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Detection of awareness in surgical patients with EEG-based indices—bispectral index and patient state index^{†‡}

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Background. Patient state index (PSI) and bispectral index (BIS) are values derived from the EEG, which can measure the hypnotic component of anaesthesia. We measured the ability of PSI and BIS to distinguish consciousness from unconsciousness during induction and emergence from anaesthesia and a period of awareness in surgical patients.

Methods. Forty unpremedicated patients were randomized to receive: (1) sevoflurane/remifentanil ($\leq 0.1 \, \mu g \, kg^{-1} \, min^{-1}$), (2) sevoflurane/remifentanil ($\geq 0.2 \, \mu g \, kg^{-1} \, min^{-1}$), (3) propofol/ remifentanil ($\leq 0.1 \, \mu g \, kg^{-1} \, min^{-1}$), (4) propofol/remifentanil ($\geq 0.2 \, \mu g \, kg^{-1} \, min^{-1}$). Every 30 s after the start of the remifentanil, patients were asked to squeeze the investigator's hand. Sevoflurane or propofol were given until loss of consciousness (LOCI). Tunstall's isolated forearm technique was used during neuromuscular block with succinylcholine. After tracheal intubation, propofol or sevoflurane were stopped until return of consciousness (ROCI). Propofol or sevoflurane were re-started to induce LOC2. After surgery, drugs were discontinued and recovery (ROC2) was observed. PSI and BIS at LOC (LOC1 and LOC2) were compared with those at ROC (ROCI and ROC2) (t-test). Prediction probability (P_k) was calculated from values at the last command before and at LOC and ROC. Values are mean (SD).

Results. At non-responsiveness, BIS (66 (17)) and PSI (55 (23)) were significantly less than at responsiveness (BIS, 79 (14); PSI, 77 (18); P<0.05). The wide variation with both BIS and PSI measurements of the 80 'awareness' values led to an erroneous classification as unconscious in some cases (BIS, six patients; PSI, nine patients). P_k was 0.68 (0.03) (BIS) and 0.69 (0.03) (PSI).

Conclusions. Despite significant differences between mean values at responsiveness and nonresponsiveness for BIS and PSI, neither measure may be sufficient to detect awareness in an individual patient, reflected by a P_k less than below 70%.

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The bispectral index (BIS) is an empirically derived multifactorial EEG measurement. BIS is a dimensionless number between 0 and 100 that correlates with hypnosis. In awake patients, BIS is between 90 and 100 while complete suppression of cortical electrical activity results in BIS of 0. BIS values below 60 are associated with a low probability of consciousness. BIS is calculated by a proprietary algorithm which combines several features of the EEG, based on spectral and bispectral EEG analysis, burst suppression ratio and a 'QUAZI suppression' component into a single numerical value.1

The patient state index (PSI) was developed as a measure of hypnosis during anaesthesia. PSI values vary from 0 to

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Table 1 Questions asked in the postoperative interviews

- 1. What was the last thing you remember before you went to sleep for your operation?
- 2. What was the first thing you remember after your operation?
- 3. Can you remember anything in between these two periods?
- 4. Did you dream during your operation?
- 5. What was the worst thing about your operation?

100 with decreasing values indicating increasing levels of hypnosis.² It is calculated by a proprietary algorithm that involves a self-norming technique in its development and is mainly based on quantitative EEG measures and their spatial fronto-occipital distribution.^{3 4}

The present study examines the capability of both indices, BIS and PSI, to detect awareness in surgical patients.

Methods

After approval from the university's ethics committee, we recruited 40 adult patients, ASA physical status I or II undergoing elective surgery under general anaesthesia. We excluded patients who required rapid sequence induction, with contraindications to the drugs used, who had recently received CNS-affecting drugs, or patients with pregnancy, psychiatric, or neurological diseases. Informed written consent was obtained from all patients. Patients received either balanced anaesthesia with sevoflurane and remifentanil (Groups 1 and 2) or total i.v. anaesthesia with propofol and remifentanil (Groups 3 and 4). Within the different anaesthesia regimens, half of the patients were given a maximum remifentanil infusion rate of 0.1 µg kg⁻¹ min⁻¹, and in the other half, the minimum infusion rate was $0.2 \mu g kg^{-1} min^{-1}$ (Groups 1 and 3, and 2 and 4, respectively). Blocked randomization was performed. For each of the four anaesthetic regimens, 10 envelopes containing a description of the group (1-4) were sealed. The 40 envelopes were mixed and numbered in order. Following patient consent, an envelope was opened in sequences to allocate the anaesthetic treatment.

