David C. Warltier, M.D., Ph.D., Editor

Anesthesiology 2003; 99:716–37

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Pharmacologic and Physiologic Influences Affecting Sensory Evoked Potentials

Implications for Perioperative Monitoring

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EVOKED potentials (EPs) are the electrophysiologic responses of the nervous system to sensory or motor stimulation.[1,2] Stimulating the nervous system initiates the transmission of neural signals that may be recorded as EPs from various points along the stimulated pathway. Intraoperative monitoring (IOM) of EP has gained popularity because EPs reflect the functional integrity of neural pathways in anesthetized patients undergoing surgical procedures that place nervous system structures in jeopardy. EPs monitored intraoperatively include somatosensory evoked potentials (SSEPs), brainstem auditory evoked potentials (BAEPs; also referred to as auditory brainstem responses), visual evoked potentials (VEPs), and motor evoked potentials. Additional EP modalities include dermatomal sensory evoked potentials, electrocochleography, and electromyography.

Intraoperative EP changes may result from surgical injury or ischemia of the specific neural pathway, or they may be due to nonspecific physiologic or pharmacologic influences. Physiologic factors that may influence EPs include temperature, blood pressure, hematocrit, acid–base balance, and oxygen and carbon dioxide tensions. Anesthetic drugs and sedatives are the most common pharmacologic causes of nonspecific EP changes.

This review discusses the physiologic and pharmacologic factors (including newer anesthetic agents and adjuncts) that influence sensory evoked potentials (SEPs), focussing on SSEPs, BAEPs, and VEPs. For ease of reference and to allow better comparisons between anesthetic agents, the discussion of anesthetic effects is separated from physiologic effects. The review intends to help clinicians recognize the important confounding perturbations so that intraoperative changes in SEPs can be interpreted optimally. It also aims to guide anesthetic planning so that reliable intraoperative EP monitoring can be accomplished during effective and safe anesthesia.

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Received from the Department of General Anesthesiology, The Cleveland Clinic Foundation, Cleveland, Ohio. Submitted for publication August 8, 2001. Accepted for publication December 9, 2002. Support was provided solely from the Department of General Anesthesiology, The Cleveland Clinic Foundation, Cleveland, Ohio.

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Describing Sensory Evoked Potential Waveforms

The single cortical sensory evoked response has a low amplitude (1–2 μV) compared with the much larger electroencephalogram waves (50–100 μV). Therefore, the EP wave has to be extracted from concurrent spontaneous electroencephalogram activity by repetitive stimulation and computer-signal averaging techniques.[3] The EP waveform consists of a series of peaks and valleys presented as a graph of voltage over time and described in terms of amplitude, latency, and morphology. For IOM, amplitude is commonly measured as the waves' peak-to-peak voltage difference. *Latency* is the time from stimulus to the peak of the response. *Interpeak latency* is the interval between the peaks of interest (fig. 1).

Evoked potential waves can have either negative or positive polarity. A negative wave occurring at a latency of approximately 20 ms would be indicated as N-20. Generally, negative waves are shown as upward deflections, while positive waves are shown as downward deflections. Evoked potentials can be of cortical or subcortical origin. Responses recorded by electrodes located within 3–4 cm of the neural generator are termed *near-field potentials* (*e.g.*, cortical SSEP waves recorded from scalp electrodes), whereas those recorded from electrodes farther from the neural generator are called *far-field potentials* (*e.g.*, BAEP recorded over the vertex).[4,5] SEPs are also classified as short latency ($<$ 30 ms), intermediate latency (30–75 ms), or long latency ($>$ 75 ms).[6]

For the purposes of this review, SEPs are considered recordable when reproducible waveforms are reported. An anesthetic regimen is described as compatible with IOM when it results in consistently recordable waveforms. Reliability of SEPs refers to their ability to detect potentially injurious conditions intraoperatively.

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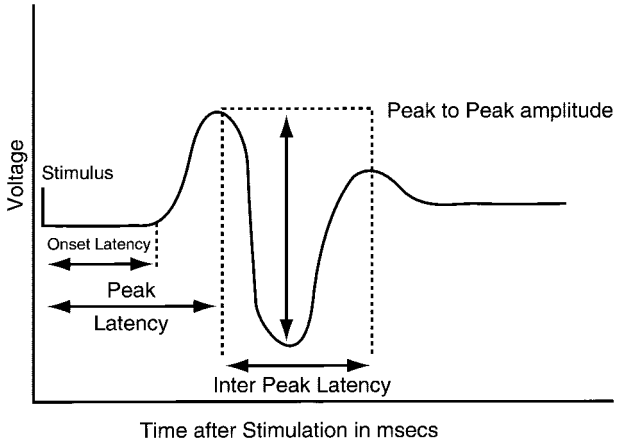

Fig. 1. Schematic evoked potential as described in terms of latency and amplitude.

Pharmacologic Effects of Anesthetics on Sensory Evoked Potentials

Somatosensory Evoked Potentials

Anatomic and Electrophysiologic Considerations. The SSEP represents the reproducible electrical activity of cortical and subcortical structures time-locked to a peripheral nerve stimulus. For perioperative applications, electrical impulses are commonly delivered to the median nerve or posterior tibial nerves using needle or surface electrodes. The impulse propagates peripherally (resulting in muscle twitches) and centrally *via* the peripheral nerve and the dorsal root to the spinal cord. The nerve cell body of the first-order neuron lies in the dorsal root ganglion. Impulses then ascend primarily in the dorsal column fibers of the spinal cord, which synapse (fig. 2) in the lower medulla near the nucleus gracilis and cuneatus, respectively. Axons of the second-order neurons cross the midline at the cervicomedullary junction, from where they regroup to form the medial lemniscus and synapse in the ventroposterior–lateral nucleus of the contralateral thalamus. Third-order neurons from the ventroposterior–lateral leave the thalamus and travel through the posterior limb of the internal capsule as the thalamocortical radiation to synapse in the primary somatosensory cortex in the postcentral gyrus of the parietal lobe. The spinocerebellar pathways, located anteriorly in the spinal cord, contribute to the rostral conduction of SSEP signals. Therefore, SSEPs can assess the sensory system from the peripheral nerves through the spinal cord and brainstem to the cerebral cortex.

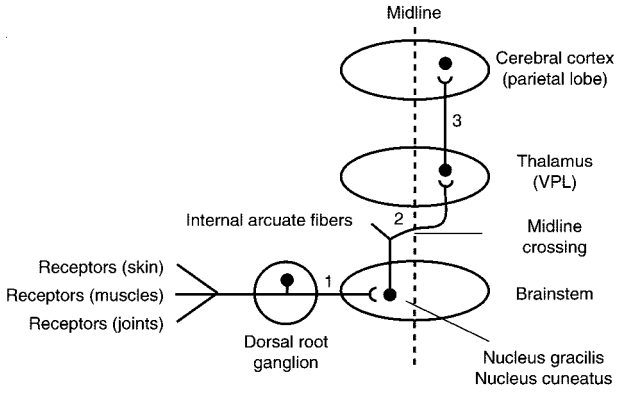

Fig. 2. Three neuron (*1*, *2*, and *3*) organization of dorsal column-medial lemniscal system. VPL = ventral posterolateral. (Redrawn with permission from Bhatnagar SC, Andy OJ: Neuroscience for the Study of Communicative Disorders. Edited by Butler JP. Baltimore, Lippincott Williams & Wilkins, 1995.)

