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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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 (N_2O). The aim of this study was to investigate the effect on entropy by graded increases in N_2O 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 N_2O, 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 N_2O administration. The absolute changes and ratios o f 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 N_2O administration. Within-group analysis revealed that entropy during N_2O administration was significantly lower than before or after N_2O administration ($P < 0.007$). While a minor clinical but statistically significant linear relationship was observed between increasing N_2O concentration and decreasing entropy from N_2O 0% to 60%, a steeper and clinically important decrease (relative change > 20%) was noted at N_2O > 60% (> 51% at sea level).

Conclusions: The M-Entropy Module S/5TM responds to increasing concentrations of N_2O in the presence of 2% (1.7% at sea level) sevoflurane, in the absence of surgical stimulation. There is a linear relationship between increasing N_2O concentrations and decreasing entropy with a steep and clinically important decrease at N_2O > 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.

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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 (N_2O) 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 N_2O, may produce anaesthesia by central overexcitation. EEG-based monitors cannot distinguish between an anaesthetic state that is induced by γ-amino butyric acid A ($GABA_A$) agonists, such as anaesthetic vapours, and NMDA antagonists, such as N_2O.[4]

Anderson and Jakobusson reported that in the absence of other anaesthetics, loss of consciousness during administration of N_2O 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™.[5] It has therefore been suggested that that monitor is insensitive to the EEG changes that are brought about by N_2O administration.[6] In contrast, when the alveolar concentration of sevoflurane or isoflurane or halothane was kept at 1 MAC, the addition of N_2O 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 N_2O on entropy depends on the relative concentrations of the concomitantly administered volatile agent and N_2O.

The aim of this study was to investigate the effects exerted by various concentrations of N_2O (0% to 70%) on entropy of the EEG, as measured by the M-Entropy S/5™ Module, in the presence of a constant concentration (2%) of sevoflurane in the absence of surgical stimulation. The null hypothesis was that N_2O 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 N_2O 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™ entropy module and the end-tidal sevoflurane and N_2O concentrations using an S/5™ gas module (GE Healthcare, Instrumentarium Corporation, Helsinki, Finland).

This study was performed at an altitude of about 1 400 m. The ambient pressure at this altitude is about 86 kPa as compared with 101 kPa at sea level. The percentages of anaesthetic gases displayed by the gas module actually represent partial pressures expressed as percentages of ambient pressure. Therefore, partial pressures measured at altitude will comprise lower proportions (percentages) at sea level. The following corrections are therefore necessary when interpreting the measurements (%): Partial pressure (kPa) at altitude = percentage displayed on monitor x (ambient pressure at altitude); for example, the partial pressure of 70% of N_2O at 1 400 m = 0.70 x 86 kPa = 60.2 kPa. At sea level, the anaesthetic gas monitor will reflect this partial pressure as (60.2/101) x 100 = 59.6% (see Table I).

Table I: Conversion of percentage at 1 400 m to percentage at sea level

% 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

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 N_2O in accordance with the random allocation (end-tidal concentrations of 0% to 70% [59.6%]) that had been made to that particular group. The N_2O was washed in with a total fresh gas flow of 6 $l.minute^{-1}$.Five minutes after the end expired concentration of N_2O had stabilised at the targeted concentration, RE and

SE were again recorded (designated RE2 and SE2 respectively). N_2O was subsequently turned off and replaced with air. Five minutes after the end expired concentration of N_2O 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] EMAC = ([sevoflurane]%/2.1%) + ([N_2O]%/104%). This formula, valid at sea level, was adjusted for altitude, namely EMAC = ([sevoflurane]%/2.4%) + ([N_2O]%/120.9%).