Monitoring

We measured non-invasive arterial pressure, heart rate, oxygen saturation, oxygen, carbon dioxide and sevoflurane concentrations, and respiratory variables, using standard monitors. The time was synchronized at all the monitors and data were transferred to and stored on a personal computer. BIS and PSI were simultaneously measured and recorded.

For EEG recordings, the skin was prepared with alcohol to obtain impedance less than 5 kOhm. BIS was recorded using the Aspect A-1000 EEG Monitor (BIS version 3.3, Aspect Medical Systems Inc., Newton, MA, USA). A two channel referential EEG was obtained with ZipPrep Ag/AgCl EEG electrodes in positions AT1, AT2, F_z (reference), and Fp_1 (ground, electrode positions according to the international 10–20 system). The high pass was set at

0.25 Hz, no low pass was used, and the notch filter (50 Hz) was enabled. Raw EEG was continuously digitized at 256 Hz per channel and simultaneously recorded with processed EEG values and cardiovascular values on the personal computer. PSI was recorded using a Physiometrix Patient State Analyser (PSA 4000, Physiometrix Inc., North Billerica, MA, USA). A specific electroencephalogram electrode device (PSArray Electrode Set) was used to obtain a four-channel EEG. The device consists of a self-adjusting flexible head strap which holds Ag/AgCl EEG recording electrodes with electrode positions at FP1, FPZ, Cz, Pz, FP2 (ground) (electrode positions according to the international 10–20 system). Electrodes at both ears were used as linked reference. Four channel raw EEG and processed EEG-parameters were stored on a PCMCIA hard disk.

Anaesthetic procedure

No premedication was given. Patients were given oxygen from a mask. Lactated ringer's solution and remifentanil infusion was started at either 0.1 or 0.2 µg kg⁻¹ min⁻¹ according to allocation, via a cannula in the cubital vein. Every 30 s, patients were asked twice to squeeze the investigator's hand. Sevoflurane was started via mask (Groups 1 and 2) or propofol was injected with a first dose of 0.7 mg kg⁻¹, followed by doses of 20 mg every 30 s (Groups 3 and 4). Loss of consciousness (LOC1) was defined as the time when the patient first did not squeeze the investigator's hand to command. Following LOC1, the circulation of the right forearm was occluded for 5 min to retain the ability to move the arm to command, and then succinylcholine (1.0 mg kg⁻¹) was given (Tunstall's isolated forearm technique).⁵ The trachea was then intubated. After intubation, sevoflurane or propofol were stopped until patients responded to command (return of consciousness, ROC1). Sevoflurane inhalation or propofol bolus injection (20 mg every 20 s until loss of consciousness), followed by continuous infusion was recommenced. When patients stopped following command again, loss of consciousness was noted (LOC2) and requests to squeeze the hand were stopped. Sevoflurane and propofol were then administered according to clinical practice. In Groups 1 and 3, the maximum remifentanil infusion rate was 0.1 µg kg⁻¹ min⁻¹, and in Groups 2 and 4, a minimum infusion rate of 0.2 µg kg⁻¹ min⁻¹ was maintained. At the end of surgery, patients were asked twice every 30 s to squeeze the hand. Sevoflurane, propofol, and remifentanil were discontinued. Return of consciousness (ROC2) was defined as the first response to command, that is a squeeze of the hand.

Following recovery from anaesthesia in the recovery room, patients were tested for recall using a standardized interview (Table 1).⁶

This interview was repeated within 48 h on the ward and by telephone between 2 and 3 weeks after anaesthesia.

Table 2 Patient data: height, weight, age, gender ASA physical status (ASA), BIS and PSI awake baseline in the four groups. Data are mean (SD) or, for age, mean (range). Group 1, sevoflurane, low dose remifentanil; Group 2, sevoflurane, high dose remifentanil; Group 3, propofol, low dose remifentanil; Group 4, propofol, high dose remifentanil. There were no significant differences between baseline BIS and PSI values in the four groups

