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Frontal electroencephalogram reveals emergence-like brain activity occurring during transition periods in cardiac surgery[†]

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Abstract

Background: Cardiac surgery has one of the highest incidences of intraoperative awareness. The periods of initiation and discontinuation of cardiopulmonary bypass could be high-risk periods. Certain frontal EEG patterns might plausibly occur with unintended intraoperative awareness. This study sought to quantify the incidence of these pre-specified patterns during cardiac surgery.
Methods: Two-channel bihemispheric frontal EEG was recorded in 1072 patients undergoing cardiac surgery as part of a prospective observational study. Spectrograms were created, and mean theta (4–7 Hz) power and peak alpha (7–17 Hz) frequency were measured in patients under general anaesthesia with isoflurane. Emergence-like EEG activity in the spectrogram during surgery was classified as an alpha peak frequency increase by 2 Hz or more, and a theta power decrease by 5 dB or more in comparison with the median pre-bypass values.
Results: Data from 1002 patients were available for analysis. Fifty-five of those patients (5.5%) showed emergence-like EEG activity at least once during surgery with a median duration of 13.2 min. These patients were younger (median age, 59 *vs* 67 yr; $P<0.001$) and the median end-tidal isoflurane concentration before cardiopulmonary bypass was higher (0.82 *vs* 0.75 minimum alveolar concentration [MAC]; $P=0.013$). There was no significant difference between those with or without emergence-like EEG activity in sex, lowest core temperature, or duration of surgery. Forty-six of these EEG changes (84%) occurred within a 1 h time window centred on separation from cardiopulmonary bypass.
Conclusion: The findings of this study suggest that approximately one in 20 patients undergoing cardiac surgery with a volatile anaesthetic agent have a sustained EEG pattern while surgery is ongoing that is often seen with emergence from general anaesthesia. Monitoring the frontal EEG during cardiopulmonary bypass may identify these events and potentially reduce the incidence of unintended awareness.
Clinical trial registration: NCT 02976584.

Keywords: cardiac procedures; cardiopulmonary bypass; electroencephalography; general anaesthesia; intraoperative awareness

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Editor's key points

- Unintended intraoperative awareness is more common during cardiac surgery than many other surgeries, and this remains a concern for clinicians and patients.
- Particular changes are commonly seen in the frontal EEG during emergence from general anaesthesia, including an increase in alpha frequency and a concurrent decrease in power in low frequency bands.
- Changes suggestive of emergence from general anaesthesia were frequently seen during cardiac surgery, especially in the period of separation from cardiopulmonary bypass; these EEG changes appear as distinct gaps in the typical pattern of the derived visual spectrogram.
- This study highlights the concern that during initiation of and separation from cardiopulmonary bypass patients might be at increased risk for unintended awareness episodes.

Cardiac surgery has one of the highest incidences of unintended intraoperative awareness out of all types of surgery, ranging from less than 1% to more than 20%, depending on the definition of awareness, the size of the study, and the method of detection.[1–4] The major contributors may be frailty and comorbidity, which lead to the goal to administer the lowest amount of anaesthetics possible in order to minimise haemodynamic consequences.[5] There are numerous challenges with delivering and dosing the right amount of anaesthetics, particularly involving cardiopulmonary bypass (CPB), with its haemodilutional effect at initiation, and changing patient temperature and CPB flows.[6,7] Depending on the centre performing the cardiac surgery, 'depth of anaesthesia' (DoA) may be monitored with the raw EEG, processed EEG, end-tidal volatile concentration, or nothing at all.[8] The attempt to minimise anaesthetic administration might contribute to a relative underdosing of anaesthetics leading to a higher incidence of awareness during cardiac surgery.[9]

Major trials investigating awareness have not involved collection of raw EEG data,[10–12] making it impossible to determine EEG patterns during hypothesised awareness events. Only DoA index numbers were recorded in these trials. It has been reported that DoA monitors are not well suited to guiding anaesthetic administration,[13] making it plausible that explicit recall might have occurred despite the fact that DoA index suggested adequate hypnosis.

