beta waveband (> 30 Hz). These changes are accompanied by analgesia and depressed consciousness.3 N-methyl-D-aspartate (NMDA) anta-
gonists, such as \(\text{N}_2\text{O}\), may produce anaesthesia by central overexcitation. EEG-based monitors cannot distinguish between an anaesthetic state that is induced by \(\gamma\)-amino butyric acid A (GABA\(_A\)) agonists, such as anaesthetic vapours, and NMDA antagonists, such as \(\text{N}_2\text{O}\).\(^4\)

Anderson and Jakobsson reported that in the absence of other anaesthetics, loss of consciousness during administration of \(\text{N}_2\text{O}\) up to a concentration of 75% was not associated with a change in entropy of the EEG as measured with the M-Entropy Module S/5\(^\text{TM}\).\(^5\) It has therefore been suggested that that monitor is insensitive to the EEG changes that are brought about by \(\text{N}_2\text{O}\) administration.\(^6\) In contrast, when the alveolar concentration of sevoflurane or isoflurane or halothane was kept at 1 MAC, the addition of \(\text{N}_2\text{O}\) 66% resulted in increased entropy, but there was no change at 1.5 MAC of those agents.\(^7\) It therefore appears that the effect of \(\text{N}_2\text{O}\) on entropy depends on the relative concentrations of the concomitantly administered volatile agent and \(\text{N}_2\text{O}\).

The aim of this study was to investigate the effects exerted by various concentrations of \(\text{N}_2\text{O}\) (0% to 70%) on entropy of the EEG, as measured by the M-Entropy S/5\(^\text{TM}\) Module, in the presence of a constant concentration (2%) of sevoflurane in the absence of surgical stimulation. The null hypothesis was that \(\text{N}_2\text{O}\) would have no effect on entropy.

**Patients and methods**

This study was approved by the local Institutional Research Ethics Committee. Informed consent was obtained from all participants. The sample comprised 80 consecutive patients older than 18 years and of American Society of Anesthesiologists (ASA) I physical status who presented for elective surgery. Patients were excluded if endotracheal intubation was not planned, if they were on psychotropic medication or when \(\text{N}_2\text{O}\) was contraindicated.

This was a single-blind, randomised, interventional study. Patients were divided into eight groups of 10 patients each by means of a computer-based randomisation method. An envelope containing the group number (0%, 10%, 20%, 30%, 40%, 50%, 60% or 70%) was drawn before induction of anaesthesia. Entropy of the EEG was recorded using an S/5\(^\text{TM}\) entropy module, in the presence of a constant concentration (2%) of sevoflurane in the absence of surgical stimulation. The null hypothesis was that \(\text{N}_2\text{O}\) would have no effect on entropy.

In order to avoid confusion, end-tidal nitrous oxide concentrations are expressed as volumes percent at 1 400 m with the equivalent percentage at sea level enclosed within square brackets, for example 70% [59.6%]. All entropy recordings were made before surgical stimulation. The entropy module updates the display every second. After readings had stabilised, entropy was recorded manually about every 10 seconds over one minute and averaged. Patients received a standard premedication of midazolam 7.5 mg orally, two hours preoperatively. Anaesthesia was induced using propofol 1–2 mg.kg\(^{-1}\) and vecuronium 0.1 mg.kg\(^{-1}\). Sevoflurane was washed into the circle anaesthetic breathing system with oxygen and air (FiO\(_2\) of 0.5) by means of a total fresh gas flow of 6 l/minute.\(^1\) After stabilisation of the end-tidal sevoflurane concentration at 2% [1.7%] for five minutes, response entropy (RE) and state entropy (SE) were recorded (designated RE1 and SE1 respectively). Thereafter, patients were administered a concentration of \(\text{N}_2\text{O}\) in accordance with the random allocation (end-tidal concentrations of 0% to 70% [59.6%]) that had been made to that particular group. The \(\text{N}_2\text{O}\) was washed in with a total fresh gas flow of 6 l/minute.\(^1\) Five minutes after the end expired concentration of \(\text{N}_2\text{O}\) had stabilised at the targeted concentration, RE and