Group	Height (cm)	Weight (kg)	Age (yr) (range)	Gender (f/m)	ASA (I/II)	BIS	PSI
1	174 (5)	80 (13)	35 (22–54)	2/8	8/2	94 (4)	99 (1)
2	169 (9)	74 (17)	53 (22–72)	6/4	3/7	97 (1)	98 (2)
3	171 (7)	80 (19)	44 (28–66)	2/8	3/7	95 (5)	98 (1)
4	169 (9)	70 (15)	51 (21–79)	6/4	6/4	96 (2)	99 (1)

Data analysis

To assess the ability of BIS and PSI to differentiate between responsiveness and non-responsiveness, the transition between these conditions was analysed. For this comparison, the values we used were adjusted for the time that is required for their computation from the raw EEG signal. In accordance with manufacturers' information and previous studies, this time was 30 s for BIS ⁷ and 55 s for PSI (R. Ortega, Physiometrix, personal communication).

Overall significance level was set at P<0.05 and we applied the Bonferroni correction.

Two repeated measurement ANOVAS were performed, using BIS and PSI data. LOC1, ROC1, LOC2, and ROC2 were used as within subject factors. The anaesthetic group (1–4) was used as between subject factor. Bonferroni corrections were used for post-hoc tests of within subject and between subject factors: BIS (or PSI) values were compared with each other at LOC1, ROC1, LOC2, and ROC2. BIS (or PSI) values of the different anaesthetic groups (1–4) were compared with each other.

Next, we considered BIS and PSI values at the transition between responsiveness and unresponsiveness. At LOC1 and LOC2 the last value with a patient response (i.e. 30 s before LOC) for 'consciousness', and the first value without patient response for 'unconsciousness', and similarly at ROC1 and ROC2 the last value without a patient response (i.e. 30 s before ROC) for 'unconsciousness', and the first value with patient response for 'consciousness'. These 320 values for each index were used to calculate sensitivity and specificity for the detection of 'unconsciousness' and 'consciousness'. For this calculation, a BIS value of 60 was taken as the threshold between 'consciousness' and 'unconsciousness'. The corresponding PSI value was 50. In addition, the 320 values were used to calculate the prediction probability (P_k) for discrimination between 'consciousness' and 'unconsciousness' for BIS and PSI as described by Smith and colleagues.8

To obtain information about the performance of both indices in subgroups, P_k was calculated for BIS and PSI in each group (1–4) using the same BIS and PSI values at 'consciousness' and 'unconsciousness' as described. Paired t-tests were used to compare P_k values for BIS and PSI in the complete data set and for each combination of drugs (Groups 1–4).

Baseline individual BIS and PSI values were obtained by averaging a 30-s interval before remifentanil administration. BIS and PSI baseline values and characteristics of subgroups were compared using one-way ANOVA, Kruskal-Wallis, and χ^2 tests. Statistical analysis was performed with SPSS (SPSS Inc., Chicago, IL, USA). P_k values were calculated with an Excel-Macro (PKMACRO). Pairwise comparisons were performed on P_k of BIS and PSI for the complete data set and each of the subgroups using tscores for paired data. Overall significance was 0.05, using the Bonferroni correction. For BIS and PSI, pairwise comparisons were performed for differences between anaesthetic groups (1-4) using z-scores for grouped data. For these comparisons, the Bonferroni correction was also used (P<0.05). Grouped and paired comparisons were performed with an Excel-Macro (PKDMACRO), provided by Smith and coworkers.⁸ Values are mean, (SD) unless stated otherwise.

Results

There were no significant differences in the awake baseline of BIS or PSI between groups (Table 2).

Repeated measurement ANOVA for BIS values found differences for within subject factors (LOC/ROC) and between subject factors (anaesthetic groups) (P<0.001). BIS (mean, (SD)) at LOC1 was 62 (19) and at LOC2 was 70 (16), which was significantly less than BIS at ROC1 which was 78 (15) (LOC1, P<0.001; LOC2, P<0.05) and ROC2 which was 81 (14) (LOC1, P<0.001; LOC2, P<0.01). BIS at LOC1 did not differ from BIS at LOC2 and BIS at ROC1 did not differ from BIS at ROC2. BIS values with sevoflurane and low dose remifentanil (anaesthetic Group 1) were different from propofol (P < 0.01), but there were no significant differences between the other groups. Repeated measurement ANOVA for PSI values found differences for within subjects (LOC/ROC) and between subjects (anaesthetic groups) (P<0.001). PSI at LOC2 was 55 (24), which was significantly less than PSI at ROC1 (P<0.01) and ROC2 (P<0.001). PSI at LOC1 was 55 (23), which was less than PSI at ROC2, 85 (9) (P<0.001), but there was no difference between the values at LOC1 and at ROC1, which was 69 (22) (P=0.06). The PSI at ROC1 was significantly less than at ROC2 (P<0.001). The PSI values in patients given sevoflurane (Groups 1 and 2) were significantly different