Somatosensory evoked potential waveform activity can be recorded at the popliteal fossa after posterior tibial nerve stimulation and at Erb's point above the clavicle after median nerve stimulation. Spinal potentials recorded over the cervical and lumbar spinous processes confirm the delivery of the stimulus to the central neural axis, after it is delivered in the arm or leg, respectively. The subcortical component of the SSEP is recorded over the second cervical vertebra as a negative deflection (N-14) 14 ms after median nerve stimulation. The earliest cortical (midlatency) component of the SSEP wave is generated by the primary somatosensory cortex and occurs approximately 20 ms after median nerve and 40 ms after posterior tibial nerve stimulation. Cortical SSEPs are recorded from scalp overlying the contralateral primary sensory cortex (fig. 3). A spinal sensory EP may be stimulated or recorded from epidural electrodes placed percutaneously or in the surgical field. The central conduction time (CCT) is the time needed for the signal to travel from the cervicomedullary junction to the contralateral cerebral cortex (CCT = N-20 to N-14 latency difference after median nerve stimulation).

The subcortical SSEP recorded over the second cervical vertebra can be very useful intraoperatively because it is not very susceptible to anesthetic effects.[7] Assuming an electromyography artifact is eliminated and technical problems are solved, the cervical response has a shorter acquisition time that allows faster feedback to the surgical team, which enhances its usefulness in surgical procedures that may jeopardize the spinal cord. The midlatency cortical SSEP is moderately sensitive to anesthetic depression, but clinically useful recordings can be obtained in most patients with modifications in anesthetic technique. Longer latency SSEP waves, which represent further neural processing of sensory inputs into the association cortex, are exquisitely sensitive to anesthetic drugs, and therefore, are not useful to monitor the integrity of the sensory pathway.[8]

What Constitutes an Important SSEP Change? Diagnostic criteria to evaluate intraoperative waveform changes diagnostic of spinal cord dysfunction have been difficult to establish. Latency changes of 7–10% and amplitude decreases of 45–50% may occur without changes in postoperative neurologic function.[9–11] The criteria for determining which event-related changes[10] should be considered significant are still empiric.[12] In patients undergoing surgical correction of neuromuscular scoliosis,

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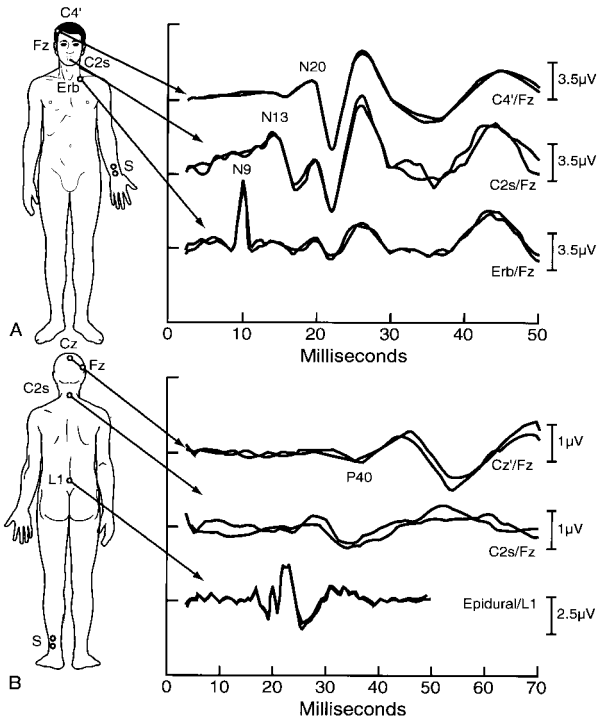

Fig. 3. (*A*) Somatosensory evoked potentials after stimulation to the left median nerve, recorded transcutaneously from points along the somatosensory pathway: from Erb's point (Erb/Fz) over the second cervical spinous process (C2s/Fz) and over the somatosensory cortex (C4'/Fz). The difference between N13 and N20 waveform peaks represents the central conduction time. (*B*) Somatosensory evoked potentials after stimulation to the left tibial nerve, recorded from points along the somatosensory pathway: from the first lumbar epidural space (epidural/L1) from the skin overlying the second cervical spinous process (C2s/Fz) and from the scalp overlying the somatosensory cortex (Cz'/Fz). (Redrawn with permission from Lake: Clinical Monitoring for Anesthesia & Critical Care. Philadelphia, WB Saunders, 1994, pp 16–4.)

sensitivity and specificity of IOM in the detection of new postoperative neurologic deficits was maximized with the use of a 50% amplitude reduction criterion.[13] An alternate criterion for sounding the alarm intraoperatively has been loss of cortical baseline amplitude greater than 30–40%.[14–16] Most, however, consider a decrease in amplitude of 50% or greater, an increase in latency of 10% or greater, or both to be significant changes reflecting loss of integrity of a neural pathway, provided these changes are not caused by anesthetics or temperature.[17–20] At least one study suggests that the use of amplitude criteria is associated with better sensitivity for detecting neurologic injury than latency criteria.[21]

Volatile Anesthetics. General anesthesia has an inhibitory effect on neurotransmission and, therefore, on the EP. The effect of anesthetics is greater on synaptic transmission than on axonal conduction.[22] For this reason, responses recorded from polysynaptic pathways (*e.g.*, cortical recordings) are affected by anesthesia to a much greater extent than those recorded from oligosynaptic pathways (*e.g.*, spinal cord and subcortical recordings).[23] For example, VEPs (which represent cortical activity) are very sensitive to the effects of anesthetics while BAEPs (representing brainstem and subcortical activities) are the least sensitive to drug effects.

All volatile anesthetics produce a dose-dependent increase in SSEP latency, an increase in CCT, and a decrease in amplitude[23–29] (table 1). They may also cause morphologic changes, such as contraction of early cortical waveforms (N-20) into a simple monophasic wave under deep isoflurane[30,31] or sevoflurane[32,33] anesthesia (fig. 4). The later cortical waveform components are most sensitive to volatile anesthetics, with marked attenuation at concentrations exceeding 0.5 minimum alveolar concentration (MAC).[30]

Satisfactory monitoring of early cortical SSEPs is possible with 0.5–1.0 MAC halothane, enflurane, or isoflurane without nitrous oxide.[24,26] At 0.67 MAC halothane or less, SSEPs were recordable in 96% of cases but only in 91% with higher concentrations.[34] During deep (1.6 MAC) isoflurane anesthesia, however, the early cortical N-20 wave was recordable[35] in 94%, and amplitude decreased severely (table 1).[30] Yet, the later N-35 wave, which is also important in IOM, could only be recorded in 47%.[35]

The effect of volatile anesthetics on cortical SSEP amplitude is compounded by nitrous oxide. Increasing isoflurane concentration from 0.5 to 1.0 MAC in the presence of nitrous oxide resulted in a 75% decrease in the cortical SSEP (from 1.2 μV to 0.3 μV).[36]

The newer volatile anesthetics desflurane and sevoflurane affect SSEPs not unlike isoflurane but may permit the use of higher inhaled concentrations (table 1). Increases in cortical latency and decreases in amplitude occur at doses of 1.5 MAC sevoflurane and desflurane or less, with minimal effects on subcortical SSEP components.[37,38] Desflurane up to 1.0 MAC without nitrous oxide is compatible with cortical median nerve SSEP monitoring during scoliosis surgery.[38] Even at 1.5 MAC (without nitrous oxide), the amplitude of cortical SSEPs was preserved at 60% of baseline.[39] However, nitrous oxide added to desflurane[40] or sevoflurane[41] severely depresses amplitude. At 1.7–2.5 MAC sevoflurane, a high-amplitude early cortical SSEP waveform is found with absence of all later waves.[32,33]

