Surrogate measures, do they really describe anaesthetic state?

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Characterization of anaesthesia is tricky, in particular, to go beyond the usual definition of a ‘state of nonresponsiveness to various types of stimulations’, and to find indicators useful for titrating drug administration. General anaesthesia is usually split into two main domains: unconsciousness (nonresponse to verbal stimulation and amnesia) and analgesia (nonresponse to noxious stimulations).1,2 Unconsciousness may be directly assessed at induction of anaesthesia (loss of verbal contact) and after recovery (absence of recall), but usually not during maintenance. The adequacy of the balance between analgesia and stimulation can be clinically estimated through movement, haemodynamic changes, and autonomic nervous system responses (sweat and lacerination, modification in pupil diameter); these clinical endpoints have limitations when used for titrating anaesthetic drugs in clinical practice, specifically in paralysed patients. Furthermore, as adequate anaesthesia is defined as nonresponsiveness, clinical assessment cannot distinguish between adequate drug delivery and overdosing if overdosing does not induce adverse effects.

Editorial IV

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Monitoring systems have been developed to compensate for these limitations. These are based on indirect (surrogate) measures, including the observation and analysis of cortical EEG. Several parameters have thus been proposed, such as the bispectral index (BIS\textsuperscript{TM})\textsuperscript{3} which still plays a predominant role, mainly due to the fact that it was the first commercially available device with a clearly defined range supposed to correspond to an adequate ‘depth of anaesthesia’. As adrenergic stimuli induce arousal reactions which can be reflected on cortical EEG, the BIS\textsuperscript{TM} has also been used to assess the adequacy of analgesia.\textsuperscript{9} The BIS\textsuperscript{TM} is a complex and not completely accessible parameter established to statistically quantify the hypnotic effect of propofol.\textsuperscript{1} It was further found able to discriminate hypnotic levels induced by isoflurane and midazolam, albeit with less precision.\textsuperscript{5} However, ‘depth of anaesthesia’ monitors based on the EEG have demonstrated their usefulness in allowing adjustments of drug delivery to individual needs in clinical practice, decreasing both the risks of overdosing and of awareness, and slightly decreasing the recovery time.\textsuperscript{6}

Liu and colleagues\textsuperscript{7} consider the sparing effect of nitrous oxide (\textit{N}_2\textit{O}) on propofol and remifentanil consumptions when those drugs are administered through a closed-loop system using the BIS\textsuperscript{TM} as the control parameter. They do not find any clinically significant difference in propofol or remifentanil consumption whether or not nitrous oxide is added to the inhaled mixture. Liu and colleagues’ system uses the BIS\textsuperscript{TM} to control both propofol and remifentanil administrations, the hypnotic being driven by progressive changes in the parameter, and the opioid by rapid changes seemingly corresponding to arousal reactions. They claim that their system, being independent from the clinician, is more reliable to detect any difference induced by nitrous oxide administration than all the other studies published so far which were based on haemodynamic and clinical observation. However, no other descriptors of ‘adequacy of anaesthesia’ are considered in their system.

Nitrous oxide has actually initiated the era of modern anaesthesia more than 150 yr ago, when it was used in dental surgery. It has a weak sedative action, with a minimum alveolar concentration (MAC) around 1.04 (0.10) (se) atm absolute, measured in hyperbaric conditions,\textsuperscript{8} and may provoke loss of consciousness through a mechanism called dissociative anaesthesia, similar to that obtained with ketamine, both agents acting through the \textit{N}-methyl-\textit{D}-aspartate (NMDA) receptor.\textsuperscript{9} However, nitrous oxide is nowadays mainly considered as an analgesic. As such, it reduces the amount of both volatile and propofol required to blunt motor responses to skin incision (MAC, EC50) by about 30%.\textsuperscript{10,11}

The influence of nitrous oxide on the central nervous system is very complex.

Conversely to GABA-ergic hypnotics which induce mainly cortical EEG depression (i.e. slowing and synchronization preceding burst suppression), nitrous oxide, antagonist of the NMDA receptor, also stimulates the EEG and increases fast frequencies activity (>30 Hz), specially in the frontal area.\textsuperscript{12,13} This activation occurs early after introducing nitrous oxide and is associated with phase coupling peaks around 4 Hz (delta) and 10 Hz (spindle).\textsuperscript{16} Thereafter, fast frequency activity decreases unmasking low frequencies activity.\textsuperscript{15} For intermediate duration administration or concentrations, both effects may neutralize and EEG-derived parameters may show no change. Moreover, nitrous oxide also acts at the spinal level, where it stimulates superficial neurones and depresses deep neurones,\textsuperscript{16} and at the midbrain level to modulate ascendant nociceptive inputs\textsuperscript{17} and stimulate reticular neurones.

As all single EEG-derived parameters, BIS\textsuperscript{TM} is unable to describe all these complex phenomena. It is recorded through a single frontal sensor, and therefore will catch accurately frontal changes but neither alterations in other territories such as the parietal area which is deeply depressed by nitrous oxide nor changes in the parietal/frontal equilibrium.\textsuperscript{18} To limit EMG and environment artifacts, BIS\textsuperscript{TM} signal processing is filtered at 32 Hz (as State Entropy and PSI). It may therefore miss fast frequency peaks, and appear ‘blind’ to nitrous oxide effect if predominant in fast frequencies. Laboratory (volunteers) studies were able to describe accurately nitrous oxide effects because they could record EEG in a quiet noise-free environment which is certainly not the case in an operating theatre. Lastly, spinal and midbrain effects of nitrous oxide, particularly relevant to the analgesic component of anaesthesia are not directly displayed on cortical EEG whatever the analysis technique used.

