Double standard: why electrocardiogram is standard care while electroencephalogram is not?

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Purpose of review

Major adverse cardiovascular and cerebrovascular events (MACCE) significantly affect the surgical outcomes. Electrocardiogram (ECG) has been a standard intraoperative monitor for 30 years. Electroencephalogram (EEG) can provide valuable information about the anesthetized state and guide anesthesia management during surgery. Whether EEG should be a standard intraoperative monitor is discussed in this review.

Recent findings

Deep anesthesia has been associated with postoperative delirium, especially in elderly patients. Intraoperative EEG monitoring has been demonstrated to reduce total anesthesia drug use during general anesthesia and postoperative delirium.

Summary

Unlike ECG monitoring, the EEG under general anesthesia has not been designated as a standard monitor by anesthesiologist societies around the world. The processed EEG technology has been commercially available for more than 25 years and EEG technology has significantly facilitated its intraoperative use. It is time to consider EEG as a standard anesthesia monitor during surgery.

Keywords

electrocardiogram, electroencephalogram, postoperative delirium, standard monitor

INTRODUCTION

The postoperative complication rate is around 30% and can be as high as 48% in cardiac surgery [1,2]. Major adverse cardiovascular and cerebrovascular events (MACCE) are a significant source of perioperative morbidity and mortality. They occur in 3% hospitalizations for noncardiac surgery, corresponding to approximately 150 000 perioperative events each year in the United States [3]. At the same time, as the population ages and more surgeries are performed, the prevalence of postoperative delirium will increase. When delirium occurs after surgery, outcomes deteriorate. Postoperative delirium has become an important postoperative complication and has been well documented as an independent predictor for adverse outcomes [3,4]. Postoperative delirium has been associated with deep anesthesia, which can be identified by monitoring the electroencephalogram (EEG). Intraoperative EEG monitoring can provide valuable information on the anesthetized state, and the effective anesthetic management guided by EEG monitoring has been suggested to reduce postoperative delirium and total anesthesia drug use during general anesthesia [5,6]. American Society of Anesthesiologists (ASA) standard monitoring includes circulation, oxygenation, ventilation and temperature. Continuous electrocardiogram (ECG) monitoring along with noninvasive blood pressure measurement has been the standard of care for patients under anesthesia. EEG monitoring has become widely available during anesthesia, however, it remains controversial whether it should be considered as part of the standard care during anesthesia as ECG [7].

ELECTROCARDIOGRAM

The ECG is a reliable monitor for heart rate, rhythm, and the cardiac conduction system and intraoperative cardiac ischemia [8]. Abnormalities of the ECG

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KEY POINTS

- Intraoperative EEG monitoring can provide valuable information on the anesthesia depth.
- Postoperative delirium has been associated with deep anesthesia which can be identified by EEG.
- Anesthetic management guided by EEG monitoring has been suggested to reduce anesthetic uses and postoperative delirium.
- Different anesthetics have distinct EEG signatures.

may also provide evidence of electrolyte abnormalities. All of these conditions may affect the hemodynamics and constitute life-threatening emergencies that can be readily treated if they are identified in a timely fashion. However, the debating on whether ECG should be monitored and whether anesthesiologists can accurately interpret its changes during surgery had been going on for years before the ASA House of Delegates' approval [9,10]. As we all know, the anesthesiologists are very comfortable with interpreting the intraoperative ECG and use it to guide their management.

ELECTROENCEPHALOGRAM

Amnesia or the depth of anesthesia is one of the three cornerstones of anesthesia together with analgesia and muscle relaxation. Meanwhile, there are EEG monitors available for perioperative use to monitor the depth of sleep/anesthesia. However, unlike ECG, the electrophysiological monitoring of the heart, has been a standard of care since 1986, there is a reluctance by anesthesiologists to regularly employ EEG, the electrophysiological monitoring of the brain, on a routine basis during everyday surgery [11]. Unlike the ECG monitoring, the EEG under general anesthesia has not been designated as a standard monitor by anesthesiologist societies around the world [12–14]. Instead, anesthesia care providers have judged the depth of anesthesia by physical signs like heart rate, blood pressure, and movement.

ELECTROENCEPHALOGRAM PATTERNS IN GENERAL ANESTHESIA

There are several EEG wave patterns that occur during general anesthesia and their frequencies are measured in Hertz (Hz), namely, delta (δ) wave, a slow brain wave from 0.1 to less than 4 Hz, theta (θ) wave from 4 to less than 8 Hz, alpha (α) wave from 8 to 13 Hz, beta (β) wave from more than 13 to 30 Hz and gamma (γ) wave more than 30 to 80 Hz (Fig. 1) [15]. Each frequency represents a different depth of anesthesia [16]. During general anesthesia with volatile agents or propofol, the changes of frontally derived EEG has been well known as a transition from the low-voltage, high-frequency pattern, to the slow wave EEG, and finally to burst suppression [17,18].