How volatile anesthetics differ quantitatively in their effects on the SSEP is not completely settled. Pathak *et al.*[26] showed that halothane had a greater effect on both amplitude and latency of the SSEP at equipotent concentrations than either isoflurane or enflurane. On the other hand, Peterson *et al.*[24] found that isoflurane and enflurane reduced SSEP amplitude and prolonged CCT more than halothane did. Sevoflurane and desflurane are associated with less amplitude reduction than isoflurane at a MAC range of 0.7–1.3.[29] In contrast to their effects on the cortical SSEP, all volatile anesthetics, even at concentrations above 1.0 MAC, only minimally affect the sub-

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Table 1. Effect of Inhaled Anesthetics on Somatosensory Evoked Potentials

	Early Cortical Waveform‖		
Anesthetic Drug/Concentration	Latency	Amplitude	Subcortical Waveform
Halothane[24,26,34]			
0.5 MAC + 60% N_2O	< 10% ↑	≈60% ↓	Negligible
1.0 MAC + 60% N_2O	< 10% ↑	≈70% ↓	Negligible
1.5 MAC + 60% N_2O	10–15% ↑	≈80% ↓	Negligible
1.5 MAC (alone)	10–15% ↑	≈70% ↓	Negligible
Isoflurane[23–28,31,35,36]			
0.5 MAC + 60% N_2O	< 10% ↑‡	50–70% ↓	Negligible
0.5 MAC (alone)	< 15% ↑	< 30% ↑	Negligible
1.0 MAC + 60% N_2O	10–15% ↑	50–75% ↓	Negligible
1.0 MAC (alone)	15% ↑	≈50% ↓	Negligible
1.5 MAC + 60% N_2O*	> 15% ↑	> 75% ↓	5% ↑ in latency
1.6 MAC (alone)*	15–20% ↑	60–70% ↓	5% ↑ in latency 20% ↓ in amplitude
Enflurane[24–26]			
0.5 MAC + 60% N_2O	< 10% ↑	≈50% ↓	Negligible
0.2–0.6 MAC (alone)	< 10% ↑	< 20% ↓	NA
1.0 MAC + 60% N_2O*	20% ↑	≈85% ↓	Negligible
1.5 MAC + 60% N_2O	Not recordable	Not recordable	Negligible
1.5 MAC (alone)*	> 25% ↑	≈85% ↓	Negligible
Sevoflurane[32,33]			
0.5 MAC + 66% N_2O	< 5% ↑	38% ↓	Negligible
1.0 MAC + 66% N_2O	< 10% ↑	≈45% ↓	Negligible
1.5 MAC + 66% N_2O	< 10% ↑	≈50% ↓	Negligible
1.7–2.5 MAC	10–15% ↑	≈100% ↑§	NA
Desflurane[38,39]			
0.5 MAC	<5% ↑	<20% ↓	Negligible
1.0 MAC	3–8% ↑	30–40% ↓	Negligible
1.5 MAC	≤ 10% ↑	< 50% ↓	Negligible
Any with 65% N_2O†	≥ 15% ↑	> 60% ↓	Negligible
Nitrous oxide[39,41,47]			
60–65 %	No effect	50–55% ↓	Negligible

NA = data not available; negligible = less than 5% change in latency; ↑ = increase; ↓ = decrease.

All data are from humans; percent changes are synthesized from multiple sources and based on reported changes in mean values.

* In a substantial fraction of patients, wave forms were not attainable at this concentration. † Complete loss of waveform observed only with 1.5 minimum alveolar concentration (MAC) desflurane plus 65% nitrous oxide (N_2O). ‡ Up to 15% in children.[229] § Fusion to a single early cortical high-amplitude wave with abolition of all later wave components. Not proven reliable for intraoperative monitoring. ‖ For example, N-20 for median nerve somatosensory evoked potentials (SSEPs) and P-40 for posterior tibial nerve SSEPs (Fig. 3).

cortical waveform, resulting in high recordability[35] and reliability (table 2).

Nitrous Oxide. Nitrous oxide (60–70%) generally diminishes cortical SSEP amplitude by approximately 50% while leaving cortical latency and subcortical waves unaffected.[36,42] Nitrous oxide potentiates the depressant effect of volatile anesthetics[24,41] and most intravenous anesthetics,[12,43,44] producing greater amplitude depression than an equipotent concentration of volatile anesthetics administered alone[24,45,46] (table 1). For example, adding 50% (0.5 MAC) nitrous oxide to a fentanyl-based anesthetic resulted in a greater decrease in amplitude than adding 1% (0.8 MAC) isoflurane, especially in patients with abnormal preoperative SSEP.[25] Likewise, during opioid-based anesthetics, nitrous oxide depressed cortical SSEP amplitude to a greater extent than did propofol when substituted for nitrous oxide.[12,47–49]

Intravenous Anesthetics. Intravenous anesthetics generally affect SSEPs less than inhaled anesthetics (table 3). This is easily seen from the fact that the human SSEP is preserved even at high doses of narcotics and barbiturates (table 3) but abolished at high volatile anesthetic concentrations. Intravenous agents only modestly affect early and intermediate (< 40 ms for median nerve stimulation and < 80 ms for posterior tibial nerve stimulation) SSEP components. Low doses of intravenous agents have minimal effects on SSEPs, whereas high doses of most agents cause slight to moderate decreases in amplitude and increases in latency. With very few exceptions, subcortical potentials are unaffected (table 3).

Barbiturates. Barbiturates produce a dose-dependent increase in latency and decrease in early cortical SSEP amplitude that does not preclude IOM. Changes in long-latency cortical waves are affected more than subcortical and midlatency waveforms. This is consistent with the notion that barbiturates, like volatile anesthetics, affect synaptic transmission more than axonal conduction. An induction dose of thiopental (5 mg/kg) increases latency

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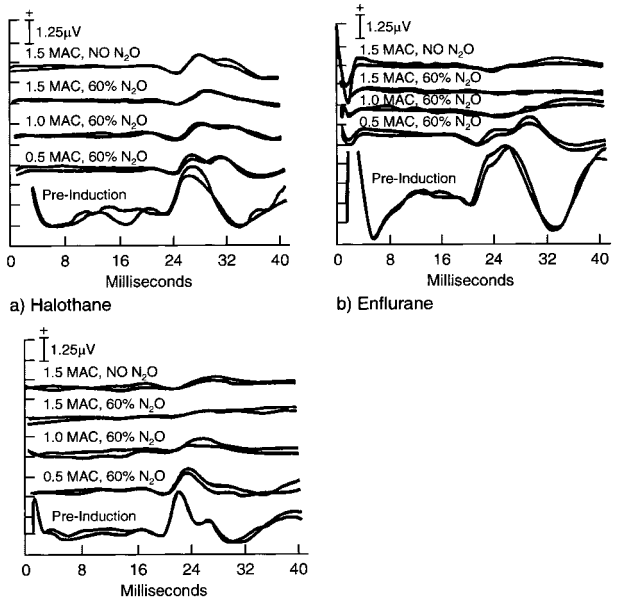

Fig. 4. Cortical somatosensory evoked potential responses at various minimum alveolar concentration (MAC) levels of halothane (*a*), enflurane (*b*), and isoflurane (*c*). (Redrawn with permission from Peterson DO, Drummond JC, Todd MM: Effects of halothane, enflurane, isoflurane, and nitrous oxide on somatosensory evoked potentials in humans. ANESTHESIOLOGY 1986; 65:35–40.)