Statistical methods

Data are reported as means, standard deviations and 95% confidence intervals (CI). To test for trend over N_2O concentrations, the treatment groups were initially compared with respect to entropy and change in entropy (absolute changes and ratios) with N_2O 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). Pair-wise 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 χ^2 test. Testing was done at a significance level of 5% ($P < 0.05$). Data analysis was performed using statistical computer software (Satistix 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

Demographics						P*
Male/ female	2/8	5/5	5/5	4/6	3/7	0.2114
Age (year)	48.6 (23.3)	38.4 (19.4)	45.7 (13.7)	39.9 (12.4)	38.4 (18.1)	0.4227
Entropy measurements						
N_2O [N_2O] EMAC	**0% 8.5% 0.82**	**20% 17.0% 0.99**	**40% 25.5% 1.15**	**60% 34.1% 1.32**	**70% 42.6% 1.40**	**P***
SE1	42.7 (10.9)	43.3 (11.4)	40.2 (7.0)	45.2 (7.2)	47.5 (12.7)	0.5682
SE2	42.4 (10.7)	41.2 (10.9)	36.2 (6.6)	40.4 (6.9)	26.1 (14.1)	0.0146
SE3	42.6 (10.6)	43.3 (11.6)	39.7 (7.0)	45.1 (6.6)	47.4 (12.4)	0.5656
SEC2	-0.3 (0.9)	-2.1 (0.9)	-4.0 (0.9)	-4.8 (0.9)	-21.4 (14.2)	<0.0001
SER2	0.99 (0.02)	0.95 (0.01)	0.90 (0.02)	0.89 (0.02)	0.54 (0.23)	<0.0001
RE1	43.4 (11.6)	44.9 (11.3)	40.8 (7.0)	46.0 (7.3)	48.1 (13.1)	0.5591
RE2	43.0 (11.2)	42.9 (11.2)	37.1 (6.8)	41.4 (6.6)	26.6 (14.5)	0.0131
RE 3	43.4 (11.2)	45.1 (11.6)	40.6 (6.9)	46.2 (6.8)	48.4 (12.1)	0.5102
REC2	-0.4 (1.0)	-2.0 (0.7)	-3.7 (1.3)	-4.6 (1.3)	-21.5 (14.8)	<0.0001
RER2	0.99 (0.02)	0.95 (0.02)	0.91 (0.03)	0.90 (0.02)	0.54 (0.24)	<0.0001

N_2O = end-tidal nitrous oxide concentration in volume percent.
[N_2O] = equivalent end-tidal nitrous oxide concentration at sea level in volume percent.
Results are expressed as mean (standard deviation).
*χ^2 test for male/female and ANOVA for the rest.
SE1, SE2 and SE3 = state entropy before, during and after N_2O administration respectively.
RE1, RE2 and RE3 = response entropy before, during and after N_2O administration respectively.
SEC2 and REC2 = change in state entropy and in response entropy during N_2O administration.
SER2 and RER2 = ratio of state entropy and of response entropy during N_2O administration relative to baseline.
EMAC = calculated equivalent MAC with 2% of sevoflurane, adjusted for altitude.

As similar findings were obtained regarding RE and SE, only SE variables were explored further and will hence be referred to as 'entropy'. Mean entropy values obtained before and after N_2O administration

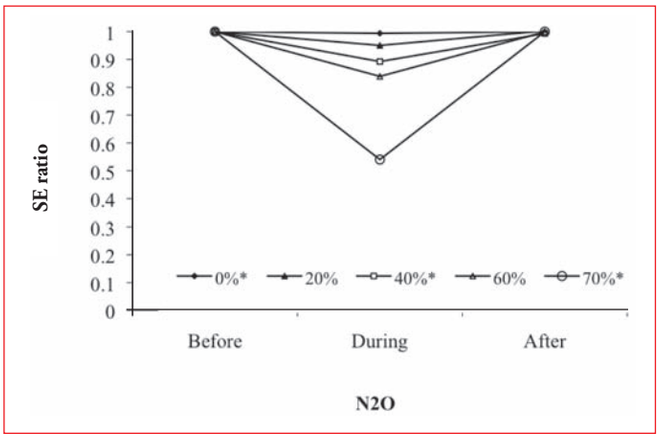
did not differ significantly when both between-group and within-group comparisons were done (ANOVA). *Within* the groups, except for the 0% group, entropy was statistically significantly lower during N_2O administration than before or after N_2O administration ($P < 0.007$) (see Table II and Figure 1). At N_2O 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 N_2O (SE2), namely $P < 0.0001$.