| % at 1 400 m | kPa at 1 400 m | % at sea level |
|-------------|---------------|---------------|
| 2           | 1.72          | 1.70          |
| 10          | 8.60          | 8.51          |
| 20          | 17.20         | 17.03         |
| 30          | 25.80         | 25.54         |
| 40          | 34.40         | 34.06         |
| 50          | 43.00         | 42.57         |
| 60          | 51.60         | 51.09         |
| 70          | 60.20         | 59.60         |
SE were again recorded (designated RE2 and SE2 respectively). N₂O was subsequently turned off and replaced with air. Five minutes after the end expired concentration of N₂O had returned to zero, RE and SE were again recorded (RE3 and SE3 respectively). Surgery was then allowed to proceed and sevoflurane concentrations and fresh gas flows were adjusted as necessary.

The following calculations were performed:
- The absolute changes in entropy (i.e. the differences between SE1 and SE2 as well as RE2 and RE1). These differences are abbreviated as SEC2 and REC2 respectively.
- The relative changes in entropy (i.e. the ratios of SE2 to SE1 and RE2 relative to RE1). These ratios are abbreviated as SER2 and RER2 respectively. Changes in entropy of more than 20% (ratios < 0.8) were regarded as constituting a clinically important change.
- Equivalent minimum alveolar concentration (EMAC) in accordance with the formula\(^8\):
\[
\text{EMAC} = \left(\frac{[\text{sevoflurane}]}{2.1}\right) + \left(\frac{[\text{N}_2\text{O}]}{120.9}\right).
\]
This formula, valid at sea level, was adjusted for altitude, namely EMAC\(^9\)
\[
\text{EMAC} = \text{EMAC}\times0.99.
\]

**Statistical methods**

Data are reported as means, standard deviations and 95% confidence intervals (CI). To test for trend over N₂O concentrations, the treatment groups were initially compared with respect to entropy and change in entropy (absolute changes and ratios) with N₂O using one-way analysis of variance (ANOVA) as well as analysis of covariance (ANCOVA) with baseline values (SE1 and RE1) as covariates. This was followed by testing the contrasts for linear trend using Scheffe's F method. The sample size of 10 subjects per group exceeded that required by convention, where at least 30 degrees of freedom for error is required, namely 48 (six per group). Pairwise comparisons between groups were done using Fisher’s least significant differences. Within groups, ANOVA for repeated measures was employed to assess actual changes and ratios relative to baseline. Categorical variables were compared using the \(\chi^2\) test. Testing was done at a significance level of 5% (\(P < 0.05\)). Data analysis was performed using statistical computer software (Statistix 8, Analytical Software Tallahassee FL).

**Results**

Complete data were collected from 80 patients, that is, 10 patients in each group. The data are presented in Table II. Due to limited space, observations at 10%, 30% and 50% are omitted from the table but are available on request.

![Table II: Demographics and entropy measurements of the various groups receiving nitrous oxide](chart.png)
did not differ significantly when both between-group and within-group comparisons were done (ANOVA). Within the groups, except for the 0% group, entropy was statistically significantly lower during N₂O administration than before or after N₂O administration (P < 0.007) (see Table II and Figure 1). At N₂O 70% [59.6%], entropy was significantly less than the values obtained at all the other concentrations (P < 0.0001). In all the groups SE1 as covariate had a significant influence on SE2 and on SEC2 (P < 0.04) but not on SER2. With ANCOVA the differences between groups were more significant for entropy after the addition of N₂O (SE2), namely P < 0.0001.