10–20% and decreases amplitude 20–30%, an effect that lasts less than 10 min.[43,50,51] Similar changes occur with thiamylal.[40] Even at much higher doses, such as those used for barbiturate coma, barbiturates allow recording of cortical SSEPs.[52–55]

Etomidate. Unlike the barbiturates, etomidate dramatically increases cortical SSEP amplitude (N-20), up to 400% above preinduction baseline in some patients.[50,43] Subcortical amplitude is decreased by up to 50% (table 3).[50,56] Etomidate is associated with a high incidence of myoclonic movements.[57] Patients with familial myoclonic epilepsy are also known to have abnormally large EPs,[58] especially noted during myoclonic jerking episodes. It is tempting to speculate that myoclonus is an indication that sensory signals are being synchronized (pathologically or by etomidate), which then result in enhanced SSEP amplitude. However, Kochs *et al.*[59] observed amplitude enhancement after etomidate whether or not myoclonic movements occurred. Based on careful electrophysiologic experiments in cats, SSEP amplitude enhancement with etomidate is thought to result from an altered balance between inhibitory and excitatory influences at the level of the cerebral cortex,[60] resulting in increased signal synchronization at the thalamic level.[56]

Ketamine. Like etomidate, ketamine increases cortical SSEP amplitude, with the maximum effect occurring within 2–10 min of bolus administration.[61] No effect on cortical latency[61] or subcortical waveforms[62] was evident. However, the addition of nitrous oxide[44] or 1.0 MAC enflurane[61] to a ketamine background anesthetic depressed SSEP amplitude by approximately 50%. Ketamine, 3 mg/kg, followed by 2 $mg \cdot kg^{-1} \cdot h^{-1}$ combined with 0.15 $mg \cdot kg^{-1} \cdot h^{-1}$ midazolam and 60% nitrous oxide was compatible with satisfactory recordings during major spine surgery.[63]

Propofol. Propofol's effect on SSEPs is similar to that of the barbiturates. This is important because propofol can be infused in anesthetic concentrations during prolonged central nervous system (CNS) surgery and still effect rapid emergence for timely postoperative neurologic assessment. A dose of 2.5 mg/kg propofol produced no changes in the amplitude of the cortical (N-20) and subcortical (N-14) waves after median nerve stimulation.[62] Cortical latency and CCT increased by 8 and 20%, respectively. In scoliosis surgery, total intravenous anesthesia with propofol and sufentanil (table 3) prolonged cortical latency 10–15% and reduced the amplitude of the cortical posterior tibial nerve SSEP by 50%. However, SSEP waveforms stabilized within 30 min after anesthetic administration and were compatible with IOM.[48]

When used as a sedative hypnotic in combination with opioids, propofol reduces SSEP amplitude less than nitrous oxide or midazolam. Cortical SSEP amplitude is approximately 50% lower during sufentanil–nitrous oxide[47,48] or alfentanil–nitrous oxide anesthesia[49] compared with sufentanil-propofol-opioid–based regimens.[47,48] Propofol was associated with higher cortical SSEP amplitude despite the use of anesthetic concentrations equivalent to nitrous oxide or sevoflurane.[64] Average cortical SSEP amplitude was higher and within-patient amplitude variability was less during propofol–alfentanil than during nitrous oxide–alfentanil anesthesia.[49] Amplitude was also greater than during midazolam–alfentanil anesthesia.[65] The typical W-shaped morphology of the cortical posterior tibial nerve SSEP was better preserved with propofol than with midazolam.

Benzodiazepines. Benzodiazepines have only mild-to-moderate depressant effects on SSEPs (table 3). Diazepam, 0.1–0.25 mg/kg, produced mild and moderate decreases in N-20 and later wave cortical amplitude, respectively. Very long latency peaks (200–400 ms) were abolished.[66]

In a dose of 0.2–0.3 mg/kg, midazolam is associated with modest[67] or no[43] reduction in amplitude and slight prolongation of median nerve SSEP latency (table 3). Adding opioids[43,68] or nitrous oxide[43] to midazolam or propofol[65] preserves the cortical SSEP better when compared to adding nitrous oxide or opioids to thiopental, etomidate,[43] or ketamine.[44] Benzodiazepines affect sensory pathways differentially. The significant decrease in the amplitude of the evoked electromyelogram response (a spinal cord response to somatosensory stimulation) after diazepam[69] indicates a peripheral action. Conversely, sedative doses of midazolam (60–70 μg/kg), while leaving the early cortical waveform (N-20) unaffected, depress late cortical waves generated in the as-

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Table 2. Relation among Anesthetic Technique, Surgical Procedure, and Predictive Quality of SSEPs

Authors	Anesthetic Maintence Technique*	Surgical Setting	n	Sensitivity, %†	Specificity, %†	SSEP Changes Unexplained by Pathology‡	Percent of Total	Low-quality SSEP Waveforms, %
Reports using subcortical potentials for IOM								
Abel[230]	N_2O opioid, VA	Scoliosis, kyphosis (AT)	58	4/5 (80)	51/53 (96)	2/58	3	0
Faberowski et al.[20]	Inhaled anesthetics	Aortic coarctation repair	87	35/35 (100)	52/52 (100)	0/87	0	0
Reports with relatively high specificity								
Kalkman et al.[12]	N_2O (66) + alfentanil (2c) or N_2O (66) propofol (100c)	Spine	93	1/1 (100)	90/92 (98)	0/93	0	13
Laureau et al.[65]	Alfentanil (0.3c) + midazolam (3.3c) or propofol (167c)	Idiopathic scoliosis	30	0/0	30/30 (100)	0/30	0	0
McPherson et al.[25]§	Fentanyl–N_2O (50) or VA (0.2–0.8)	Spine, cranial	29	3/3 (100)	26/26 (100)	0/29	0	NA
Propkop et al.[231]	Propofol, fentanyl	CEA	200	2/4 (50)	190/196 (97)	1/200	0.5	NA
Samra et al.[77]	Isoflurane (0.5–0.8) + remifentanil (0.0005c) or N_2O (50)	Spine	41	1/1 (100)	41/41 (100)	0/41	0	NA
Schweiger et al.[232]	N_2O (66); moderate dose enflurane	CEA	400	8/13 (62)	371/387 (96)	2/400	0.5	0.5
Taniguchi et al.[233]	Propofol–alfentanil	Cerebral aneurysm	62	7/8 (88)	62/62 (100)	0/62	0	2–5
Reports with relatively low specificity								
Haupt and Horsch[234]	Droperidol-isoflurane (low dose)	CEA	994	7/8 (88)	782/986 (79)	206/994	21	9.9
Lubicky et al.[10]	N_2O, fentanyl; "few" cases with VA	Scoliosis (AT), fractures, and tumors	291	0/1 (0)	226/290 (80)	49/291	17	16
More et al.[14]	N_2O, fent; isoflurane in 6	Scoliosis, kyphosis	152	0/0	127/152 (84)	15/152	10	2.6
Noordeen et al.[13]	N_2O, enflurane (0–1.8)	Neuromuscular scoliosis	99	36/41 (88)	31/53 (58)	31/99	31	5
Russ et al.[235]	N_2O (50%), halothane (moderate dose)	CEA	106	6/6 (100)	86/100 (86)	8/106	8	NA
Sbarigia et al.[15]	Local anesthesia	CEA	50	0/1 (0)	42/50 (84)	8/50	16	NA
Salzman et al.[34]	N_2O (66), halothane (0.67)	Spinal fusion	78	0/3 (0)	75/78 (96)	78	3.8	3.8

