Increasing isoflurane concentration may cause paradoxical increases in the EEG bispectral index in surgical patients†

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We have studied the effects of increases in isoflurane concentration on the EEG bispectral index (BIS) in 70 patients anaesthetized with isoflurane–nitrous oxide–sufentanil for major abdominal surgery. During surgery, baseline BIS was recorded at 0.8% end-tidal isoflurane with nitrous oxide in oxygen ($F_{I_{O_2}}$ 0.35). After this, end-tidal isoflurane was increased to 1.6% for 15 min and decreased subsequently to 0.8% for 20 min to assess recovery. In 20 patients, BIS decreased from a mean value of 40 (SD 9) during baseline to 25 (10) at 1.6% isoflurane. In contrast, BIS did not change in 23 patients and increased in 27 patients from 35 (6) to 46 (8) as isoflurane was increased to 1.6%. In all patients, BIS recovered to baseline values at 0.8% isoflurane. The changes in BIS with increasing isoflurane concentration were not related to drugs or differences in physiological variables, which did not differ between groups. Patients with a decrease in BIS were significantly younger (38 (range 18–68) yr) than those with unchanged (55 (26–70) yr) or increased (60 (40–70) yr) BIS values ($P<0.001$). It is possible that the paradoxical increase in BIS is related to continuous pre-burst EEG patterns consisting of high-frequency activity. This suggests that the use of BIS as a guide for isoflurane administration may be misleading in some patients undergoing surgical procedures.

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Previous studies have shown that several variables from the processed EEG correlate with clinical measures of depth of anaesthesia.[1 2] For example, the EEG-derived bispectral index (BIS) appears to be sensitive to the hypnotic component of anaesthesia.[3] As a consequence, BIS has been introduced into clinical practice to guide administration of volatile anaesthetics.[4 5]

BIS decreases with increasing concentration of anaesthetic (i.e. as depth of anaesthesia increases). BIS values of 90–100 are present in the awake individual and BIS=0 during EEG isoelectricity.[2 6] We observed that BIS increased during increasing end-tidal isoflurane concentration in some surgical patients during routine intraoperative EEG monitoring. Therefore, in this study we systematically investigated the effects of low and high isoflurane concentrations (i.e. different levels of depth of anaesthesia) on the raw EEG and BIS during isoflurane–nitrous oxide–sufentanil anaesthesia.

Patients and methods

After obtaining approval from the Institutional Review Board, we studied prospectively 70 patients (aged 18–70 yr; ASA I–III) of both sexes (33 females, 37 males) undergoing elective abdominal surgery. Patients had no history of neurological or psychiatric disorders. After oral premedication with midazolam, anaesthesia was induced with propofol 1.5–2.0 mg kg^{-1} and sufentanil 0.2–0.3 μg kg^{-1}. Atracurium 0.5 mg kg^{-1} was administered for neuromuscular block which was monitored using a nerve stimulator. The trachea was intubated and the lungs ventilated with 65% nitrous oxide in oxygen using a semi-closed system with a fresh gas flow of 6 litre min^{-1}. Ventilation was adjusted to maintain an end-tidal carbon dioxide partial pressure of 4.5–5.0 kPa. Before the study, isoflurane was set at 0.8%. Sufentanil was given according to general clinical assessment (haemodynamic responses, sweating, lacrimation). Non-invasive or invasive mean arterial pressure (MAP), electrocardiographic heart rate (HR), pulse oximetry ($S_{p_{O_2}}$) and nasopharyngeal temperature were monitored continuously.

Body temperature was maintained using heating blankets.

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Norepinephrine (range 0–10 μg min^{-1}) was given i.v. if needed to maintain arterial pressure.

EEG recording

EEG recordings (two-channel referential montage; impedances <2 kΩ) were performed using surface electrodes (according to the international 10–20 system) placed at F7 and F8, with Fz as the reference and Fp1 as the ground. All quantitative EEG (QEEG) and electromyographic (EMG) data were averaged from the bifrontal leads. The EEG/EMG data were obtained using an Aspect A 1000 monitor (BIS v. 3.12, Aspect Medical Systems Inc., Natick, USA). The low pass was set at 0.25 Hz, no high pass was used, and the notch filter was enabled. The raw EEG was digitized continuously at 256 Hz per channel. QEEG/EMG variables were stored on a microcomputer at 5-s intervals. The burst suppression ratio (BSR) was calculated as the percentage of isoelectric periods occurring over the last 63 s. The burst-compensated spectral edge frequency 95% $(BcSEF)^2$ was calculated off-line as:

$$BcSEF = SEF \times \left(1 - \frac{BSR}{100}\right)$$

Electromyographic activity was calculated as absolute power (dB) in the 70–300 Hz (EMG high) and 70–110 Hz (EMG low) power bands.