There were progressive decreases in mean entropy values as N₂O concentrations increased, but these differences were statistically insignificant until exposure to 70% [59.6%] N₂O. For example, at 60% [51.1%] N₂O, mean SEC2 was -4.80 (95% CI -5.45 to -4.14) whereas at 70% [59.6%] N₂O, SEC2 was -21.4 and significant (95% CI -31.5 to -11.2). Entropy ratios (SER2) in group N₂O 70% [59.6%] (0.54; CI 0.37 to 0.70) were significantly less than in group 40% [34.1%] N₂O (0.90; 95% CI 0.88 to 0.91), which in turn were significantly less than in group 0% N₂O (0.99; 95% CI 0.98 to 1.01) (see Table II, Figure 1). N₂O 70% [59.6%] was also the only concentration at which the change in entropy (actual and ratio) was both statistically significant and clinically important (i.e. a change of 20% or more).

The association between N₂O concentrations and entropy values was assessed using Scheffe’s F method for testing linear trend. Linearity was tested over all N₂O concentrations as well as with the omission of the 70% [59.6%] group. In both cases, a significant trend was found to exist (P < 0.0001). Note that at N₂O 70% [59.6%] a steep and clinically significant change (decrease > 20%) was demonstrated (see figures 1 and 2).

The main finding of this study is that the addition of end-tidal N₂O (0% to 70% [59.6%]) to a constant end-tidal concentration of sevoflurane (2% [1.7%]) is accompanied by a significant, dose-dependent, downward trend in entropy ratios, with a steep and clinically important decrease observed at N₂O 70% [59.6%].

Discussion
In this study, we investigated the effect of increases in end-tidal N₂O concentrations from 0% to 70% [59.6%] on entropy of the EEG as assessed by the M-Entropy S/5® Module (GE Healthcare) in the presence of a fixed end-tidal concentration of 2% [1.7%] sevoflurane in the absence of surgical stimulation. We demonstrated significant decreases in entropy with the addition of increasing concentrations of N₂O. Within groups, except for the control group (N₂O 0%), the administration of N₂O was associated with statistically significantly lower entropy values than those measured before or after N₂O. We therefore rejected the null hypothesis.

Although we could demonstrate a significantly downward trend of entropy values with increasing N₂O concentrations, an important decrease was only reached at N₂O > 60% [51.1%]. The entropy module was nonetheless able to detect gradual changes in frontal cortical
EEG. The potentiation of sevoflurane by N₂O observed in our study corresponds with the clinical effects noted by sevoflurane-N₂O studies that involved noxious stimuli. Fragan and Dunn demonstrated that N₂O 65% suppressed movement during surgery by 50% in the presence of 1 MAC of sevoflurane. At an intubation MAC of sevoflurane (2.33%), N₂O 66% decreased the intubation response (movement during intubation) by 40%. The MAC of sevoflurane for the insertion of a laryngeal mask in children (1.57%) was decreased by 49% with the addition of 67% of N₂O. N₂O 65% suppressed movement during surgical incision by 50%. N₂O 66% decreased the response to intubation by 40% and N₂O 67% attenuated the response to laryngeal mask insertion by 49%. In our study, during administration of N₂O 59.6% at sea level (1.4 EMAC) there was a decrease in entropy of about 46%. In the aforementioned studies, N₂O concentrations were > 65%. There appears to be an N₂O concentration threshold at about 60% in the presence of approximately 2% sevoflurane above which enhancement of the cortical effect of sevoflurane is significantly greater than at lower N₂O concentrations.

This apparent threshold effect of N₂O may be explained by the cortical and subcortical activities of anaesthetic agents. The effect of the volatile anaesthetics on consciousness probably involve mainly cortical structures, while N₂O may disrupt subcortical activity. Hans et al are of the opinion that the decreases in BIS and 95% spectral edge frequency (SEF95) that they observed with increasing N₂O concentrations during surgical stimulation may reflect either a direct increase in the hypnotic effects or increased analgesia that may secondarily affect the hypnotic component of anaesthesia. This was explained by the predominantly subcortical antinociceptive action of N₂O combined with a weak depressant effect on cortical neurons.