* Numbers in parentheses refer to mg/kg dose for bolus intravenous anesthetics and to minimum alveolar concentration (MAC) for anesthetic gases; continuous infusion doses are given in $\mu g \cdot kg^{-1} \cdot min^{-1}$ and are identified as "c." Unless otherwise noted, anesthetic regimen refers to maintenance. † Outcome = postoperative neurologic deficit, stratified by occurrence of significant intraoperative SSEP change. Significant somatosensory evoked potential (SSEP) changes were predominantly defined as those having an amplitude reduction of > 50% and/or a latency increase by 10% from baseline. In some studies, complete disappearance of sensory evoked potential was also used. ‡ Intraoperative SSEP changes not followed by neurologic deficit or occurring in clear association with an intraoperative injury, such as distraction, vessel clamping, or hypotension. § One patient with preexisting neurologic deficit lost SSEPs due to nitrousoxide (N_2O). ‖ 30% amplitude reduction criterion for significant SSEP change.

n = number of monitored anesthetics reported in study; CEA = carotid endarterectomy; NA = not available; AT = all types; VA = volatile anesthetics.

sociation cortex.[69] This is consistent with the notion that sedative doses of benzodiazepines might blunt the emotional response to pain perception.[70]

Opioids. Most authors report clinically unimportant changes in SSEP latency and amplitude after the administration of opioids, whether given in analgesic or anesthetic doses (table 3).

McPherson *et al.*[50] found minimal SSEP changes after 25 μg/kg fentanyl for induction of anesthesia in adults. A small increase (5–6%) in cortical median nerve SSEP latency and a variable decrease (0–30%) in amplitude resulted after 36–71 μg/kg fentanyl, which was compatible with IOM.[71] No significant effects on SSEP from fentanyl up to 130 μg/kg were observed during hypothermic cardiopulmonary bypass. The effect of fentanyl was greater with boluses compared to a continuous infusion[72] during maintenance of anesthesia.

A bolus dose of 5 μg/kg sufentanil produced 5% increases in early cortical SSEP latency and a 15% increase in CCT.[73] The 40% decrease in cortical amplitude did not interfere with waveform acquisition.[73] Sufentanil, 0.5–1.0 μg/kg, followed by 0.25–0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ with 50% nitrous oxide and 0.5% isoflurane prompted a 50% reduction in cortical amplitude and a 5–10% increase in cortical latency and CCT but no changes in subcortical waves.[74]

Alfentanil is associated with only modest SSEP amplitude depression while leaving latency unchanged[43,75] (table 3). Three doses of remifentanil (table 3) combined with 0.4 MAC isoflurane produced a 20–30% decrease in early cortical amplitude that was not dose dependant. By contrast, late cortical waves showed a 10–30% increase in amplitude.[76] Compared with the combination of fentanyl and nitrous oxide, remifentanil reduces cortical amplitude less, with lower amplitude variability.[77]

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Table 3. Effect of Intravenous Anesthetics on Somatosensory Evoked Potentials

Drug/Dose	Early Cortical Waveform§		Subcortical Waveform
	Latency	Amplitude	
Thiopental[43,50,51,53]			
2.5–5.0 mg/kg	<10% ↑	5–30% ↓	Negligible
75 mg/kg	15% ↑	60% ↓	Negligible
Pentobarbital[54,55]			
Up to 20 mg/kg	≈10% ↑	45% ↓	None (latency) 20% ↓ (amplitude)
Ketamine[44,63,236,237]			
0.5 mg/kg	No effect	No effect	No effect
2–3 mg/kg + 2 $mg \cdot kg^{-1} \cdot h^{-1}$	No effect	0–30% ↑	Negligible
Etomidate[43,50,56]			
0.3–0.4 mg/kg + 2 $mg \cdot kg^{-1} \cdot h^{-1}$	<10% ↑	40–180% ↑	None (latency) 50% ↓ (amplitude)
1 mg/kg	10% ↑	150% ↑	Negligible
Propofol[62]			
2.5 mg/kg	< 10% ↑	No change	Negligible
Propofol			
2.5 mg/kg, then 10 $mg \cdot kg^{-1} \cdot h^{-1}$ + sufentanil[48]	10–15% ↑	50%	NA
0.5 $\mu g/kg$, then 0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$			
Midazolam[43,63,65,238]			
0.1–0.3 mg/kg*	< 5% ↑	25–40% ↓	Negligible
Diazepam[66,69]			
0.1–0.25 mg/kg	Minimal	↓	NA
Morphine[72]			
0.25 mg/kg	< 10% ↑	≈20% ↓	NA
Lidocaine[74, 239, 240]			
1.5 mg/kg, then 3 $mg \cdot kg^{-1} \cdot h^{-1}$	5% ↑	25–30% ↓†	Negligible
Fentanyl[28,50,71,72]			
2.5 $\mu g/kg$ + N_2O	5–10% ↑	Variable‡	No change
25–100 $\mu g/kg$	<10% ↑	10–30% ↓	Negligible
Sufentanil[68,73,74]			
Sufentanil + N_2O + 0.5%isoflurane/1 $\mu g/kg$ + infusion	5–10% ↑	≈50% ↓	No change
5 $\mu g/kg$ Sufentanil (alone)	≈5% ↑	≈40% ↓	No change (latency) Amplitude: 40% ↓
1 $\mu g/kg$ + Sufentanil propofol	5–10% ↑	No change	NA
Remifentanil[76] (with 0.4 MAC isoflurane)			
1 $\mu g/kg$ + 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$	NA	15–30% ↓	NA
2.5 $\mu g/kg$ + 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$		30–40% ↓	
5.0 $\mu g/kg$ + 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$		≈40% ↓	
Clonidine[84–86]			
2–10 $\mu g/kg$	No effect	No effect	10% Amplitude ↓ No effect (latency)
Alfentanil[75,241]			
10 $\mu g/kg$ alone	NA	50% ↓	NA
100 $\mu g/kg$ + 2 with N_2O	No effect	40% ↓	NA
Dexmedetomidine[87]			
Low sedative dose	NA	≈10% ↓	≈20% Amplitude ↓
High sedative dose	NA	≈30% ↓	≈10% Amplitude ↓

All data are from humans.

* In several studies, <10 $\mu g/kg$ fentanyl was added. † In isolated cases, bolus administration of 1–1.5 mg/kg resulted in loss of severe attenuation of the cortical somatosensory evoked potential (SSEP) with preservation of subcortical components.[240] ‡ At times, amplitude depression was severe.[76] § For example, N-20 for median nerve SSEPs (Fig. 3).

MAC = minimum alveolar concentration; NA = data not available; N2O = nitrous oxide; ↑ = increase; ↓ = decrease.

Pathak *et al.*[72] reported posterior tibial nerve SSEP latency to increase by approximately 10–15% and amplitude to decrease by 20% after induction of anesthesia with 0.25 mg/kg morphine. Amplitude continued to decrease to approximately 10% of control during subsequent morphine infusion. This study could not isolate the effect of morphine from residual effects of the barbiturate used for induction and the effect of a background nitrous oxide anesthetic, but it shows that this regimen is not desirable for IOM. As with fentanyl, the magnitude of morphine's effect was greater with bolus administration than with continuous infusion.