Band	Frequency (Hz)	Anesthesia Significance	EEG waves
Gamma (γ)	> 30 ~ 80	Associated with Ketamine	
Beta (β)	> 13 ~ 30	Awake with eyes open	
alpha (α)	8 ~ 13	Intermediate anesthesia	
theta (θ)	4 ~ < 8	Deep anesthesia	
delta (δ)	0.1 ~ < 4	Deep anesthesia	
Burst suppression		Excessively deep anesthesia	

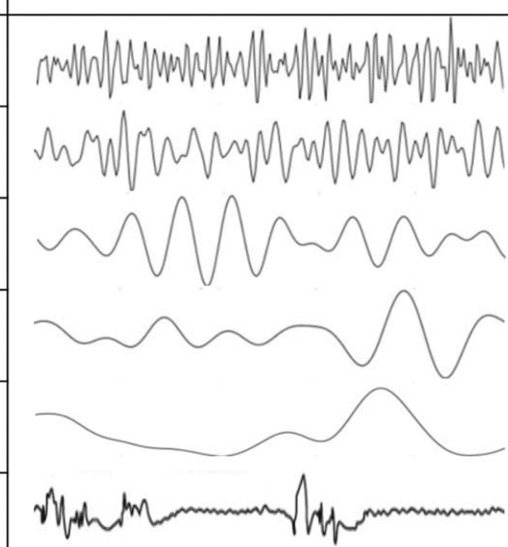

FIGURE 1. Schematic electroencephalogram (EEG) pattern with anesthesia significance.

ELECTROENCEPHALOGRAM GUIDED ANESTHETIC MANAGEMENT AND OUTCOMES

Postoperative delirium has become an important postoperative complication that occurs from 15 to 20% following major operations in patients at 65 years and older [3,4,19]. Postoperative delirium is an independent predictor for adverse outcomes [4], and it is also associated with prolonged hospital stay, increased risk of morbidity and mortality, decreased quality of life, and increased healthcare costs [20–23]. The postoperative delirium-associated EEG changes have been described as an increased δ and θ and a decreased α activity [24,25]. Moreover, there is reduced global cortical connectivity and disruption of posterior to anterior information flow [26]. Deep anesthesia has been associated with postoperative delirium. Studies on optimization of anesthesia depth guided EEG have found intraoperative neuromonitoring was associated with a lower incidence of postoperative delirium [5,6,27]. A meta-analysis with a total of 2654 individuals demonstrated the use of EEG-guided anesthesia was associated with a 38% reduction in odds for developing postoperative delirium [28▪].

Studies also reported that special EEG pattern, such as burst suppression (Fig. 2), was an independent predictor of increased risks of delirium and death at 6 months in ICU patients [29,30]. The relationship between burst suppression during general anesthesia and postoperative delirium has also been identified [31]. Burst suppression reflects a brain state of relative cortical quiescence not observed during normal wake or sleep states, and they are closely associated with excessively deep anesthesia and pathological states such as traumatic brain injury, coma, severe hypothermia, hypoxia, hypoglycemia, encephalopathies, or hypoperfusion of the brain [32,33]. Studies suggested that longer duration of intraoperative burst suppression was associated with an increased incidence of postoperative delirium and burst suppression is an independent risk factor for postoperative delirium [31,34]. Fritz and colleagues found that patients with burst suppression at lower anesthetic concentrations had a higher incidence of postoperative delirium [35▪▪]. However, in one recent study, the authors did not find the differences in postoperative delirium between EEG-guided and the usual care groups in older adults undergoing major surgery. The 30-day mortality was significantly lower in the EEG-guided group compared with the usual care group [36▪].