Study interval

At least 15 min after skin incision and the last sufentanil dose (0.2 μg kg^{-1}), the end-tidal isoflurane concentration was adjusted and maintained constant at 0.8% for 20 min and baseline recordings were performed. End-tidal isoflurane was then increased rapidly to 1.6% for 15 min and all measurements repeated. Subsequently, the end-tidal isoflurane concentration was decreased rapidly to 0.8% for 20 min to assess recovery. No additional drugs were given over the study period.

Data analysis

EEG and EMG data, and physiological variables (MAP, HR, Sp_{O_2}, body temperature measured at 1-min intervals) were averaged from the last 5 min of each phase (baseline, 1.6% isoflurane, recovery). The BIS response to increased isoflurane was retrospectively classified as 'BIS decrease' (mean BIS at 1.6% isoflurane < mean BIS–2 SD at 0.8% isoflurane), 'BIS constant' (mean BIS at 1.6% isoflurane= mean BIS±2 SD at 0.8% isoflurane) or 'BIS increase' (mean BIS at 1.6% isoflurane > mean BIS+2 SD at 0.8% isoflurane). Data are given as mean (SD). For statistical analysis, multiple Friedman and Kruskal–Wallis tests followed by Wilcoxon and Mann–Whitney *U* tests were performed, as appropriate. ASA status, sex, number of patients with BSR = 0 (at 1.6% isoflurane) and number of patients requiring norepinephrine (at 1.6% isoflurane) were compared using chi-square tests. A Bonferroni-adjusted $P<0.05$ was considered significant.

Table 1 Quantitative EEG and EMG data during baseline (0.8% end-tidal isoflurane), 1.6% isoflurane and recovery (0.8% isoflurane): bispectral index (BIS), burst suppression ratio (BSR) and burst-compensated spectral edge frequency 95% (BcSEF) (mean (SD)). *$P<0.05$ *vs* baseline; †$P<0.05$ *vs* 'BIS increase'; ‡$P<0.05$ *vs* 'BIS constant'

	BIS increase ($n=27$)	**BIS constant ($n=23$)**	**BIS decrease ($n=20$)**
BIS			
Baseline	35 (6)	36 (6)	40 (9)
Isoflurane 1.6%	46 (8)*	37 (7)†	25 (10)*†‡
Recovery	35 (6)	34 (4)	39 (8)
BSR (%)			
Baseline	0 (0)	0 (2)	0 (0)
Isoflurane 1.6%	10 (9)*	8 (10)*	14 (27)*
Recovery	0 (0)	0 (1)	0 (0)
BcSEF (Hz)			
Baseline	8.2 (2.9)	8.4 (1.7)	12.0 (4.0)†‡
Isoflurane 1.6%	8.0 (2.2)	5.5 (1.1)*†	5.7 (2.3)*†
Recovery	8.7 (4.1)	9.3 (2.3)	11.5 (4.4)
EMG high (dB)			
Baseline	45 (4)	44 (4)	45 (4)
Isoflurane 1.6%	44 (3)	44 (3)	46 (5)
Recovery	43 (2)	43 (2)	43 (1)
EMG low (dB)			
Baseline	31 (5)	31 (5)	31 (6)
Isoflurane 1.6%	30 (4)	31 (4)	33 (7)
Recovery	28 (3)	30 (4)	30 (2)

Results

EEG data are summarized in Table 1. In 20 patients, BIS decreased with increasing isoflurane concentration (BIS decrease group) and was unchanged in 23 patients (BIS constant group). In 27 patients (BIS increase group), BIS increased significantly (maximum increase 195%). Changes in BIS with increased isoflurane concentration occurred 5–8 min after the increase in isoflurane and remained stable until isoflurane was decreased for assessment of recovery. During baseline or recovery, no burst suppression patterns were detected in any patient. With 1.6% isoflurane the burst suppression ratio did not differ significantly between groups (Table 1). The number of patients with no detected isoelectric periods (BSR=0) during 1.6% isoflurane differed significantly between groups (BIS increase six of 27; BIS constant eight of 23; BIS decrease 12 of 20) ($P<0.02$).