There were progressive decreases in mean entropy values as N_2O concentrations increased, but these differences were statistically insignificant until exposure to 70% [59.6%] N_2O. For example, at 60% [51.1%] N_2O, mean SEC2 was -4.80 (95% CI -5.45 to -4.14) whereas at 70% [59.6%] N_2O, SEC2 was -21.4 and significant (95% CI -31.5 to -11.2). Entropy ratios (SER2) in group N_2O 70% [59.6%] (0.54; CI 0.37 to 0.70) were significantly less than in group 40% [34.1%] N_2O (0.90; 95% CI 0.88 to 0.91), which in turn were significantly less than in group 0% N_2O (0.99; 95% CI 0.98 to 1.01) (see Table II, Figure 1). N_2O 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 N_2O concentrations and entropy values was assessed using Scheffe's F method for testing linear trend. Linearity was tested over all N_2O 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 N_2O 70% [59.6%] a steep and clinically significant change (decrease > 20%) was demonstrated (see figures 1 and 2).

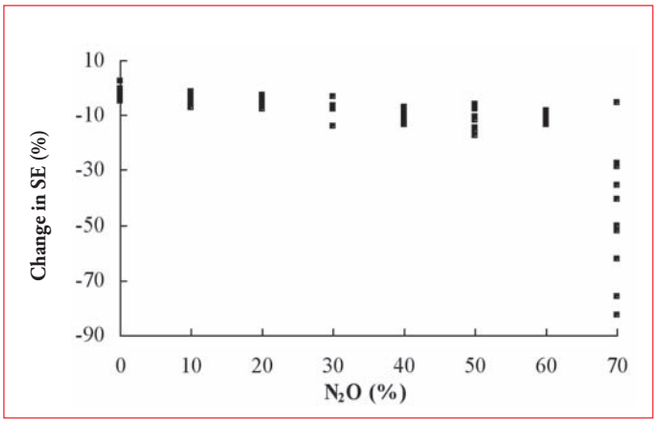
The main finding of this study is that the addition of end-tidal N_2O (0% to 70% [59.6%]) to a constant end-tidal concentration of sevoflurane (2% [1.7%]) is accompanied by a significant, dose-dependent, downward trend in entropy ratios, with a steep and clinically important decrease observed at N_2O 70% [59.6%].

Figure 1: SE ratios before, during and after various end-tidal N_2O concentrations at 1 400m



*Ratios during N_2O administration differed significantly from each other (ANCOVA; $P < 0.0001$). Except for the 0% group, ratios differed significantly in comparison with before and after N_2O ($P < 0.007$).

Figure 2: Percentage change in SE with increasing end-tidal concentrations of N_2O at 1 400 m



Discussion

In this study, we investigated the effect of increases in end-tidal N_2O 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 N_2O. Within groups, except for the control group (N_2O 0%), the administration of N_2O was associated with statistically significantly lower entropy values than those measured before or after N_2O. We therefore rejected the null hypothesis.