Recently, the different trajectories displayed in the EEG by patients during intentional emergence at the end of surgery have been reported.[14–16] In the majority of patients the primary EEG spectral features during emergence are an increase in alpha oscillation frequency, sometimes followed by a loss of alpha power, and a decrease in theta (4–7 Hz) and low frequency (0.5–4 Hz) power before consciousness returns.[17,18] These EEG patterns during wakeup can be well seen with a spectrogram.[17] However, it is currently unknown if or how often these EEG patterns arise during general anaesthesia for cardiac surgery, which might be a sign of unintended lightening of anaesthesia. Our goal was to detect changes in EEG spectral patterns that may be associated with transitions in anaesthesia during high-risk periods of cardiac surgery (e.g. initiation and termination of CPB), in order to identify potential periods of unintended return of consciousness and awareness.

Methods

The ethics committee of the canton of Bern, Switzerland, approved the prospective observational study (KEK#210/15). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for observational studies was used to guide the methods of the study and to structure the manuscript.[19]

Patient selection

A total of 1072 adult patients undergoing general anaesthesia for cardiac surgery on CPB were enrolled between July 2016 and January 2018 as part of a single-centre study in a tertiary hospital (ClinicalTrials.gov identifier: NCT02976584). Inclusion criteria for this *post hoc* analysis were the use of isoflurane as general anaesthetic, and the availability of complete datasets of intraoperative EEG and end-tidal volatile concentrations.

Data acquisition and EEG processing

EEGs were recorded from a bipolar derivation (FP1–TP9, with FpZ as a common reference in the 10–20 system) using a Narcotrend® DoA-monitor (MonitorTechnik, Bad Bramstedt, Germany) on patients undergoing cardiac surgery. The raw EEG was extracted via an IntelliBridge module connected to a Philips IntelliVue anaesthesia monitor (Philips Medical Systems, Eindhoven, The Netherlands) using the Rugloop II software (Demed Medical, Temse, Belgium). From the respirator (Primus by Draeger, Luebeck, Germany), we also extracted end-tidal volatile concentrations at a sampling rate of 1 s^{-1}. Volatile anaesthetic concentrations of the oxygenator during CPB were extracted from the electronic perfusionist records, and values were interpolated from every 5 min to every second for illustrative purposes. This was reasonable, as the recorded values mostly did not change more than 0.2% isoflurane.

The sampling frequency of the EEG was 125 Hz. In order to minimise the effect of the electrocardiogram in the EEG, we used a method based on that of Strobach and colleagues.[20] Briefly, in Matlab (R2017b; The MathWorks Inc., Natick, MA, USA), the R peak of the QRS complex was first detected using 'findpeaks.m', set to a minimum peak prominence of 0.4 units. After this, within non-overlapping periods of 40 s, 0.8 s sections of the EEG centring on the R peak of the ECG were averaged to give a mean interference signal in the EEG over 40 s. This average was then tapered using a Blackman window before being reconstituted at the time points of the R peak in the ECG, creating an artificial reference signal, which was subsequently subtracted from the EEG. Further pre-processing of the EEG included the integrated high (0.5 Hz) and low (45 Hz) pass filters of the Narcotrend monitor. Any EEG activity with absolute slopes greater than 50 μV per 8 ms was considered as noise.[21] We considered the EEG to be suppressed when amplitudes were below 5 μV for at least 1 s.

For spectral analysis, we used Matlab to create spectra using the 'spectrogram.m' function from 10 s moving windows of EEG, overlapping by 9 s, yielding one spectrum every second. We chose to use 1250 nFFT points, giving a frequency resolution of 0.1 Hz (fs/nFFT). Peak alpha frequency was defined as