The administration of subarachnoid meperidine produced a 60% decrease in cortical posterior tibial nerve SSEP amplitude and a 10% increase in latency. The response was abolished in 40% of patients.[78] This is attributed to the local anesthetic-like effect of meperidine in blocking voltage-dependent sodium channels. In contrast, subarachnoid fentanyl (25 μg),[78] morphine (20 $\mu g/kg$) combined with sufentanil (50 μg),[79] or morphine alone (15 $\mu g/kg$)[80] produced no significant changes in latency or amplitude of cortical posterior tibial nerve SSEPS in the awake or anesthetized states, nor did the lumbar epidural administration of 0.1 mg/kg diamor-

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phine in adolescents undergoing corrective surgery for idiopathic scoliosis.[81]

Butyrophenones. Droperidol is an acceptable anesthetic adjunct with minimal effects of SSEPs.[8]

Clonidine and Dexmedetomidine. Clonidine, an α_2 receptor agonist, reduces anesthetic requirements.[82,83] However, clonidine administered alone[84] or added to 1 MAC isoflurane[85] did not change latency or amplitude of the cortical SSEP. At a dose of 10 μg/kg, subcortical amplitude decreased by 10%, and latency increased 2%.[86] Clonidine can be used as an anesthetic adjuvant without compromising SSEP monitoring. Dexmedetomidine affects SSEP amplitude minimally at sedative doses. During isoflurane anesthesia, it blunts isoflurane's effect on SSEP amplitude.[87] In two patients undergoing spinal surgery, dexmedetomidine maintained good conditions for SSEP monitoring.[88]

Adenosine. During isoflurane–nitrous oxide anesthesia, adenosine triphosphate does not affect human SSEPs.[89]

Neuromuscular Blocking Drugs. Neuromuscular blocking drugs do not directly influence SSEP, BAEP, or VEP.[90] However, they may improve waveform quality by favorably increasing the signal-to-noise ratio through elimination of the electromyography artifact,[90] which introduces noise at higher frequencies, especially when EPs are acquired at lower stimulation frequency and higher frequency cutoffs.[90]

Regional Administration. Complete local anesthetic block of the sensory pathway abolishes SSEPs. Local infiltration of lidocaine eliminates the cortical evoked response to painful dental stimulation[91,92] as does bupivacaine[93] or lidocaine subarachnoid block.[78]

On the other hand, epidural administration of bupivacaine[93,94] or clonidine[95] variably affects the lower-extremity SSEP depending on dose and dermatome stimulated. The SSEP response to L_1 dermatome stimulation is reliably abolished by bupivacaine epidural blockade. By contrast, because the S1 nerve root is often incompletely blocked during epidural anesthesia, posterior tibial nerve stimulation can still generate an SSEP response. Thoracic epidural anesthesia (to T7) with 1.5% etidocaine was associated with decreased cortical amplitude (by 60–80%) and increased cortical SSEP latency, while 1% etidocaine resulted in less pronounced changes.[96] Similarly, bupivacaine (0.5–0.75%) injected into the lumbar epidural space significantly prolonged latency and decreased amplitude of posterior tibial nerve SSEPs, contrasted with only slight latency prolongation with 0.25% bupivacaine.[97] Therefore, neuraxial administration of local anesthetics at higher concentrations is not suitable to supplement general anesthesia in scoliosis surgery if SSEPs are to be monitored.[97]

Intravenously administered lidocaine affects cortical SSEPs but is unlikely to interfere with IOM. Systemically administered lidocaine at therapeutic plasma concentrations (3–6 μg/dl) in patients anesthetized with sufentanil–nitrous oxide–low dose ($< 0.5\%$) isoflurane further decreased amplitude of the cortical SSEP by approximately 25–30% and produced a small (5%) latency prolongation.[74]

Implications for Perioperative Monitoring. The volume of information about effects of anesthetics on SEP waveform morphology and metrics is daunting. Ideally, reliable multicenter evidence should be available for each major anesthetic and anesthetic technique to assess the specificity and sensitivity of SEPs in the identification of impending neural injury to allow prompt and successful intervention. Yet, much of the published data of anesthetic effects on SEPs were gathered in neurologically normal patients or were obtained before surgical trespass on the nervous system. Data such as those presented in tables 1–4 represent merely a proxy for assessment of the reliability of IOM in identifying and predicting neural injury during various anesthetics.

It stands to reason that an identifiable, reproducible waveform (which we refer to as recordable) must persist during the anesthetic for critical events to be detectable with IOM. Anesthetic regimens during which even a small number of neurologically normal patients' waveforms disappear are not suitable for successful IOM. Similarly unsuitable are anesthetics that result in amplitude depression and latency prolongation on the order that would confuse the interpretation of SSEP changes and potentially risk either not detecting a critical event or providing excessive false-negative interpretations. Such regimens include volatile anesthetics alone at a dose greater than 1–1.3 MAC and volatile anesthetics at greater than 0.5 MAC in combination with nitrous oxide (table 1). Therefore, volatile anesthetics alone at up to 1.0 MAC can be used. Desflurane or sevoflurane may allow successful IOM at even higher (1.5–1.75) MAC. Some intravenous anesthetic regimens, such as propofol–sufentanil, reduce amplitude sufficiently to be of concern (table 3). In general, however, intravenous anesthetic techniques result in less amplitude and latency perturbation than volatile anesthetics.

Somatosensory evoked potential waveform reproducibility is directly related to amplitude and inversely related to amplitude variability.[10,12] The smaller the amplitude of the SSEP waveform, the more is it subject to baseline variation, electrical noise, and other confounding influences. Therefore, amplitude preservation should be one of the important goals of the intraoperative monitoring team. This is particularly important when baseline amplitude is low and variability is high, as occurs in elderly (> 50 yr) patients and those with congenital scoliosis, paralytic scoliosis, spinal stenosis, spinal tumor, or other preexisting neurologic deficits.[9,10,18]

Given the negative correlation between cortical SSEP amplitude and within-patient amplitude variability, the highest possible SSEP amplitude should be maintained.

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Table 4. Anesthetic Effect on Brainstem Auditory Evoked Potentials

Anesthetic Drug	Dose/Concentration	Latency Wave V	Amplitude Wave V
Volatile agents[27,36,122–130]	Up to 1.5 MAC	<10% ↑	No effect
Nitrous oxide[132–134]*	50%	No effect	Inconsistent
Thiopental[53,131]	4–6 mg/kg	No effect	No effect
	75 mg/kg	≈10% ↑	< 20% ↓
Pentobarbital[54,55]	Up to 20 mg/kg	< 5% ↑	No effect
Propofol[135–137]	10–50 $\mu g \cdot kg^{-1} \cdot min^{-1}$	No effect	No effect
Etomidate[138]	10–15 mg	No effect	No effect
Midazolam[145]	0.2–0.3 mg/kg	No effect	NA
Diazepam[145]	0.3–0.4 mg/kg	No effect	NA
Fentanyl[141,142]	10–50 $\mu g/kg$	No effect	No effect
Morphine/scopolamine[144]†	10 mg Morphine	No effect	40% Amplitude ↓
Premedication[141]	0.4 mg scopolamine		
Sufentanil[143]	5 $\mu g/kg$	No effect	NA
Alfentanil[142]	100–500 $\mu g/kg$	No effect	No effect
Morphine[142]	1–3 mg/kg	No effect	No effect
Lidocaine[242,243]	60 $\mu g \cdot kg^{-1} \cdot min^{-1}$	< 5% ↑‡	No effect
Ketamine[140]	2 mg/kg	No effect	No effect
Clonidine[86]	10 $\mu g/kg$	No effect	No effect

All data are from humans except as indicated.