Not only burst suppression has been associated with postoperative delirium, but also EEG δ oscillations have associated with postoperative delirium. A study aimed to develop an EEG-based tool for delirium detection found that the relative δ power from an eyes-closed EEG recording with only two electrodes in a frontal-parietal derivation can distinguish delirium from nondelirium [37]. Numan *et al.* [38▪] detected postoperative delirium in older patients based on a 1-min single-channel EEG

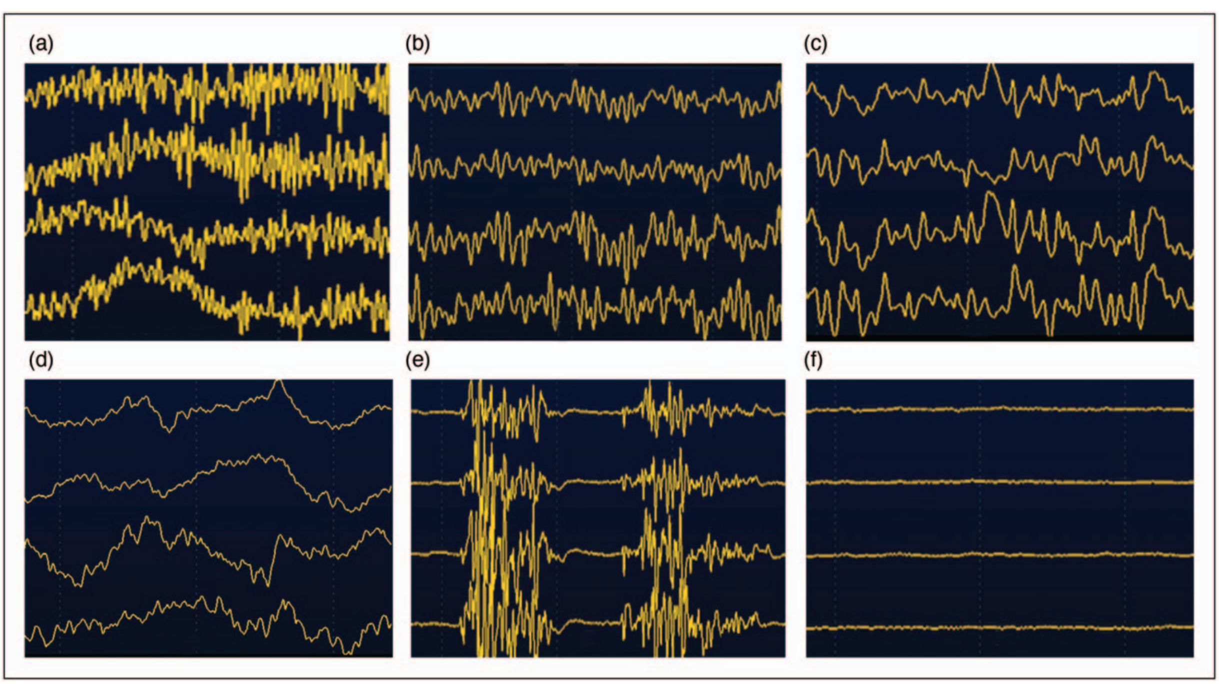

FIGURE 2. Representative raw electroencephalogram (EEG) pattern under general anesthesia. (A) Gamma (γ) wave, (B) beta (β) wave, (C) alpha (α) wave, (D) delta (δ) wave and some other waves, (E) burst suppression, and (F) isoelectric flat line.

recording and found an association between postoperative delirium and EEG slow wave (δ and θ) oscillations. Eyal *et al.* [39■] demonstrated that a composite of generalized θ or δ waves had been strongly associated with delirium and poor clinical outcomes.

Intraoperative EEG monitoring has been shown to reduce anesthetic exposure. A study found that EEG-guided anesthesia management reduced propofol delivery by 21% and reduced volatile anesthetic use by 30% compared with routine care in 921 elderly patients undergoing major noncardiac surgery [5]. Furthermore, EEG monitoring has led to reduced emergence time after general anesthesia. Another meta-analysis of 9537 patients compared bispectral index (BIS) guided and non-BIS guided anesthetic protocols. It demonstrated that BIS monitoring was associated with shortened emergence time compared to the non-BIS monitoring methods [40]. Similar studies found EEG-guided anesthesia can improve anesthetic delivery and postoperative recovery from relatively deep anesthesia [41,42■].

Accidental awareness during general anesthesia (AAGA) is a very serious anesthesia complication. Although the incidence was relatively low, it may develop a spectrum of psychological injury ranging from mild, transient symptoms to severe. The disabling symptoms of posttraumatic stress disorder (PTSD) occurred in 79% of patients who experienced AAGA [43]. The AAGA varied from 0.017 to 4%, and the relatively reliable incidence of intraoperative awareness with postoperative recall is 0.02% [44,45]. There are many factors for awareness and the insufficient anesthetic dosing was thought to be the principal cause. Studies have demonstrated that EEG guided anesthesia reduces the risk of awareness in at-risk adult surgical patients undergoing general anesthesia with muscle relaxation and total intravenous anesthesia [46,47]. A systematic review examined 36 randomized controlled studies comparing EEG guided general anesthesia with standard practice for anesthetic delivery, and the results found that EEG guided general anesthesia reduced risk of AAGA in those patients who are at risk. However, they did not show any difference in terms of intraoperative awareness compared to studies using end tidal anesthetic gas (ETAG) monitoring as a guide for anesthesia management [41].