Subanaesthetic concentrations of sevoflurane decrease the analgesic effect of N₂O, which is explained by the stimulation by supraspinal GABAₐ agonists, such as volatile anaesthetics and benzodiazepines. The interplay of mechanisms may explain the differences in the EEG effects that have been observed during different drug concentrations and combinations. The interaction between N₂O and volatile anaesthetics is often quantified as a calculation of EMAC. As N₂O and vapours have different, albeit overlapping, modes of action, the concept of EMAC should be further considered. An EMAC of, for example, 1.5 can be achieved by different sevoflurane/N₂O combinations, for example 1.5/78; 2/52; 2.5/26; and 3/0 (% at sea level). In our study, the EMAC was increased from 0.8 to 1.4 by keeping end-tidal sevoflurane constant at 2% [1.7%] and adding N₂O. In other studies, vapour concentrations were decreased as N₂O concentrations were increased to maintain a constant EMAC. This approach may shift the balance between the cortical and subcortical effects of the drugs.

Concomitant administration of GABA receptor agonists may have an impact on N₂O analgesia. Orii et al have demonstrated that GABA-ergic neurons differentially modulate the antinociceptive effects of N₂O at supraspinal and spinal levels. N₂O stimulates the release of endogenous opioid peptides. Stimulation of opioid receptors by these peptides inhibits the inhibitory supraspinal GABA-ergic pathway, causing disinhibition (stimulation) of the descending noradrenergic pathways. Activation of the noradrenergic pathways modulates spinal pain processing by two different pathways. One pathway involves noradrenaline-induced activation of α₂ adrenoceptors. Activation of the α₂ receptors inhibits neurotransmission in the primary afferent neuron by presynaptic inhibition of the release of calcitonin gene-related peptide and substance P and by inhibiting activation of ascending second order neurons. The other adrenergic pathway involves activation of inhibitory spinal GABA-ergic neurons through α₂ adrenoceptors. GABA is therefore pronociceptive supraspinally but antinociceptive at spinal level. Orii et al demonstrated in rats that midazolam has a mainly supraspinal effect that attenuates the antinociceptive effect of N₂O. They suggested that if these findings are extrapolated to humans, the analgesic effect of N₂O might be attenuated by systemically administered midazolam.

The patients in our study received midazolam as premedication and propofol as induction agent. In some studies, no premedication was allowed, while in others, intravenous induction agents were avoided and anaesthesia was induced using a volatile anaesthetic and/or N₂O. Although GABAₐ agonists, such as midazolam, may decrease the analgesic effect of N₂O, a small dose (7.5 mg) was administered two hours preoperatively in our study. It is therefore unlikely that it exerted a significant influence at the time of induction of anaesthesia.

The relationship between altitude and the effect of anaesthetic vapours and gases must be considered. The S/5™ module used in our study measures ambient pressure every 30 minutes and is calibrated accordingly. According to the manufacturer, the
monitor reflects the relative concentrations of gases, in other words percentages (not partial pressures). The sevoflurane vapour and N\textsubscript{2}O concentrations in the fresh gas flows were adjusted until the end-tidal gas concentrations stabilised at the target levels. The partial pressures (kPa) of N\textsubscript{2}O, sevoflurane and O\textsubscript{2} were therefore lower than at sea level. At 1 400 m, 2% sevoflurane exerts only 1.72 kPa, while 2 kPa at our altitude is about 2.3% by volume.

Administering high concentrations of N\textsubscript{2}O at high altitudes may give rise to hypoxic inspiratory gas mixtures. When 70% N\textsubscript{2}O is added to fresh gas in a circle system at 1 400 m, and taking into account the effect of sevoflurane 2% and water vapour of about 2%, the oxygen concentration delivered to the patient is about 28% (22.4 kPa).