Figure 1 shows the time course of a typical EEG response (increasing BIS) to increased inspired isoflurane in a patient with EEG burst suppression patterns. Figure 2 shows the raw EEG tracings of patients with increasing (Fig. 2A) and decreasing (Fig. 2B) BIS in response to increased isoflurane. EMG baseline values or the time course of EMG values did not differ significantly between groups. EEG and EMG values during recovery did not differ from baseline values.

Table 2 shows patient data, sufentanil dose and norepinephrine infusion rates. Patients with a decreased BIS were significantly younger than those with unchanged or

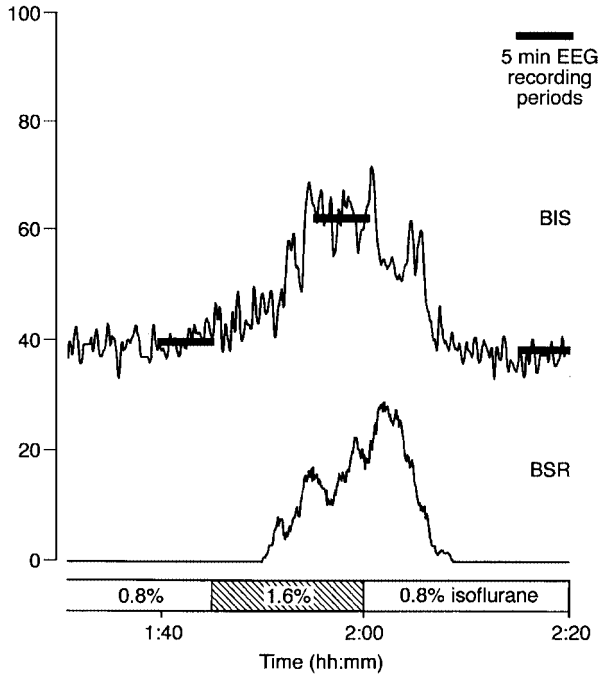

Fig 1 Representative EEG response (bispectral index (BIS) upper panel; burst suppression ratio (BSR) lower panel) to increasing isoflurane from 0.8% (mean baseline BIS 39 (SD 2)) to 1.6% (BIS 62 (3)) and recovery after a decrease to 0.8% isoflurane (BIS 38 (2)). In this patient, the EEG response was classified as a 'BIS increase' as BIS (62) during 1.6% isoflurane exceeded mean baseline BIS +2 SD (43) at 0.8% isoflurane.

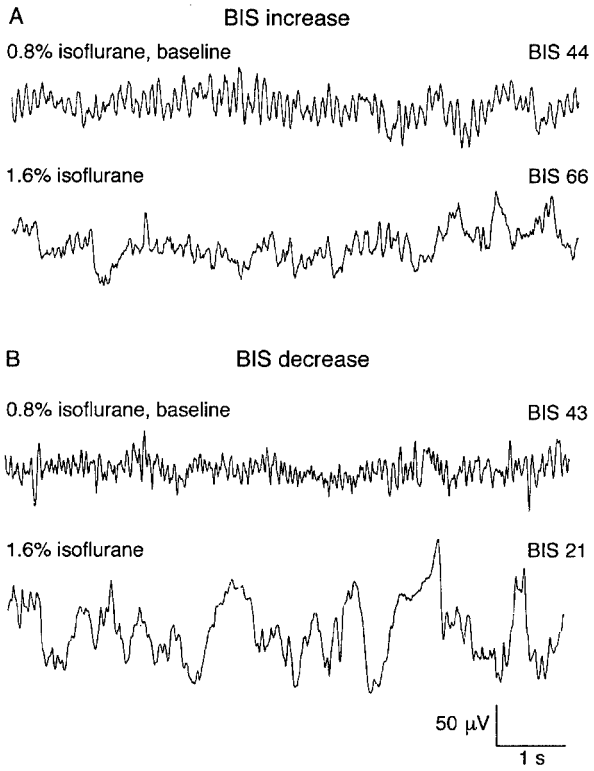

Fig 2 Characteristic raw EEG signals (approximately 8 s each) of two patients (one in the 'BIS increase' group (A) and one in the 'BIS decrease group (B)) during baseline (0.8% isoflurane) and during the increase in isoflurane to 1.6%. The raw signals are representative for the preceding 5 min of EEG activity in both patients. Note that in both patients, no isoelectric periods were present.

increased BIS values ($P<0.001$). There were no differences in sex, ASA status or total sufentanil dose between groups. There were no significant differences in norepinephrine infusion rates or number of patients given norepinephrine (at 1.6% isoflurane) between groups. No patient needed an infusion of norepinephrine for MAP support during baseline or recovery.