ELECTROENCEPHALOGRAM PATTERNS AND ANESTHESIA DRUG FOOT PRINT

Different anesthetics, which have differently specific molecular targets and neural circuits mechanisms of action, translate into distinct brain states that are associated with different EEG signatures (Fig. 3). Propofol has most commonly been used intravenous anesthetic for sedation and maintenance of general

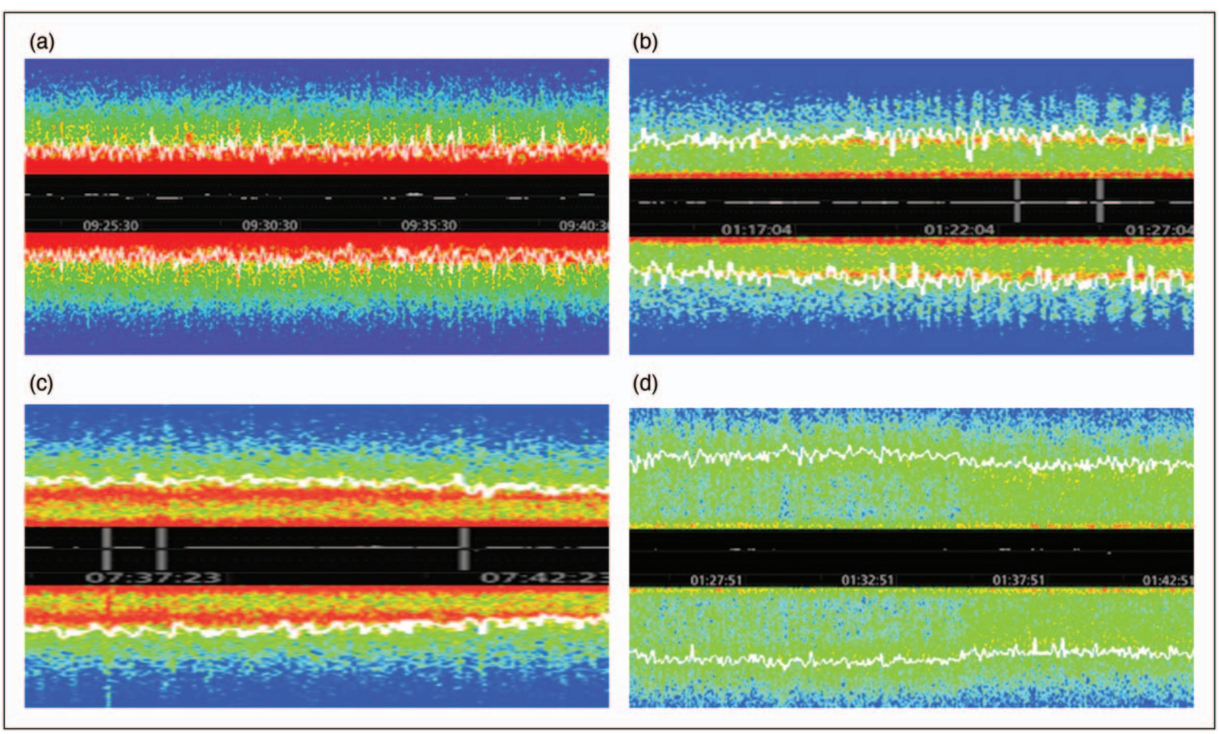

FIGURE 3. Representative electroencephalogram (EEG) density spectral array (DSA) pattern of anesthesia drug foot prints. (A) Sevoflurane, (B) dexmedetomidine, (C) propofol, and (D) ketamine.

anesthesia. Propofol primarily acts at $GABA_A$ receptors throughout the brain and spinal cord to lead to inhibition in neural circuits [48,49]. The EEG characteristic of propofol induced unconsciousness is alpha (8–13 Hz) oscillations that are coherent across the frontal cortex, delta (1–4 Hz) oscillations, and high amplitude incoherent slow (0.1–1 Hz) oscillations [32,50–53].

Ketamine is primarily a noncompetitive *N*-methyl-d-aspartate (NMDA) antagonist and increases activity of pyramidal neurons throughout the brain [54]. The EEG patterns of ketamine has distinctive electrophysiologic profiles, including an increase of high β and γ oscillations (Figs. 2 and 3) [55,56].