* In patients with hearing impairment, nitrous oxide may increase brainstem auditory evoked potential latency.[133,134] † In primates. ‡ No change in interpeak latency.

MAC = minimum alveolar concentration; NA = data not available; ↓ = decrease; ↑ = increase.

High-pass 30-Hz digital filtering significantly reduced cortical SSEP amplitude variability in patients undergoing spine surgery and improved amplitude.[12] During nitrous oxide–isoflurane anesthesia, intense surgical stimulation may increase cortical amplitude by more than 45%, contributing to amplitude variability.[98] The substitution of propofol for nitrous oxide increases cortical SSEP amplitude by up to 100% during an opioid-based anesthetic.[47–49] Eliminating nitrous oxide from the background anesthetic has been shown to improve cortical amplitude sufficiently to make IOM more reliable.[25,42] Substitution of remifentanil for fentanyl and nitrous oxide during a low-dose isoflurane anesthetic also decreased SSEP waveform variability, which should improve reliability. If nitrous oxide is to be used in situations in which amplitude needs to be maximized, it should be used in combination with midazolam, where it depresses amplitude the least (16 *vs.* 40–50% with opioids).[43] Anesthetic adjuncts with little or no effect on SSEPs, such as dexmedetomidine, clonidine, and neuroaxial opioids (table 3), may also be considered. Their MAC-reducing effect should allow lower doses of anesthetics to be used, with less depression of SSEP waveforms.

Alternatively, using agents known to increase the EP amplitude, such as etomidate or ketamine, can be beneficial.[99,44] Several investigators[99,100] were able to use etomidate to improve IOM in patients with abnormally small SSEP waves due to preoperative pathology. Bolus administration of etomidate, 0.5–1 mg/kg, followed by the infusion of 20–30 mg $\cdot$ kg^{-1} $\cdot$ min^{-1} augmented waveforms and allowed clinical monitoring that otherwise would not have been possible. Transient increases in the amplitude of SSEP ("injury current") may represent an early warning sign of CNS hypoxia,[101,102] and etomidate theoretically could interfere with early detection of CNS hypoxia.[50] Nevertheless, Sloan *et al.*[99] were able to detect intraoperative events leading to spinal cord compromise in patients in whom etomidate had been used to enhance the SSEP recordings, indicating that etomidate did not mask neural tissue ischemia.

Limiting the inspired volatile anesthetic concentration in an attempt to optimize IOM may be associated with undesirable consequences. Low concentrations of volatile anesthetics are often used during IOM, and anesthesia may be insufficient to prevent awareness and recall. Practitioners should consider using strategies or devices that assist in the assessment of anesthetic depth. Adding etomidate or propofol is preferable to beginning nitrous oxide or increasing volatile anesthetic concentrations when anesthetic depth is inadequate. Volatile anesthetics are also used to control blood pressure and myocardial stress. Vasodilator and β-adrenergic receptor blocker therapy may need to be substituted when IOM contraindicates the use of higher volatile anesthetic concentrations. Optimal airway resistance should be achieved through nonanesthetic pharmacologic means in bronchospastic patients because high volatile anesthetic concentrations are incompatible with successful IOM. If a volatile anesthetic is nevertheless needed rapidly, sevoflurane permits faster SSEP recovery after the acute need for volatile anesthetic has been resolved.[103]

Several strategies can be used to enhance the amplitude and reproducibility of SSEPs during volatile anesthesia. Recording quality depends in large measure on the technical skill and knowledge of the monitoring team. Technical strategies such as keeping electrode

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impedance low and using appropriate bandpass filters[12] are important. Increasing the rate of stimulation in patients with normal baseline SSEPs may improve the preservation of SSEP waves, particularly at higher volatile anesthetic concentrations. Reliance on far-field subcortical waveforms for IOM, if technically feasible, allows the use of higher volatile anesthetic doses.[104] The robust subcortical SSEP responses are still adequately recorded at up to 1.6 MAC isoflurane alone[30] or 1.0 MAC in the presence of nitrous oxide[27] (fig. 4). Subcortical potentials can also be recorded near field epidurally or from spinous processes rostral to the area of surgical trespass.[17,18]

The effects of anesthesia on the EP can be greater in neurologically impaired patients than in patients without preoperative deficits.[25,47,105] The baseline waveform is often diminished[10] and may become completely abolished with the combination of nitrous oxide and low-dose volatile anesthetics.[25,47] In patients with preexisting stroke, ipsilateral cortical SSEPs were of lower amplitude but could be used effectively for IOM during carotid endarterectomy.[106] Eliminating nitrous oxide can restore SSEP amplitude sufficiently to allow useful IOM. Slowing the stimulus presentation rate increased SSEP amplitude in this situation, which suggests a fatigue effect in abnormally responding neurons.[107]

Data showing the effect of anesthetic regimens on the specificity and sensitivity of SSEPs in detecting reversible neurologic compromise are scarce. This limitation arises from small sample sizes in reported studies and from the low incidence of intraoperative neurologic injury for most surgical interventions (table 2). Only studies with large populations, such as might be gathered in a prospective multiinstitution trial, would have the capability to demonstrate reliable predictive information for IOM under different anesthetic conditions.[12] Nevertheless, available data suggest a relation between anesthetic techniques and good IOM conditions. Some techniques seem to minimize distraction from "false-positive" SSEP changes and possibly enhance the ability to detect neurologic injury more efficiently (table 2).

In an attempt to relate reliability of IOM to anesthetic regimen, table 2 summarizes sensitivity and specificity for a number of representative reports. Postoperative neurologic deficit has been used as the outcome against which SSEP changes are assumed, but it is useful to consider another dimension. Many intraoperative SSEP changes prompt surgical and circulatory interventions (such as changing the degree of spinal distraction or increasing blood pressure), which reverse potential neurologic injury and consequently result in the absence of postoperative neurologic deficits. In addition to calculating sensitivity and specificity, we therefore also present the incidence of SSEP changes unexplained by perioperative pathology (*e.g.*, spinal distraction or hypotension) in table 2. It seems that the use of subcortical recordings is associated with a high (> 90% specificity) and low rate of unexplained SSEP changes. The same is true for anesthetic techniques that either carefully limit the concentration of volatile anesthetics to less than 1 MAC or avoid nitrous oxide. Interestingly, carefully controlled conditions associated with a general anesthetic seem to result in higher specificity of SSEP monitoring than during local anesthesia. Still, the incidence of "false negatives" and "true positives" is very low, and it is difficult to discern a relation between sensitivity and anesthetic regimen.