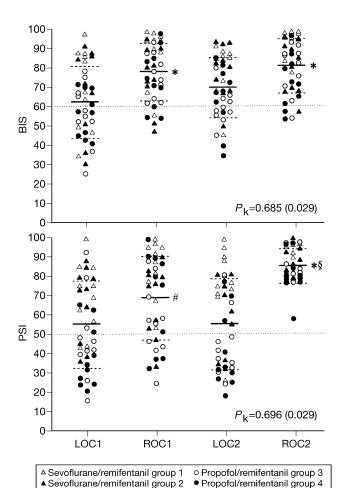


Fig 1 BIS (upper graph) and PSI (lower graph) at loss of consciousness (LOC1), awareness reaction (ROC1), loss of consciousness following the awareness reaction (LOC2) and at return of consciousness at the end of anaesthesia (ROC2). Graphs show individual values, mean (black line) and SD (dashed line) in all patients. An open symbol is used for the low infusion rate of remifentanil (0.1 μg kg⁻¹ min⁻¹, Groups 1 and 3), and a closed symbol for the high infusion rate of remifentanil (0.2 μg kg⁻¹ min⁻¹, Groups 2 and 4). Prediction probability (P_k) (SEM) for awareness is given for each index. The dotted lines show the recommended value for the (upper) level of each index for general anaesthesia. *Significantly different from LOC1 and 2. *Significantly different from ROC1. *Significantly different from LOC2 (P<0.05).

from PSI values in those given propofol (Groups 3 and 4) (P<0.001 except 2 vs 3 where P<0.05). There were no significant differences between the other groups.

With loss of consciousness (LOC1 and LOC2), BIS was 66 (17), at return of consciousness (ROC1 and ROC2) BIS was 79 (14). PSI at LOC was 55 (23), and PSI at ROC was 77 (18). Both BIS and PSI values were less in unconscious (LOC1 and LOC2) than in conscious patients (ROC1 and ROC2). Figure 1 shows the individual BIS and PSI values at the specific events. In two of the 80 measurements at ROC1 and ROC2, the BIS value was less than 60 and at the same time PSI was less than 50. In seven other measurements during ROC1 and ROC2, BIS was less than 60. In seven

Table 3 Sensitivity, specificity, positive and negative predictive value of BIS and PSI for detection of consciousness (defined as response to command). Values are calculated for a BIS threshold of 60 and a PSI threshold of 50

Index Threshold	BIS (60)	PSI (50)
Sensitivity	90.6%	85.6%
Specificity	26.3%	38.8%
Positive predictive value	55.1%	61.2%
Negative predictive value	73.7%	72.9%

Table 4 Prediction probability (P_k) for detection of consciousness in the four groups. P_k of BIS did not differ from P_k of PSI. Data are given as mean (SEM). *Significantly different from Pk in Group 1 (P<0.01)

Group	BIS (mean (SEM))	PSI (mean (SEM))
Sevoflurane, low dose remifentanil	0.684 (0.061)	0.597 (0.065)
Sevoflurane, high dose remifentanil	0.668 (0.061)	0.707 (0.059)
Propofol, low dose remifentanil	0.743 (0.056)	0.683 (0.061)
Propofol, high dose remifentanil	0.721 (0.057)	*0.835 (0.046)*
Combined groups	0.685 (0.029)	0.696 (0.029)

other patients, PSI was less than 50 at ROC1. All PSI values less than 50 at ROC were measured during ROC1. Three patients showed BIS values less than 60 at both ROC1 and ROC2, the remaining three patients either at ROC1 or at ROC2.

Table 3 gives values of sensitivity and specificity for BIS (≤60: unconsciousness) and PSI (≤50: unconsciousness) for detection of awareness (responsiveness) and unconsciousness.

The prediction probability P_k for all patients was significantly greater than 0.5: 0.685 (0.029) for BIS and 0.696 (0.029) for PSI. Table 4 gives values for P_k of BIS and PSI for the anaesthetic groups (1–4). There was no significant difference between P_k of BIS and P_k of PSI for the complete data set, nor in any of the subgroups (i.e. for each drug combination). The P_k of BIS was not significantly different between groups, but P_k of PSI was significantly different between Groups 1 and 4. In the postoperative interviews, no patient remembered being aware.