Dexmedetomidine, a highly selective α2-adrenergic receptor agonist, induces its sedative effects primarily by actions on presynaptic α2-adrenergic receptors on neurons that project from the locus ceruleus [57,58]. Sedation with dexmedetomidine closely resembles nonrapid eye movement sleep with a characteristic spindle wave (12–16 Hz) in the frontal area (Fig. 3) [59,60].

Sevoflurane, an inhaled anesthetic, produces its physiologic and behavioral effects through binding at multiple targets in the brain and spinal cord. Action at these targets include binding to $GABA_A$ receptors and enhancing GABAergic inhibition, blocking glutamate release by binding to NMDA receptors, moreover, blockade of two-pore potassium channels and hyperpolarization-activated cyclic nucleotide-gated channels [61]. The EEG signatures of sevoflurane GA shows coherent α oscillations and slow-delta oscillations like propofol. Furthermore, sevoflurane also exhibited a distinct theta coherence signature (Fig. 3) [59].

It is also known that aging can influence the EEG during general anesthesia, and the changes in the EEG power across all frequency bands decreased significantly with age, anesthesia-induced frontal alpha oscillation power have a specific age-dependent decrease [62–64]. Akeju *et al.* studied age-related changes in the EEG during sevoflurane anesthesia in pediatric patients, and showed that total EEG power (1–50 Hz) have an increase from infancy, peaked at 5–8 years, and subsequently declining to a plateau at 18–21 years. Moreover, Infants (<1 year) did not present prominent power or coherence in the α band [65].

ELECTROENCEPHALOGRAM MONITORS

There are several processed EEG monitors commercially available for monitoring level of consciousness using different indexes during sedation and general anesthesia. Those include BIS, narcotrend index, state entropy and response entropy, cerebral state index, patient state index, index of consciousness [66–70]. Most of these monitors are focused on targeting proprietary dimensionless index values, the meaning of which are not well understood. Some of the EEG monitors such as SedLine sedation monitor by Masimo (Irvine, CA) and BIS brain monitoring system by Medtronic (Fridley, MN) can simultaneous display four channels frontal EEG waveforms, density spectral array (DSA), burst suppression, together with bilateral spectral edge frequency by colored two-dimensional contour plot which contains left and right spectrograms representing the power of the EEG on both sides of the brain.

However, anesthesia providers employing EEG monitoring need to be familiar with different raw EEG waves and the signatures of the different anesthesia drugs to maximize the benefit of EEG monitoring. It seems likely that most anesthesiologists should be able to reliably judge the effects of anesthetic by observing raw EEG after just 1 or 2 weeks of training [71]. Despite these difficulties, the application of electrophysiological monitoring of the brain and spinal cord are growing [72].

CONCLUSION

No monitor is perfect. The ECG for example does not provide any information about cardiac output and therefore only delivers limited information about the cardiovascular system. Considering the capability of EEG to provide the information about the brain and that it can be used to guide the intraoperative anesthesia management, it seems that we are applying a double standard when we monitor the ECG for every anesthesia case but only use EEG monitoring for specific indications. It is conceivable that the information gained from current EEG monitoring, especially, DSA, SEL, burst suppression and four channel raw EEG tracings give anesthesia care providers an overall picture of anesthesia depth. EEG should, therefore, be designated as a standard anesthesia monitor during general anesthesia for a personalized anesthesia care.

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Conflicts of interest

H.L. was a speaker for Masimo in the past 36 months. There are no conflicts of interest for Y.L. and C.B.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■■ of outstanding interest