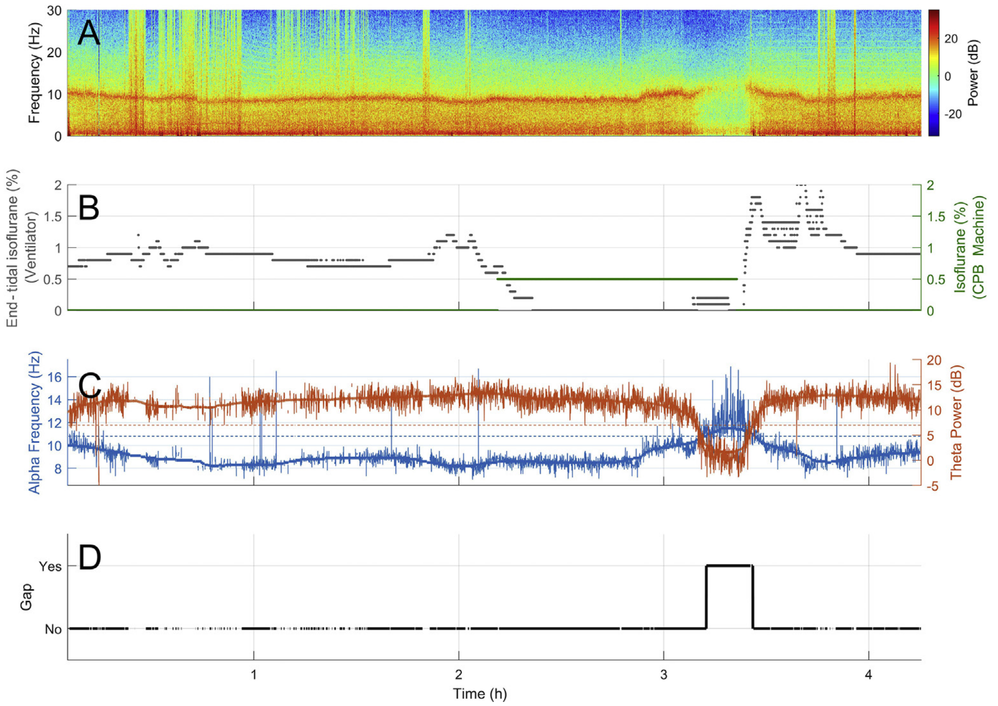

Fig. 1. Graphic depiction of our method for detecting 'gaps', that is periods of high alpha frequency and low theta power in the EEG, reminiscent of signatures seen during emergence from general anaesthesia. (a) 'Gaps' can be seen visually in a spectrogram of the operation. (b) End-tidal isoflurane concentrations (in %, left axis, in grey) from the ventilator and from the cardiopulmonary bypass (CPB) machine (right axis, in green). (c) Peak alpha frequency (left axis, in blue) and mean theta power (right axis, in red). Horizontal dotted lines show the gap detection thresholds, where peak alpha frequency has to be greater than 2 Hz of the median pre-bypass alpha frequency, and theta power less than 5 dB than the median pre-bypass theta power. (d) When thresholds were exceeded, we considered this to be a gap.

the frequency at the highest power in the spectrum between 7 and 17 Hz when the underlying broadband power had been removed, as detailed elsewhere.[22] Theta power was defined as the mean power between 4 and 7 Hz and delta power as the median between 0.5 and 4 Hz.

A rudimentary method of quantifying the presence of these EEG signatures that are similar to those seen during genuine emergence is to set frequency and power thresholds. To do this, we first smoothed both peak alpha frequency and theta power over the course of the operation using a median filter (order of 1000 s). We classified a 'gap' as being an increase in peak alpha frequency greater than 2 Hz from a patient's median pre-bypass peak alpha frequency value, and concurrently a theta power decrease of 5 dB or more in comparison with their median pre-bypass theta power. All potential gaps were checked by visually inspecting the spectrogram in order to reduce the influence of noise, and any gaps shorter than 30 s were excluded. Figure 1 shows an example of a suggested 'gap' detected by this approach. In addition, changes in delta power were investigated by comparing the values during the 'gap' against the 30 min average power before.

Sensitivity of 'gap' power and frequency thresholds

To run a basic sensitivity test of our threshold values, we repeated the analysis twice with thresholds made both more stringent (requiring a decrease of 6 dB in theta power, and an increase in 2.5 Hz alpha frequency), and more permissive (requiring only a decrease of 4 dB in theta power, and an increase in 1.5 Hz alpha frequency).

Statistical analysis

The Mann–Whitney *U*-test was used to test for differences in median values of continuous variables such as age, and a χ^2 statistic was used to test for differences in proportions, with the threshold for significance set at 0.05. We also used a *t*-test to compare mean delta (0.5–4 Hz) power levels in the 30 min before a 'gap' with mean delta power during the gap.