Discussion

We found that both BIS and PSI were significantly different between responsive and non-responsive patients.

At LOC1 and LOC2, BIS and PSI were significantly less than at ROC1 and ROC2. This difference was statistically significant for all comparisons except for PSI values at LOC1 and ROC1, where only a trend was evident (P=0.06). Despite these differences, the values of both BIS and PSI had a wide variance. Thus, despite significant differences between groups of patients, these measures may be of limited value to detect awareness in the individual patient.

Interestingly, PSI-but not BIS-also showed a significant difference between ROC1 and ROC2. This could be because neuromuscular block might have been present at ROC1. Neuromuscular block does not influence BIS, but no data are available for PSI. However, the time between succinylcholine administration and ROC1 was more than 5 min in 90% of the patients. Out of the remaining four patients, only two showed low PSI values at ROC1, and only one out of these four patients showed a low BIS during ROC1. Thus, neuromuscular block is not likely to account for the difference in PSI between ROC1 and ROC2. ROC1 occurred during remifentanil infusion, whereas remifentanil was stopped before ROC2. Although the PSI algorithm was tested on patients receiving remifentanil together with sevoflurane or propofol, 10 no explicit data are available on the influence of remifentanil alone on PSI. The present results suggest that remifentanil may affect PSI, which could result in unexpected awareness despite a low PSI. An additional factor for the difference between PSI at ROC1 and ROC2 could be postoperative pain at ROC2, whereas ROC1 occurred before surgery (and under the influence of remifentanil).

We found that neither BIS nor PSI were independent of the anaesthetic regimen. Repeated measurement ANOVA showed that BIS values in patients receiving sevoflurane anaesthesia with low dose remifentanil (0.1 µg kg⁻¹ min⁻¹. Group 1) were significantly different from values measured in patients with propofol/remifentanil TIVA (Groups 3 and 4). These results contrast with previous findings suggesting that BIS measures hypnosis independently of the anaesthetic drug used to induce this level. 11 12 However, our findings support a previous study that found differences in $P_{\rm k}$ during sedation induced by midazolam, sevoflurane, or propofol. This study measured P_k for OAAS scores, and found no difference when response to voice was used as clinical endpoint. 13 In the present study, the anaesthetic regimen also affected PSI levels, as PSI in patients with sevoflurane (Groups 1 and 2) was significantly different from PSI in patients receiving propofol (Groups 3 and 4). Although this has not been examined for PSI, previous studies also suggested a drug-independent effect.³ 10

BIS at LOC was 66 (17), and BIS at ROC was 79 (14). These results support a previous study where BIS was found to be 66 during unconscious and 85 during conscious periods. In that study, a BIS threshold of 75 for consciousness gave a sensitivity of 88% and a specificity of 80%. In the BIS threshold of 60 used in the present study gave a 90.6% sensitivity and a 26.3% specificity. These differences of sensitivity and specificity are caused by different threshold values. In our study, patients with a BIS value between 60 and 75 were also classified as 'conscious', reflected by a higher sensitivity. At the same time, the greater number of patients already 'unconscious' in the range between 60 and 75 decreases specificity for awareness. Similarly, the selection of a threshold value for 'unconsciousness' also influences sensitivity and

specificity, consistent with less sensitivity and greater specificity with a BIS threshold of 55 for unconsciousness in the study mentioned above. The BIS threshold of 60 in the current study is based on a previous study and the manufacturer's statement that BIS values lower than 60 are associated with a 'low probability of consciousness'.

Compared with BIS with a threshold of 60, the recommended threshold of 50 for PSI gives sensitivity values that are slightly decreased (85.6%) and specificity values that are slightly increased (38.8%). The PSI threshold of 50 was based on the manufacturer's recommendations and was used in a multicentre study to guide the administration of anaesthetic drugs.⁴

With both BIS and PSI there were nine values below the threshold for unconsciousness during ROC. Minimum values at ROC for both BIS (46) and PSI (24) were in a range that is thought to represent adequate or even excessively deep general anaesthesia. With BIS, these falsely low values were measured at both ROC1 and ROC2, with PSI, all of the falsely low values were measured during ROC1. Only in two patients in the present study, were unexpectedly low values obtained simultaneously with both BIS and PSI. All the other falsely low BIS and PSI values were measured in different patients. This supports the view that falsely low index values are not because of abnormal EEGs, as these measures showed falsely low values in different patients. This suggests different problems in data processing, and that neither BIS nor PSI is an ideal index of awareness in the individual patient.