1. Tevis SE, Kennedy GD. Postoperative complications and implications on patient-centered outcomes. J Surg Res 2013; 181:106–113.
2. Ji F, Li Z, Nguyen H, *et al.* Perioperative dexmedetomidine improves outcomes of cardiac surgery. Circulation 2013; 127:1576–1584.
3. Zenilman ME. Delirium: an important postoperative complication. JAMA 2017; 317:77–78.
4. Gleason LJ, Schmitt EM, Kosar CM, *et al.* Effect of delirium and other major complications on outcomes after elective surgery in older adults. JAMA Surg 2015; 150:1134–1140.
5. Chan MT, Cheng BC, Lee TM, *et al.* Bis-guided anesthesia decreases postoperative delirium and cognitive decline. J Neurosurg Anesthesiol 2013; 25:33–42.
6. Punjasawadwong Y, Chau-In W, Laopaiboon M, *et al.* Processed electroencephalogram and evoked potential techniques for amelioration of postoperative delirium and cognitive dysfunction following noncardiac and nonneurosurgical procedures in adults. Cochrane Database Syst Rev 2018; 5:CD011283.
7. Berger M, Mark JB, Kreuzer M. Of parachutes, speedometers, and EEG: what evidence do we need to use devices and monitors? Anesth Analg 2020; 130:1274–1277.
8. John AD, Fleisher LA. Electrocardiography: the ECG. Anesthesiol Clin 2006; 24:697–715v-vi.
9. Raftery EB. Diagnosis and management of myocardial infarction during anaesthesia. Proc R Soc Med 1973; 66:1209–1211.
10. Lizasoain A, Tort LF, Garcia M, *et al.* Standards for basic anesthetic monitoring: committee of origin: standards and practice parameters. Am Soc Anesthesiol 2015; 1:1–4.
11. Kemp H, Marinho S, Cook TM, *et al.* An observational national study of anaesthetic workload and seniority across the working week and weekend in the UK in 2016: the 6th national audit project (nap6) activity survey. Br J Anaesth 2018; 121:134–145.
12. Checketts MR, Alladi R, Ferguson K, *et al.* Recommendations for standards of monitoring during anaesthesia and recovery 2015: Association of Anaesthetists of Great Britain and Ireland. Anaesthesia 2016; 71:85–93.
13. Gelb AW, Morriss WW, Johnson W, *et al.* World Health Organization-World Federation of Societies of Anaesthesiologists (WHO-WFSA) international standards for a safe practice of anesthesia. Anesth Analg 2018; 126:2047–2055.
14. Apfelbaum JL. Update from the 2015-16 ASA Committee on Standards and Practice Parameters. ASA Newsletter 2016; 80:58–59.
15. Kane N, Acharya J, Benickzy S, *et al.* A revised glossary of terms most commonly used by clinical electroencephalographers and updated proposal for the report format of the EEG findings. Revision 2017. Clin Neurophysiol Pract 2017; 2:170–185.
16. Shander A, Lobel GP, Mathews DM. Brain monitoring and the depth of anesthesia: another goldilocks dilemma. Anesth Analg 2018; 126: 705–709.
17. Bennett C, Voss LJ, Barnard JP, *et al.* Practical use of the raw electroencephalogram waveform during general anesthesia: the art and science. Anesth Analg 2009; 109:539–550.
18. Purdon PL, Sampson A, Pavone KJ, *et al.* Clinical electroencephalography for anesthesiologists. Part I: Background and basic signatures. Anesthesiology 2015; 123:937–960.
19. Trzepacz PT. Delirium. Advances in diagnosis, pathophysiology, and treatment. Psychiatr Clin North Am 1996; 19:429–448.
20. Lat I, McMillian W, Taylor S, *et al.* The impact of delirium on clinical outcomes in mechanically ventilated surgical and trauma patients. Crit Care Med 2009; 37:1898–1905.
21. Witlox J, Eurelings LS, de Jonghe JF, *et al.* Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. JAMA 2010; 304:443–451.
22. Leslie DL, Marcantonio ER, Zhang Y, *et al.* One-year healthcare costs associated with delirium in the elderly population. Arch Intern Med 2008; 168:27–32.
23. Koster S, Hensens AG, Schuurmans MJ, *et al.* Consequences of delirium after cardiac operations. Ann Thorac Surg 2012; 93:705–711.
24. Plaschke K, Hill H, Engelhardt R, *et al.* EEG changes and serum anticholinergic activity measured in patients with delirium in the intensive care unit. Anaesthesia 2007; 62:1217–1223.
25. Thomas C, Hestermann U, Kopitz J, *et al.* Serum anticholinergic activity and cerebral cholinergic dysfunction: An EEG study in frail elderly with and without delirium. BMC Neurosci 2008; 9:86.
26. Numan T, Slooter AJC, van der Kooi AW, *et al.* Functional connectivity and network analysis during hypoactive delirium and recovery from anesthesia. Clin Neurophysiol 2017; 128:914–924.
27. Radtke FM, Franck M, Lendner J, *et al.* Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. Br J Anaesth 2013; 110(Suppl 1): i98–i105.
28. ■ MacKenzie KK, Britt-Spells AM, Sands LP, *et al.* Processed electroencephalogram monitoring and postoperative delirium: a systematic review and meta-analysis. Anesthesiology 2018; 129:417–427.

The study shows that the use of EEG-guided anesthesia was associated with a 38% reduction in odds for developing postoperative delirium.