Results

Of the original 1072 completed recordings, 70 had to be excluded from this *post hoc* analysis either because of missing data (17 patients lacked EEG and end-tidal volatile concentration data) or because isoflurane was not being used as the primary maintenance anaesthetic (53 patients). The median age of the remaining 1002 patients was 67 yr (range, 21–86 yr; inter-quartile range, 15 yr). This patient group consisted of 250 females and 752 males. The median duration of surgery was 264 min. Using our threshold method, we found 128 gaps, but we had to exclude 73 of them on visual inspection as the algorithm identified either EEG noise or periods of deep

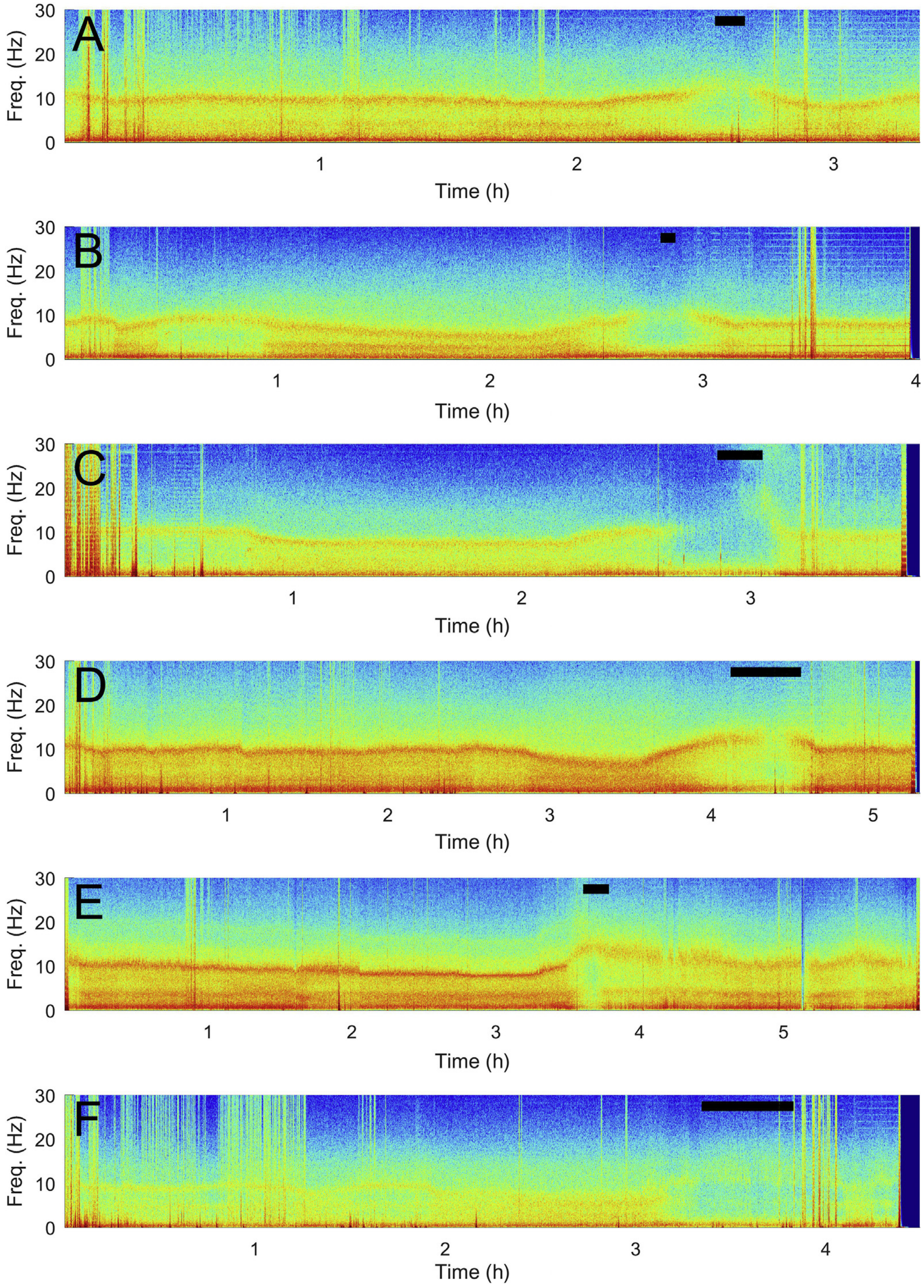

Fig. 2. Spectrograms of six example 'gap' EEG signatures occurring during cardiac surgery (a–f). Black horizontal rectangles indicate where we found a 'gap', as reflected in the method shown in Figure 1. Most gaps (a–e) were easy to see in the spectrogram, but example f was less clear. Some gaps showed a loss of the alpha oscillation (e.g., patient c), whereas others did not (e.g. patient e).

anaesthesia without burst suppression where an alpha oscillation was not present.

Thus 55 out of 1002 patients (5.5%) displayed EEG signatures during surgery that resemble patterns also seen during genuine emergence from general anaesthesia according to our criteria ('gaps'). The median gap duration was 13.2 min, but it ranged from 1 to 74.3 min. Patients with gaps were younger (median age, 59 yr) than patients without (median age, 67 yr; $P<0.001$). The proportion of males and females with gaps did not differ (males, 5.5%; females, 5.6%; $P=0.9$). Overall, 65.5

(n=36) had received a neuromuscular blocking agent right before or during the gap. The median age-adjusted end-tidal isoflurane concentration before bypass (expressed as minimum alveolar concentration [MAC]) was higher in patients who had gap EEG signatures (0.82 MAC) than in those without (0.75 MAC, P=0.013). The minimal temperature during bypass was not lower in patients with a gap (32.6°C) compared with those without (32.5°C, P=0.99). There was no significant difference in duration of surgery between those with gaps (286 min) and those without (261 min, P=0.15).