Table 3 shows physiological variables over time. There were no differences in the time course of physiological variables between groups and recovery values did not differ significantly from baseline.

Discussion

We found significant increases in BIS in approximately 40% of patients and unchanged BIS values in 33% during major abdominal surgery when the anaesthetic concentration was increased from 0.8% to 1.6% end-tidal isoflurane. This EEG pattern is a paradoxical BIS response, as BIS is supposed to decrease continuously with increasing anaesthetic concentration.[2 6 7]

In general, the characteristic EEG effect of increasing concentrations of volatile anaesthetic is a progressive slowing until burst suppression patterns occur.[8–10] The progressive EEG depression should be reflected by the QEEG variables in order to consider these as reasonable values for monitoring anaesthetic dose and depth. The EEG variable BIS was introduced recently into clinical practice as a measure of the hypnotic effect of anaesthetics.[2] Numerous studies have demonstrated a close correlation of BIS and various clinical measures of depth of anaesthesia, despite the fact that these lack sensitivity and specificity.[3 6 11] Some have suggested that the concentration of anaesthetics (including volatile anaesthetics) should be adjusted according to changes in BIS.[4 5 12] However, our results challenge the concept of administration of anaesthetics guided by BIS as BIS may increase paradoxically when isoflurane concentration is increased.

The BIS algorithm combines a variety of calculated EEG sub-parameters[2] which have not been published in detail. Although the underlying mechanisms of a paradoxical BIS increase remain speculative, some mathematical limitations may apply. In patients undergoing hypothermic cardiopulmonary bypass (propofol and alfentanil background anaesthetic), during cooling (<32°C), BIS values were considerably variable and sometimes overlapped with awake values. Also, high BIS values (>60) were associated with the occurrence of EEG burst suppression patterns and the authors suggested that the algorithm was insufficient to calculate BIS in the presence of isoelectric periods.[13] These authors examined the same BIS version (v. 3.12) as used here. However, the BIS algorithm seems to include burst suppression patterns via two separate calculations, BSR and

Table 2 Patient data and sufentanil doses in the 'BIS increase', 'BIS constant' and 'BIS decrease' groups (mean (SD or range)). Norepinephrine infusion rate for MAP support (>70 mm Hg) and number of patients who received norepinephrine infusion during administration of 1.6% isoflurane are shown (mean (SD) and number). †$P<0.001$ *vs* 'BIS increase'; ‡$P<0.001$ *vs* 'BIS constant'

	BIS increase ($n=27$)	**BIS constant ($n=23$)**	**BIS decrease ($n=20$)**
Age (yr)	60 (40–70)	55 (26–70)	38 (18–68) †‡
Sex (F/M)	11/16	11/12	11/9
ASA status (I/II/III)	9/17/1	5/16/2	8/10/2
Height (cm)	170 (9)	170 (9)	173 (12)
Weight (kg)	75 (14)	77 (13)	72 (16)
Total sufentanil (μg kg^{-1})	0.6 (0.2)	0.6 (0.4)	0.5 (0.3)
Norepinephrine (μg min^{-1})	2.8 (4.0)	1.2 (2.0)	1.0 (2.6)
(No.)	(11)	(7)	(5)

Table 3 Physiological variables during baseline (0.8% end-tidal isoflurane), 1.6% isoflurane and recovery (0.8% isoflurane): heart rate (HR), mean arterial pressure (MAP), pulse oximetry (Sp_{O_2}) and nasopharyngeal temperature (mean (SD)). *$P<0.05$ *vs* baseline