Clinical results illustrate these limitations. Quite a few clinical works have studied the influence of nitrous oxide on BIS\textsuperscript{TM} values before and during surgery and their results are deeply confusing. When nitrous oxide 70% was used as the sole hypnotic administered to healthy volunteers, it induced loss of consciousness without modifying the BIS\textsuperscript{TM}, in contrast with what was observed with sevoflurane.\textsuperscript{19} In another study including 48 patients with epidural analgesia, inhalation of increasing nitrous oxide concentrations resulted in a progressive reduction in the OAA/S without corresponding decrease in BIS\textsuperscript{TM} values.\textsuperscript{20}

Similar results were observed with cerebral state index (CSI)\textsuperscript{21} and Entropy:\textsuperscript{22} During sevoflurane anaesthesia titrated on BIS\textsuperscript{TM} (40–60), adding nitrous oxide consistently decreased BIS\textsuperscript{TM} and Entropy\textsuperscript{23,24} with the deepening of anaesthesia. This decrease was not observed with propofol,\textsuperscript{24} possibly because propofol inhibited reticular neurones, whereas sevoflurane did not. During gynaecological surgery with very low dose of alfentanil given at induction, adding nitrous oxide allowed decreasing the amount of sevoflurane necessary to maintain a chosen MPF (2–3 Hz) linearly with nitrous oxide fraction.\textsuperscript{25} During a deeper sevoflurane anaesthesia (BIS\textsuperscript{TM} ~35), adding nitrous oxide slightly decreased BIS\textsuperscript{TM}, markedly decreased State Entropy but left PSI unchanged.\textsuperscript{26} During an isoflurane anaesthesia deep enough to achieve burst suppression, adding nitrous oxide decreased the burst suppression ratio and seemed to lighten anaesthesia.\textsuperscript{27} Several mechanisms have been proposed, such as an increase in cerebral blood flow or an activation of reticular neurones countering the effect on cortical neurones.\textsuperscript{27} After a noxious stimulation such as intubation, paradoxical BIS\textsuperscript{TM} and SEF decreases have been observed in the presence of nitrous oxide, but this effect disappeared
when an opioid bolus was added. In another study, nitrous oxide inhibited both BISTM changes during intubation and clinical response (isolated forearm) suggesting that an adequate level of analgesia had been achieved.

In summary, the effect of nitrous oxide on EEG and EEG-derived parameters during anaesthesia is only one of all nitrous oxide pharmacodynamic effects, along with sedation, immobility, or haemodynamic control. It depends on both excitation/depression and cortical/subcortical balances. These balances vary with the associated drugs (volatile vs propofol), on the degree of EEG depression, and on the nociception/anti-nociception equilibrium.

The results achieved by Liu and colleagues, titrating anaesthesia entirely on a single EEG parameter, confirm a small influence of nitrous oxide to maintain a chosen value of this surrogate parameter through dosing of GABA-ergic drugs. These authors were unable to demonstrate any influence on the level of sedation in the absence of stimulation, because nitrous oxide was introduced after intubation, at a time when the doses required for surgery were far above those required for loss of consciousness. Moreover, considering control over adrenergic stimuli, one may even suspect that both groups were not at the same depth of analgesia (despite similar BISTM), since the incidence of movement was divided by three on the degree of EEG depression, and on the nociception/anti-nociception equilibrium.

At a time when instrumental monitoring is more and more prominent in our anaesthesia practice, this work is a useful reminder of the fact that a mathematical construction based on cortical EEG may not (yet?) include all the complexity surrounding pharmacological loss of consciousness and control over adrenergic stimuli, and thus be unable to completely describe anaesthesia. The future of drug adjustments might well include more complex algorithms combining surrogate measures of sedation (EEG), surrogate measures of analgesia (i.e. pupil dilatation reflex), and clinical signs considered in their surgical context.

**Abbreviations and definitions**

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<tr>
<td>BISTM</td>
<td>Bispectral index of EEG including bispectrum, quasi burst, and β ratio.</td>
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<td>SEF</td>
<td>Spectral edge frequency. Frequency of the spectrum below which are gathered 95% of the frequency components of an EEG epoch.</td>
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<td>MPF</td>
<td>Median power frequency is the frequency of the spectrum below which are gathered 50% of the frequency components of an EEG epoch.</td>
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<td>Entropy</td>
<td>This returns two indexes both expressing the irregularity, complexity, or unpredictability characteristics of EEG signal: state entropy (including frequencies from 0.5 to 32 Hz) and response entropy.</td>
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**Patient state index**

Q EEG-derived parameter including EEG power, frequency, and phase information from anterior-posterior relationships of the brain and coherence between bilateral brain regions.

**Declaration of interest**

None declared.

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EDITORIAL V

‘For now we see through a glass, darkly’: the anaesthesia syndrome

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In this issue of the British Journal of Anaesthesia, Zand and colleagues1 revisit the isolated forearm technique (IFT) pioneered in obstetric anaesthesia by Tunstall.2 Their data are consistent with Tunstall’s early studies during anaesthesia for Caesarean section showing that 33–42% of patients may respond intra-operatively.2,3 Zand and colleagues1 made similar observations after rapid sequence induction with thiopental: 41, 46, and 23% of the subjects responded at laryngoscopy, intubation, and skin incision, respectively. Prima facie, these are potentially alarming statistics, raising questions over the ‘adequacy of anaesthesia’ provided during and after rapid sequence induction, and hence a thorough critique of their methodology is warranted.

Strengths of this paper include the standardized and clinically relevant approach (including drug dosing), relatively large

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