Forty-six of the 55 gaps (84%) occurred within a 1 h time window centring on the time of separation from CPB. Figure 2 shows six spectrograms with examples of gaps. Using a basic visual check, we observed that around half of the 55 patients who had gaps also had a period within the gap EEG signature where a distinct alpha oscillation was absent. The mean delta power of the group of gaps patients in the 30 min before a gap was 9.4 dB and decreased to 6.7 dB during the gaps. The mean delta power difference was −2.7 dB. Fifty-two out of 55 patients (95%) had a statistically significant decrease in mean delta power during the gap.

Of the 1002 patients included in the original analysis, with the permissive thresholds 247 patients were noted as having 'gap' EEG patterns, but visual checking reduced the number of genuine 'gap' patterns to 141. Under the stringent condition, 72 patients with gap EEG patterns were identified, but visual checking reduced the number of actual gap patterns to 23. Hence, a shift of 1 dB in theta power threshold combined with a 0.5 Hz shift in alpha frequency threshold led to an approximate halving or more than doubling of pattern detecting in the stringent or permissive threshold condition, respectively. When permissive thresholds were used, gap patients were still significantly younger than non-gap patients (62 *vs* 68 yr, respectively; $P<0.01$); the same trend was also observed when the stringent thresholds were used (58 *vs* 67 yr, respectively; $P<0.01$).

Discussion

In this observational study of patients undergoing general anaesthesia for cardiac surgery, we detected EEG activity consistent with substantial lightening of anaesthesia in 55 of 1002 patients (5.5%); 84% of these EEG patterns occurred within a 1 h window centred on the time of separation from CPB, and around two-thirds of these patients had received neuromuscular blocking agents close to or at the time of the arousal pattern. This lightening is reflected as alpha frequency increase and power attenuation, which can be seen as 'gaps' in the spectrogram, and might prove clinically useful to decrease the incidence of awareness with or without explicit recall during cardiac or general surgery.[23,24]