	BIS increase ($n=27$)	**BIS constant ($n=23$)**	**BIS decrease ($n=20$)**
HR (beat min^{-1})			
Baseline	70 (14)	73 (11)	69 (14)
Isoflurane 1.6%	72 (13)	77 (13)	76 (14)
Recovery	72 (16)	78 (10)	76 (15)
MAP (mm Hg)			
Baseline	87 (16)	85 (13)	84 (14)
Isoflurane 1.6%	76 (4)*	77 (7)*	76 (6)*
Recovery	84 (13)	93 (16)	88 (11)
Sp_{O_2} (%)			
Baseline	98 (1)	98 (1)	98 (1)
Isoflurane 1.6%	98 (1)	98 (1)	98 (1)
Recovery	98 (1)	98 (1)	98 (1)
Temperature (°C)			
Baseline	35.3 (0.5)	35.2 (0.5)	35.3 (0.5)
Isoflurane 1.6%	35.1 (0.6)	35.2 (0.5)	35.1 (0.6)
Recovery	35.1 (0.6)	35.2 (0.6)	35.1 (0.6)

the 'QUAZI suppression index'.[2] It is unlikely that in our study a simple algorithm failure could explain the increase in BIS as BSR did not differ between groups. Furthermore, with 1.6% isoflurane, in all three groups there were patients with a BSR of 0 (i.e. without isoelectric periods). Visual inspection of the raw EEG tracings confirmed the absence of isoelectric periods in patients with a BSR of 0 (see Fig. 2).

Patients showing paradoxical BIS responses were significantly older than patients with decreases in BIS. As age is an important variable in isoflurane requirements,[14 15] the susceptibility to EEG effects of isoflurane may increase with age.[16 17] This is reflected by markedly higher baseline BcSEF in the 'BIS decrease' group. Similarly, the number of patients without isoelectric periods during 1.6% isoflurane was higher in younger patients. This supports the notion of increased susceptibility to isoflurane with age and thus the greater probability of causing proper burst suppression patterns during 1.6% isoflurane. The increase in BIS in patients with no isoelectric periods may be caused by continuous 'pre-burst' patterns in the EEG (i.e. the EEG shows continuous bursts without intermingled isoelectric periods). As high-frequency EEG activity is preserved or even increased during bursts,[2 9 18] BIS remains unchanged or increases. In pigs, paroxysmal alpha and beta activity was recorded during 1.5% isoflurane, which was also observed frequently in this study.[10] This phenomenon could be the correlate of a pre-burst EEG state. As patients with the paradoxical BIS increase were older, these patients were more likely to develop such a pre-burst state. We used BIS v. 3.12. It is not clear if the latest version of BIS software (v. 3.3) recognizes described EEG patterns and hence avoids displaying misleading information to the anaesthetist.

Our hypothesis that a paradoxical BIS response is caused by a pre-burst pattern is supported by the fact that the BcSEF did not change in the BIS increase group. As SEF95% is sensitive to burst suppression phenomena, we used burst-compensated SEF to allow for computation of SEF in the presence of isoelectric periods.[2 18] Interestingly, in addition to BIS, BcSEF also showed a paradoxical response in some patients.

Several confounding factors may have been present during our study. The EEG recordings were made during surgery. However, the observed differences in EEG responses are unlikely to be related to differences in surgical stimulation as there was no difference in the type of surgery (abdominal surgery) and the EEG recording was started after opening of the peritoneal cavity. Thus there was constant stimulation but no prominent stimulus. This is consistent with previous data showing no effect of ongoing surgery on the EEG during isoflurane anaesthesia.[19] In addition, the subsequent return to baseline data after a decrease in isoflurane supports the hypothesis that the observed changes were independent of changes in surgical stimulation.

Our results are not related to changes in physiological variables which did not differ between groups. There were no significant differences in mean norepinephrine dose or in the number of patients given norepinephrine. As there were patients who did not receive norepinephrine in all three groups, a direct interaction between norepinephrine infusion and EEG response is unlikely. In addition, norepinephrine has little effect on cerebrovascular resistance and does not cross the intact blood–brain barrier.[20] Thus the effects of norepinephrine are not a major mechanism of a paradoxical BIS increase. It is possible that the increase in BIS is related to an increase in high frequency activity

(i.e. EMG activity). However, there were no differences in EMG activities between groups. Thus it is also unlikely that this factor contributed to the paradoxical BIS response.

In summary, our results indicate that increasing concentrations of isoflurane may induce paradoxical BIS increases during surgery using an isoflurane–nitrous oxide–sufentanil anaesthetic technique in some patients. It is unclear if the increase in BIS in patients without isoelectric periods reflects continuous pre-burst EEG activity consisting of high-frequency waves. Irrespective of the underlying mechanism, the presence of paradoxical BIS responses challenges the concept of monitoring depth of anaesthesia during isoflurane anaesthesia using the BIS technique.

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