29. Watson PL, Shintani AK, Tyson R, *et al.* Presence of electroencephalogram burst suppression in sedated, critically ill patients is associated with increased mortality. Crit Care Med 2008; 36:3171–3177.
30. Andresen JM, Girard TD, Pandharipande PP, *et al.* Burst suppression on processed electroencephalography as a predictor of postcoma delirium in mechanically ventilated ICU patients. Crit Care Med 2014; 42:2244–2251.
31. Fritz BA, Kalarickal PL, Maybrier HR, *et al.* Intraoperative electroencephalogram suppression predicts postoperative delirium. Anesth Analg 2016; 122:234–242.
32. Brown EN, Lydic R, Schiff ND. General anesthesia, sleep, and coma. N Engl J Med 2010; 363:2638–2650.
33. Akeju O, Brown EN. Neural oscillations demonstrate that general anesthesia and sedative states are neurophysiologically distinct from sleep. Curr Opin Neurobiol 2017; 44:178–185.
34. Soehle M, Dittmann A, Ellerkmann RK, *et al.* Intraoperative burst suppression is associated with postoperative delirium following cardiac surgery: a prospective, observational study. BMC Anesthesiol 2015; 15:61.
35. ■■ Fritz BA, Maybrier HR, Avidan MS. Intraoperative electroencephalogram suppression at lower volatile anaesthetic concentrations predicts postoperative delirium occurring in the intensive care unit. Br J Anaesth 2018; 121:241–248.

The study demonstrated that the phenotype of burst suppression at lower anesthetic concentrations appear to be a strong predictor of postoperative delirium.

36. ■ Wildes TS, Mickle AM, Ben Abdallah A, *et al.* Effect of electroencephalography guided anesthetic administration on postoperative delirium among older adults undergoing major surgery: the engages randomized clinical trial. JAMA 2019; 321:473–483.

The trials indicates that the 30-day mortality was significantly lower in the EEG-guided group compared with the usual care group.

37. van der Kooi AW, Zaal IJ, Klijn FA, *et al.* Delirium detection using EEG: what and how to measure. Chest 2015; 147:94–101.
38. ■ Numan T, van den Boogaard M, Kamper AM, *et al.* Delirium detection using relative delta power based on 1-min single-channel EEG: A multicentre study. Br J Anaesth 2019; 122:60–68.

This study demonstrated that postoperative delirium can be detected in older postoperative patients using a 1 min single channel EEG recording analyzed automatically.

39. ■ Kimchi EY, Neelagiri A, Whitt W, *et al.* Clinical EEG slowing correlates delirium severity and predicts poor clinical outcomes. Neurology 2019; 93:e1260–e1271.

The study demonstrated that a composite of generalized θ or δ waves had been strongly associated with delirium and poor clinical outcomes.

40. Chiang MH, Wu SC, Hsu SW, *et al.* Bispectral index and nonbispectral index anesthetic protocols on postoperative recovery outcomes. Minerva Anestesiol 2018; 84:216–228.
41. Punjasawadwong Y, Phongchiewboon A, Bunchungmongkol N. Bispectral index for improving anaesthetic delivery and postoperative recovery. Cochrane Database Syst Rev 2014; CD003843.
42. ■ Lewis SR, Pritchard MW, Fawcett LJ, *et al.* Bispectral index for improving intraoperative awareness and early postoperative recovery in adults. Cochrane Database Syst Rev 2019; 9:CD003843.

The meta-analysis did not show any difference in terms of intraoperative awareness in studies with ETAG monitoring as a guide to management of anesthesia.

43. Nightingale P. Accidental awareness under general anaesthesia in the united kingdom and ireland. J R Coll Physicians Edinb 2014; 44:289–290.
44. Pandit JJ, Andrade J, Bogod DG, *et al.* The 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: summary of main findings and risk factors. Anaesthesia 2014; 69:1089–1101.
45. Chang L, Luo Q, Chai Y, *et al.* Accidental awareness while under general anaesthesia. Biosci Trends 2019; 13:364–366.
46. Myles PS, Leslie K, McNeil J, *et al.* Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial. Lancet 2004; 363:1757–1763.
47. Zhang C, Xu L, Ma YQ, *et al.* Bispectral index monitoring prevent awareness during total intravenous anesthesia: A prospective, randomized, double-blinded, multicenter controlled trial. Chin Med J (Engl) 2011; 124: 3664–3669.
48. Hemmings HC Jr, Akabas MH, Goldstein PA, *et al.* Emerging molecular mechanisms of general anesthetic action. Trends Pharmacol Sci 2005; 26:503–510.
49. Bai D, Pennefather PS, MacDonald JF, *et al.* The general anesthetic propofol slows deactivation and desensitization of gaba(a) receptors. J Neurosci 1999; 19:10635–10646.