To date, all large RCTs on awareness have been based on processed EEG indices *vs* standard of care (no EEG monitoring) or a lower limit of MAC.[10–12] Thus, typical EEG changes during hypothesised awareness episodes could not be assessed; however, indices might have been in the target range during some episodes. It can only be hypothesised that episodes of awareness might be reflected in the raw EEG or spectrogram, such as the emergence reactions from general anaesthesia recently reported by Hesse and colleagues[16] with decreasing theta power and loss of alpha oscillations. Previous studies revealed that DoA monitors using processed EEG indices might not be well suited to prevent awareness,[25] but might be useful to decrease the incidence of postoperative delirium or even death.[26,27] This may be attributable to the avoidance of burst suppression. However, randomising patients to a low *vs* high target processed EEG index did not show a statistically significant difference in the number of deaths at 1 yr.[28]

Using the minimal alveolar concentration of a volatile anaesthetic as a clinical surrogate for measuring depth of hypnosis did not prove useful to decrease the incidence of awareness either,[11,12] which might be explained by the derivation of the MAC through a painful stimulus.[29] The sensitivity of the brain to an anaesthetic agent can be detected by EEG and displayed as a spectrogram,[30,31] because EEG patterns of different hypnotic depths of general anaesthesia have been described.[32] Despite the consistent decrease in delta power during the 'gaps', we are cautious about using this decrease as a criterion for defining 'gaps'. One of our recent studies has shown that during emergence after surgery about 30% of patients do not show a decrease in delta power.[33]

The sensitivity analysis yielded an approximate halving or more than doubling of gap pattern detection incidence with stringent or permissive threshold rules, respectively. When visually checking, it is clear that the stringent threshold condition was missing EEG patterns that should be considered clinically relevant to maintaining adequate hypnotic depth (i.e. creating false negatives). In contrast, in the permissive threshold condition it was much more difficult to judge if the gap patterns detected were suggestive of near-awakening or only of a lighter period of anaesthesia (false positives). As there are no gold-standard theta power and alpha frequency thresholds to determine near-awakening, we reiterate our main conclusion that these patterns can be discerned from the spectrogram, and might sometimes represent inadequate hypnotic depth of anaesthesia.

Patients with EEG gaps were younger than those without. Gaps might have been more likely in younger patients because their higher volatile anaesthetic needs were not being met. Alternatively, gaps might have been more readily detected in younger patients because the theta power decrease required for detection was too high for older patients, who have lower amplitude EEG oscillations.

There are important limitations in this study. Although the anteriorisation or frontal presence of alpha oscillations has been postulated as a characteristic pattern of unconsciousness, a recent study using the isolated forearm technique calls this into question. Despite a frontal alpha/delta EEG pattern, six out of 90 patients in the study followed a simple command, albeit without recall after surgery.[34] Thus whether an EEG pattern of alpha anteriorisation is sufficient to determine unconsciousness during surgery is controversial.[35]

A second concern is that this was a *post hoc* analysis of prospectively collected observational data. Although we detected gaps in the spectrogram in 55 patients, presumably corresponding to lightening of anaesthesia,[16] we cannot infer that these occurred during periods of intraoperative awareness, as we did not assess patients for responsiveness at these times during their surgeries. As other studies correlating the EEG spectrogram with periods of awareness do not yet exist, the thresholds for the increase of alpha frequency and decline in theta power were determined arbitrarily. Thus, if the thresholds were not defined stringently enough, every instance of decreasing DoA would be picked up as a gap, which would not be clinically useful. Recently, it was demonstrated that alpha power depends on age and probably on comorbidities.[31] It is unclear whether thresholds for the increase of alpha frequency and the decline in theta power have to be individualised.

Our analysis is of a single centre in Switzerland, and limited to cardiac surgery; it is not known to what degree variations in clinical practice between locations might contribute to the occurrence of emergence-like EEG patterns during cardiac surgery, or how often such patterns are observed in noncardiac surgery. In this report we have not analysed the role of cross frequency coupling (e.g. between the alpha and delta waveforms).