We defined 'consciousness' as the appropriate response to a verbal command (awareness reaction). The ability to respond to a verbal command indicates intact short-term or working memory, that is a memory function of limited capacity that spans a few seconds. This differs from explicit long-term memory, which is usually considered when the term 'memory' is used. The difference between short-term and explicit long-term memory explains why none of our patients had recall (reflecting long-term memory) even though all patients were aware (reflecting short-term memory). The absence of recall in our patients reflects their hypnotic state during awareness, with intact short-term and disrupted long-term memory, as no patient had received amnesic benzodiazepine premedication. Some consider that 'absence of recall' is not sufficient for general anaesthesia, because implicit (unconscious) memory may be present¹⁵ and associated with awareness, and could have long-term consequences. 16 17

Both BIS and PSI values showed considerable variation at specific levels of anaesthesia (i.e. loss and return of consciousness). Values in conscious patients overlap with those measured in unconscious patients. Our data show that for both BIS and PSI the recommended values for anaesthesia could result in excessively deep anaesthesia and unnecessarily high drug doses in some patients (the ones that are already unconscious at higher index values) whereas other patients (the ones that show 'consciousness' even at

low index values) may be conscious or aware. This variability has been shown for BIS, 12 14 18 19 but we have now found the same for PSI.

A monitor of depth of anaesthesia should separate consciousness from unconsciousness. In a recently published review, Drummond defined requirements that must be met by a 'depth of anaesthesia'-monitor.²⁰ Not only must the average values of an index be statistically different between different levels of anaesthesia or sedation, but also in the individual patient the measurement must indicate the actual level. An overlap between the range of values for different stages of sedation and anaesthesia must be avoided.21 Our data show this was not achieved for BIS or PSI, indicated by a prediction probability (P_k) lower than 70% for both measures. In contrast to sensitivity and specificity calculations, prediction probability is not influenced by the selection of a certain threshold and indicates how well an index can discriminate different stages of anaesthesia. A P_{k} of 0 is obtained when an index reflects exactly the opposite of the clinical status, that is every awake patient is classified as unconscious and vice versa. A $P_{\rm k}$ of 100% indicates a correct classification of the patient status in every case, and an index value of 50% is the result that would be obtained by chance (e.g. flipping a coin). In the present study, the overall P_k was less than 70% for both BIS and PSI. For PSI, no previous data for P_k are available. For BIS, previous studies gave $P_{\rm k}$ values greater than 0.7 (0.77–0.976). The reduced performance of BIS in our study may have several reasons. Three previous studies 12 24 25 were of volunteers. A volunteer about to be sedated for a study may be in a different condition than a patient, knowing that surgery will be performed. Anxiety, expectations about the surgery, and maybe even the fear of waking up during surgery cause stress in the patient. These factors can affect memory of awareness. 26 27 All but one of the previous studies measured sedation or anaesthesia with a single agent, that is without concomitant opioid administration. 12 13 22 23 25 In the only study where an opioid was used, alfentanil did affect P_k . ²⁴ Thus, the use of remifentanil in our patients may contribute to the lower P_k in the present study. In addition, differences in P_k may result from the study protocol, as the dynamic changes in our study may differ from steady-state conditions measured in previous studies. 12 22 24 25 Of the cited studies, the study on patients during surgery gave the lowest P_k values (0.80 for sevoflurane, 0.77 for midazolam, and 0.90 for propofol).¹³ These values are still greater than our P_k data, but were measured during sedation with regional anaesthesia in patients not intubated. An awareness response of intubated patients during the anaesthetic conditions used in our study may be more realistic than the responses obtained in previous studies and closer to the clinical situation of a patient experiencing unintended awareness during general anaesthesia.

We conclude that a sensitivity for 'consciousness' of 90 (BIS) and 86% (PSI) suggest that the use of either BIS or

PSI as an additional monitor during anaesthesia may help to detect unintentional awareness in some patients. However, as the values found in conscious and unconscious patients overlap, the use of these indices as a guide to the administration of anaesthetic drugs requires caution to avoid awareness.

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