There are aspects of our study design and methods that could be confounders. With regard to the wash-in and wash-out times, using a fresh gas flow of 6 l\cdot minute\textsuperscript{-1}, the low blood-gas partition coefficient of N\textsubscript{2}O ensures rapid attainment of steady-state levels. After end-tidal N\textsubscript{2}O concentrations and entropy had stabilised, a further five minutes were allowed before observations were made; the wash-in and wash-out times were therefore of the order of 10 minutes. N\textsubscript{2}O reaches approximately 90% equilibration within 10 minutes.\textsuperscript{26}

Our study was done before surgery commenced, which may explain why some of our findings differ from those of other studies. Furthermore, opioids were avoided until after the final observation had been made. Surgical stimuli increase cortical electrical activity as measured by BIS, SEF95 and median power frequency.\textsuperscript{27} Using the same entropy module as we did during surgical stimulation, Soto et al.\textsuperscript{24} and Prabhakar et al.\textsuperscript{7} found increased entropy after the addition of N\textsubscript{2}O during volatile agent administration. Prabhakar et al.\textsuperscript{21} observed an increase in entropy in the presence of N\textsubscript{2}O 66% and isoflurane or sevoflurane adjusted to an EMAC of 1.0 but a nonsignificant decrease when end-tidal vapour concentrations were kept constant at 1.1% and 2% with the addition of N\textsubscript{2}O 66% (1.5 EMAC). Our findings concur partly with the finding of Soto et al.\textsuperscript{24} During laparoscopy, they demonstrated a dual effect of N\textsubscript{2}O on entropy: When > 65% N\textsubscript{2}O was added to 2% sevoflurane, entropy decreased. When the sevoflurane concentration was decreased to maintain EMAC at 1.3, entropy increased. In our study, the decrease in entropy was approximately twice the decrease observed in their study when N\textsubscript{2}O was added to 2% sevoflurane (1.7% at sea level). This may be due to the absence of surgical stimulation in the presence of sevoflurane and at an EMAC value greater than unity. It therefore appears that entropy decreases with the addition of > 60% N\textsubscript{2}O to approximately 1 MAC sevoflurane and that this occurs in the presence of as well as in the absence of noxious stimuli.

Our protocol differed from the usual anaesthetic practice. Most patients are anaesthetised for the performance of painful procedures and will often receive opioids, which potentiate the analgesic effect of N\textsubscript{2}O.\textsuperscript{18} Furthermore, most anaesthetists administer N\textsubscript{2}O at a constant concentration and adjust the dosage of the primary hypnotic (vapour or intravenous agent) to deepen anaesthesia. However, in order to demonstrate the potentiating effect of N\textsubscript{2}O on the cortical effect of sevoflurane, as represented by entropy of the EEG, it was necessary to avoid the confounding influence of the effects of surgery.

This study highlights one of the factors that confound the interpretation of anaesthetic depth by EEG monitoring. Is entropy as applied by the M-Entropy S/5\textsuperscript{TM} Module blind to the effect of N\textsubscript{2}O? Probably not, but the effect of N\textsubscript{2}O depends on its partial pressure and on the presence and doses of other suppressants and stimulants of the central nervous system. We agree with the opinion that Jantti and Alahuhta expressed, namely that there is no uniform EEG spectral entropy, but entropy varies with the range of anaesthetic concentrations that we encounter in clinical practice.\textsuperscript{28}

**Conclusion**

We have demonstrated that the M-Entropy S/5\textsuperscript{TM} Module is not blind to N\textsubscript{2}O in the presence of 2% [1.7%] of sevoflurane in the absence of surgical stimulation. We found that a linear relationship exists between the change in entropy and end-tidal concentrations of N\textsubscript{2}O ≤ 60% with a steep and clinically important decrease at N\textsubscript{2}O = 70% [59.6%]. When comparing these results with those from previous studies, the influence of ambient pressure on the partial pressures, and therefore the effect of anaesthetic agents, must be taken into account.

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