A final limitation concerns the variability of EEG changes during emergence. As has been noted before, not all patients show the classic increase in alpha frequency and loss of theta power during emergence.[14,15] A minority of patients can retain an alpha oscillation right until the point immediately before waking. The biological reasons for this hysteresis are not known,[36] and to date have only been examined in the slow-wave range of the EEG.[33] Our proposed detection method is thus limited to the majority of patients who would show the typical alpha and theta changes during emergence, and who do not have the added safety buffer of neural inertia.[37]

In conclusion, we have observed that about 5% of patients showed EEG patterns during cardiac surgery similar to the patterns commonly seen with emergence from anaesthesia. These patterns (an increase in alpha frequency concurrent with a decrease in theta power) occurred predominantly around the time of separation from CPB, a period when volatile concentrations at the effect sites can fluctuate. Given these observations, we highlight the potential utility of routine frontal EEG monitoring (spectrogram), especially during transition periods in high-risk cardiac surgery. A careful visual inspection of the spectrogram, and adjusting volatile anaesthetic dosing accordingly, may act as a useful method to avoid potential unintended emergence events and to decrease the incidence of awareness. Mind the gap!

Authors' contributions

Conception and design: HAK, DH
Acquisition of data: HAK, ML, FL, VK, DR, DH
Analysis of data: HAK, JS, DH
Interpretation of data: HAK, MP, ML, FL, VK, JS, DH
Drafting of the article: HAK, MP, DH
All authors were involved in the critical revision of the manuscript, approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

Declarations of interest

The authors declare that they have no conflicts of interest.

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References

1. Avidan MS, Mashour GA. The incidence of intraoperative awareness in the UK: under the rate or under the radar? *Br J Anaesth* 2013; **110**: 494–7
2. Ranta SOV, Herranen P, Hynynen M. Patients' conscious recollections from cardiac anesthesia. *J Cardiothorac Vasc Anesth* 2002; **16**: 426–30
3. Sandin RH, Enlund G, Samuelsson P, Lennmarken C. Awareness during anaesthesia: a prospective case study. *Lancet* 2000; **355**: 707–11
4. Smith D, Goddard NG. Awareness in cardiothoracic anaesthetic practice – where now after NAP5? *Anaesthesia* 2015; **70**: 130–4
5. Kaplan JA. *Essentials of cardiac Anesthesia for noncardiac surgery*. Amsterdam: Elsevier Health Sciences; 2018
6. Barry AE, Chaney MA, London MJ. Anesthetic management during cardiopulmonary bypass: a systematic review. *Anesth Analg* 2015; **120**: 749–69
7. Nitzschke R, Wilgusch J, Kersten JF, et al. Changes in sevoflurane plasma concentration with delivery through the oxygenator during on-pump cardiac surgery. *Br J Anaesth* 2013; **110**: 957–65
8. Montupil J, Defresne A, Bonhomme V. The raw and processed electroencephalogram as a monitoring and diagnostic tool. *J Cardiothorac Vasc Anesth* 2019; **33**: S3–10
9. Nickalls RWD, Mahajan RP. Awareness and anaesthesia: think dose, think data. *Br J Anaesth* 2010; **104**: 1–2
10. Myles PS, Leslie K, McNeil J, Forbes A, Chan MTV. Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial. *Lancet* 2004; **363**: 1757–63
11. Avidan MS, Zhang L, Burnside BA, et al. Anesthesia awareness and the bispectral index. *N Engl J Med* 2008; **358**: 1097–108
12. Avidan MS, Jacobsohn E, Glick D, et al. Prevention of intraoperative awareness in a high-risk surgical population. *N Engl J Med* 2011; **365**: 591–600
13. Whitlock EL, Villafranca AJ, Lin N, et al. Relationship between bispectral index values and volatile anesthetic concentrations during the maintenance phase of anesthesia in the B-Unaware trial. *Anesthesiology* 2011; **115**: 1209–18
14. Chander D, García PS, MacColl JN, Illing S, Sleigh JW. Electroencephalographic variation during end maintenance and emergence from surgical anesthesia. *PLoS One* 2014; **9**, e106291
15. Hight DF, Dadok VM, Szeri AJ, García PS, Voss L, Sleigh JW. Emergence from general anesthesia and the sleep-manifold. *Front Syst Neurosci* 2014; **8**: 146
16. Hesse S, Kreuzer M, Hight D, et al. Association of electroencephalogram trajectories during emergence from anaesthesia with delirium in the postanaesthesia care unit: an early sign of postoperative complications. *Br J Anaesth* 2019; **122**: 622–34
17. Purdon PL, Pierce ET, Mukamel EA, et al. Electroencephalogram signatures of loss and recovery of consciousness from propofol. *Proc Natl Acad Sci U S A* 2013; **110**: E1142–51
18. Hight D, Voss LJ, García PS, Sleigh J. Changes in alpha frequency and power of the electroencephalogram during volatile-based general anesthesia. *Front Syst Neurosci* 2017; **11**: 36
19. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology

(STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**: 1453–7

20. Strobach P, Abraham-Fuchs K, Härer W. Event-synchronous cancellation of the heart interference in biomedical signals. *IEEE Trans Biomed Eng* 1994; **41**: 343–50
21. Schindler K, Wiest R, Kollar M, Donati F. EEG analysis with simulated neuronal cell models helps to detect pre-seizure changes. *Clin Neurophysiol* 2002; **113**: 604–14
22. Sleigh JW, Leslie K, Voss L. The effect of skin incision on the electroencephalogram during general anesthesia maintained with propofol or desflurane. *J Clin Monit Comput* 2010; **24**: 307–18
23. Hight DF, Gaskell AL, Kreuzer M, Voss LJ, García PS, Sleigh JW. Transient electroencephalographic alpha power loss during maintenance of general anaesthesia. *Br J Anaesth* 2019; **122**: 635–42
24. Pereira RM, Salgado-Seixas F, Cavaleiro C, Machado H. Misinterpretation and limitations of bilateral depth of anesthesia monitoring with Propofol plus Dexmedetomidine – a case of awareness? *Eur J Anaesthesiol* 2019; **36**: 56–7
25. Avidan MS, Mashour GA. Prevention of intraoperative awareness with explicit recall: making sense of the evidence. *Anesthesiology* 2013; **118**: 449–56
26. Aldecoa C, Bettelli G, Bilotta F, et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. *Eur J Anaesthesiol* 2017; **34**: 192–214
27. Wildes TS, Mickle AM, Ben Abdallah A, et al. Effect of electroencephalography-guided anesthetic administration on postoperative delirium among older adults undergoing major surgery. *JAMA* 2019; **321**: 473–83
28. Short TG, Campbell D, Frampton C, et al. Anaesthetic depth and complications after major surgery: an international, randomised controlled trial. *Lancet* 2019; **394**: 1907–14
29. Paul M, Fisher DM. Are estimates of MAC reliable? *Anesthesiology* 2001; **95**: 1362–70
30. Purdon PL, Sampson A, Pavone KJ, Brown EN. Clinical electroencephalography for anesthesiologists: Part I. Background and basic signatures. *Anesthesiology* 2015; **123**: 937–60
31. Kaiser HA, Hirschi T, Hartwich V, et al. Decreasing frontal electroencephalogram alpha power and increasing sensitivity to volatile anesthetics over 3 surgeries within 7 months: a case report. *A A Pract* 2019; **13**: 274–7
32. Bennett C, Voss LJ, Barnard JPM, Sleigh JW. Practical use of the raw electroencephalogram waveform during general anesthesia: the art and science. *Anesth Analg* 2009; **109**: 539–50
33. Warnaby CE, Sleigh JW, Hight D, Jbabdi S, Tracey I. Investigation of slow-wave activity saturation during surgical anesthesia reveals a signature of neural inertia in humans. *Anesthesiology* 2017; **127**: 645–57
34. Gaskell AL, Hight DF, Winders J, et al. Frontal alpha-delta EEG does not preclude volitional response during anaesthesia: prospective cohort study of the isolated forearm technique. *Br J Anaesth* 2017; **119**: 664–73
35. Sanders RD, Tononi G, Laureys S, Sleigh JW. Unresponsiveness ≠ unconsciousness. *Anesthesiology* 2012; **116**: 946–59
36. Kuizenga MH, Colin PJ, Reyntjens KMEM, et al. Test of neural inertia in humans during general anaesthesia. *Br J Anaesth* 2018; **120**: 525–36
37. Sepúlveda PO, Tapia LF, Monsalves S. Neural inertia and differences between loss of and recovery from consciousness during total intravenous anaesthesia: a narrative review. *Anaesthesia* 2019; **74**: 801–9

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