Although we could demonstrate a significantly downward trend of entropy values with increasing N_2O concentrations, an important decrease was only reached at N_2O > 60% [51.1%]. The entropy module was nonetheless able to detect gradual changes in frontal cortical

EEG. The potentiation of sevoflurane by N_2O observed in our study corresponds with the clinical effects noted by sevoflurane-N_2O studies that involved noxious stimuli. Fragan and Dunn demonstrated that N_2O 65% suppressed movement during surgery by 50% in the presence of 1 MAC of sevoflurane.[9] At an intubation MAC of sevoflurane (2.33%), N_2O 66% decreased the intubation response (movement during intubation) by 40%.[10] 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 N_2O.[11] N_2O 65% suppressed movement during surgical incision by 50%,[9] N_2O 66% decreased the response to intubation by 40%[10] and N_2O 67% attenuated the response to laryngeal mask insertion by 49%. In our study, during administration of N_2O 59.6% at sea level (1.4 EMAC) there was a decrease in entropy of about 46%. In the aforementioned studies, N_2O concentrations were > 65%. There appears to be an N_2O 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 N_2O concentrations.

This apparent threshold effect of N_2O 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,[12] while N_2O may disrupt subcortical activity.[13] Hans et al[14] are of the opinion that the decreases in BIS and 95% spectral edge frequency (SEF95) that they observed with increasing N_2O 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 N_2O combined with a weak depressant effect on cortical neurons.[13]

Subanaesthetic concentrations of sevoflurane decrease the analgesic effect of N_2O,[15] which is explained by the stimulation by supraspinal $GABA_A$ agonists, such as volatile anaesthetics[16] and benzodiazepines.[17] 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 N_2O and volatile anaesthetics is often quantified as a calculation of EMAC.[8] As N_2O 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/N_2O 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 N_2O. In other studies, vapour concentrations were decreased as N_2O 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 N_2O analgesia. Orii et al have demonstrated that GABA-ergic neurons differentially modulate the antinociceptive effects of N_2O at supraspinal and spinal levels.[17] N_2O 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.[18] Activation of the noradrenergic pathways modulates spinal pain processing by two different pathways. One pathway involves noradrenalin-induced activation of α_2 adrenoceptors.[19,20] Activation of the α_2 receptors inhibits neurotransmission in the primary afferent neuron by presynaptic inhibition of the release of calcitonin gene-related peptide and substance P[21] and by inhibiting activation of ascending second order neurons.[22] The other adrenergic pathway involves activation of inhibitory spinal GABA-ergic neurons through α_1 adrenoceptors.[23] 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 N_2O. They suggested that if these findings are extrapolated to humans, the analgesic effect of N_2O might be attenuated by systemically administered midazolam.[17]

The patients in our study received midazolam as premedication and propofol as induction agent. In some studies, no premedication was allowed,[7, 11, 24] while in others, intravenous induction agents were avoided and anaesthesia was induced using a volatile anaesthetic and/or N_2O.[2, 5, 10] Although $GABA_A$ agonists, such as midazolam, may decrease the analgesic effect of N_2O, 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.[25] 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_2O 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_2O, sevoflurane and O_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_2O at high altitudes may give rise to hypoxic inspiratory gas mixtures. When 70% N_2O 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 26% (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 $l.minute^{-1}$, the low blood-gas partition coefficient of N_2O ensures rapid attainment of steady-state levels. After end-tidal N_2O 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_2O reaches approximately 90% equilibration within 10 minutes.[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.[27] Using the same entropy module as we did during surgical stimulation, Soto et al[24] and Prabhakar et al[7] found increased entropy after the addition of N_2O during volatile agent administration. Prabhakar et al[7] observed an increase in entropy in the presence of N_2O 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_2O 66% (1.5 EMAC). Our findings concur partly with the finding of Soto et al.[24] During laparoscopy, they demonstrated a dual effect of N_2O on entropy: When > 65% N_2O 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_2O 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_2O 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_2O.[18] Furthermore, most anaesthetists administer N_2O 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_2O 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™ Module blind to the effect of N_2O? Probably not, but the effect of N_2O 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.[28]

Conclusion

We have demonstrated that the M-Entropy S/5™ Module is not blind to N_2O 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 $N_2O \leq 60\%$ with a steep and clinically important decrease at N_2O = 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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