50. 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:E1142–1151.
51. Lewis LD, Weiner VS, Mukamel EA, *et al.* Rapid fragmentation of neuronal networks at the onset of propofol-induced unconsciousness. Proc Natl Acad Sci U S A 2012; 109:E3377–3386.
52. Feshchenko VA, Veselis RA, Reinsel RA. Propofol-induced alpha rhythm. Neuropsychobiology 2004; 50:257–266.
53. Akeju O, Westover MB, Pavone KJ, *et al.* Effects of sevoflurane and propofol on frontal electroencephalogram power and coherence. Anesthesiology 2014; 121:990–998.
54. Gao M, Rejaei D, Liu H. Ketamine use in current clinical practice. Acta Pharmacol Sin 2016; 37:865–872.
55. Akeju O, Song AH, Hamilos AE, *et al.* Electroencephalogram signatures of ketamine anesthesia-induced unconsciousness. Clin Neurophysiol 2016; 127:2414–2422.
56. Vlisides PE, Bel-Bahar T, Lee U, *et al.* Neurophysiologic correlates of ketamine sedation and anesthesia: a high-density electroencephalography study in healthy volunteers. Anesthesiology 2017; 127:58–69.
57. Chiu TH, Chen MJ, Yang YR, *et al.* Action of dexmedetomidine on rat locus coeruleus neurones: intracellular recording in vitro. Eur J Pharmacol 1995; 285:261–268.
58. Bohringer C, Liu H. Is it time for an expanded role of dexmedetomidine in contemporary anesthesia practice? - a clinician's perspective. Transl Perioper Pain Med 2018; 5:55–62.
59. Akeju O, Pavone KJ, Westover MB, *et al.* A comparison of propofol- and dexmedetomidine-induced electroencephalogram dynamics using spectral and coherence analysis. Anesthesiology 2014; 121: 978–989.
60. Huupponen E, Maksimow A, Lapinlampi P, *et al.* Electroencephalogram spindle activity during dexmedetomidine sedation and physiological sleep. Acta Anaesthesiol Scand 2008; 52:289–294.
61. Campagna JA, Miller KW, Forman SA. Mechanisms of actions of inhaled anesthetics. N Engl J Med 2003; 348:2110–2124.
62. Purdon PL, Pavone KJ, Akeju O, *et al.* The ageing brain: age-dependent changes in the electroencephalogram during propofol and sevoflurane general anaesthesia. Br J Anaesth 2015; 115(Suppl 1):i46–i57.
63. Beekoo D, Yuan K, Dai S, *et al.* Analyzing electroencephalography (EEG) waves provides a reliable tool to assess the depth of sevoflurane anesthesia in pediatric patients. Med Sci Monit 2019; 25:4035–4040.
64. Hight D, Voss LJ, Garcia PS, *et al.* Changes in alpha frequency and power of the electroencephalogram during volatile-based general anesthesia. Front Syst Neurosci 2017; 11:36.
65. Akeju O, Pavone KJ, Thum JA, *et al.* Age-dependency of sevoflurane-induced electroencephalogram dynamics in children. Br J Anaesth 2015; 115(Suppl 1):i66–i76.
66. Sigl JC, Chamoun NG. An introduction to bispectral analysis for the electroencephalogram. J Clin Monit 1994; 10:392–404.
67. Aho AJ, Yli-Hankala A, Lyytikainen LP, *et al.* Facial muscle activity, response entropy, and state entropy indices during noxious stimuli in propofol-nitrous oxide or propofol-nitrous oxide-remifentanil anaesthesia without neuromuscular block. Br J Anaesth 2009; 102:227–233.
68. Jensen EW, Litvan H, Revuelta M, *et al.* Cerebral state index during propofol anesthesia: a comparison with the bispectral index and the A-line ARX index. Anesthesiology 2006; 105:28–36.
69. Drover D, Ortega HR. Patient state index. Best Pract Res Clin Anaesthesiol 2006; 20:121–128.
70. Jensen EW, Jospin M, Gambus PL, *et al.* Validation of the index of consciousness (IOC) during sedation/analgesia for ultrasonographic endoscopy. Conf Proc IEEE Eng Med Biol Soc 2008; 2008:5552–5555.
71. Hagihira S. Changes in the electroencephalogram during anaesthesia and their physiological basis. Br J Anaesth 2015; 115(Suppl 1):i27–i31.
72. Nunes RR, Bersot CDA, Garritano JG. Intraoperative neurophysiological monitoring in neuroanesthesia. Curr Opin Anaesthesiol 2018; 31:532–538.