In summary, volatile anesthetics at up to 0.5 MAC with nitrous oxide or up to 1.0 MAC without nitrous oxide are compatible with IOM of cortical SSEPs. The newer volatile anesthetics, desflurane and sevoflurane, seem to allow IOM at even higher concentrations. Baseline recordings should be obtained after induction of anesthesia when a steady anesthetic state has been reached. The postinduction latency and amplitude values then serve as a new baseline with which to compare subsequent event-related changes. It is critical to avoid sudden changes in volatile anesthetic depth or bolus administration of intravenous anesthetics during surgical manipulations that could jeopardize the integrity of the neural pathways being monitored. If step changes in volatile anesthetic concentration are undertaken, it must be appreciated that cortical SSEP latency will take 5–8 min after the change to stabilize.[108] The use of continuous infusions of intravenous anesthetics and opioids,[72] as well as the use of constant low doses of volatile anesthetics, is therefore recommended.[72] Modifications in recording technique and anesthetic regimen can improve IOM. Anesthetic regimens consisting primarily of intravenously administered drugs, without the addition of nitrous oxide, are associated with reliable SSEP monitoring. The combination of propofol and an opioid, administered by continuous infusion, is particularly appealing because of favorable emergence characteristics.[68,77] Remifentanil's relative lack of depression of cortical SSEP amplitude and lower amplitude variability make it an attractive choice for IOM. A midazolam–opioid anesthetic may be preferable if intraoperative wake-up testing is contemplated.[109] When such strategies still fail to allow satisfactory IOM, anesthetic regimens known to enhance SSEP amplitude should be considered.

Brainstem Auditory Evoked Potentials

Anatomic and Electrophysiologic Considerations. The short-latency brainstem components of the auditory evoked potential are referred to as the brainstem auditory evoked potential (BAEP) or the auditory brainstem response. The stimulus is a loud, repetitive click delivered to the external auditory canal. Computer signal averaging allows the response to be extracted from the background electroencephalogram, time-locked to the stimulus. Signals are recorded from elec-

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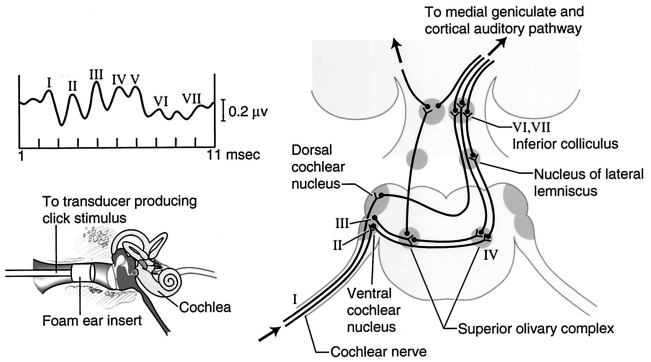

Fig. 5. Schematic of auditory neural pathway. The brainstem auditory evoked potential is initiated by stimulation of the cochlea with a broadband click stimulus *via* an ear insert in the external auditory canal. Neural generators of the brainstem auditory evoked potential peaks are shown. Wave *I* = distal extracranial portion of the eighth nerve; wave *II* = intracranial portion of the eighth nerve; wave *III* = dorsal and ventral cochlear nuclei of the medulla; wave *IV* = superior olivary complex of the caudal pons; wave *V* = lateral lemniscus and its nuclei in the midpons; wave *VI* = inferior colliculus; wave *VII* = medial geniculate nucleus and the auditory thalamocortical radiation. (Redrawn with permission from Black S, Mahla ME, Cucchiara RE: Neurologic Monitoring, 5th edition. Edited by Miller RD. Philadelphia, Churchill Livingston, 2000, p 1339.)

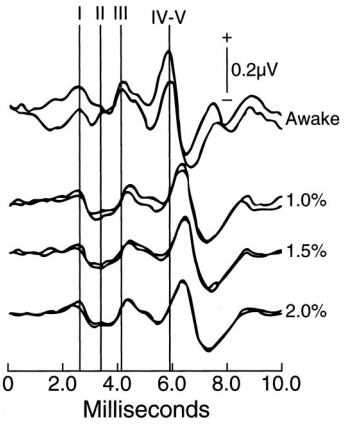

Fig. 6. Influence of isoflurane alone on brainstem auditory evoked potential in a typical subject. Latency of peaks *III* and *IV–V* increased at 1.0% isoflurane but plateaued with increasing anesthetic depth. (Redrawn with permission from Manninen PH, Lam AM, Nicholas JF: The effects of isoflurane-nitrous oxide anesthesia on brainstem auditory evoked potentials in humans. Anesth Analg 1985; 64:43–7.)

trodes placed over the vertex with the reference electrodes over the mastoid process. BAEPs are considered far-field potentials because their neural generators are far from the recording electrodes.[110–113]

Brainstem auditory evoked potentials are particularly useful in assessing the structural integrity of the brainstem during certain surgical procedures in the posterior cranial fossa, *e.g.*, resection of acoustic neuromas and other cerebellopontine tumors, as well as microvascular decompression of the trigeminal and facial nerves.[114–116] BAEPs have also been used to monitor brainstem function in comatose patients and those receiving high-dose barbiturates.[117] The BAEP is generated in the brainstem. It represents auditory sensory electrophysiologic activity starting with the eighth cranial nerve and extending through the medulla and pons. Seven waveform peaks occur within the first 10 ms after stimulus presentation[118] (fig. 5). Of primary importance for IOM are waves I, III, and V. The interpeak latency (IPL) I–III provides information regarding the integrity of the peripheral component of the auditory pathway including the eighth cranial nerve, while IPL III–V reflects central brainstem conduction pathways.[119] Waves VI and VII are more sensitive to anesthetics and are not routinely used for IOM.[116,120,121] IPL is less influenced by hearing impairment, stimulus rate, or stimulus intensity than are individual wave latencies.

Transient increases in wave I–V IPL are generally without clinical significance. However, persistent prolongation by more than 1 ms is associated with neurologic injury and auditory impairment.[16]

Inhaled Anesthetics. Potent volatile anesthetics are associated with small increases in BAEP latency but do not affect wave I–V amplitude[122–130] (table 4). The prolongation of wave I–V latency and IPL reflects the depressant effect of volatile anesthetics on brainstem neuronal activity.

Duncan *et al.*[131] reported no changes in BAEP in children anesthetized with halothane. In adults, the effect of volatile anesthetics on BAEP latency is dose dependent[122,123] up to 0.9 MAC enflurane[124] and 0.85–1.3 MAC isoflurane.[125,126] The IPL III–V, reflecting brainstem conduction time, was also prolonged with isoflurane[125,126] (fig. 6). Sevoflurane at 0.5–1.5 MAC with 66% nitrous oxide produced a minor prolongation of wave III and V latencies as well as IPL I–III, III–V, and I–V. These changes are similar to those produced by isoflurane.[37]

In contrast to cortical SSEPs, the action of volatile anesthetics on BAEP latency or amplitude is not affected by 50–70% nitrous oxide. Ten to 50% nitrous oxide alone also had no effect on the latency, interpeak latency, or amplitude of waves I–V in healthy volunteers.[132] However, in patients with certain forms of hearing impairment, BAEP latency was increased by nitrous oxide, perhaps due to nitrous oxide–induced increases in middle-ear pressure.[133,134]

Intravenous Anesthetics. Barbiturates in doses used for induction of anesthesia do not affect the BAEP, even when thiopental was administered to children already anesthetized with halothane and nitrous oxide.[131] At higher doses (up to 77.5 mg/kg), thiopental prolonged individual waveform latencies as well as interpeak latencies by approximately 10%.[53] Amplitude was unchanged in doses used for induction of anesthesia, and BAEP waveforms were easily recorded even in the presence of an isoelectric electroencephalogram.[53] Similar results were reported with pentobarbital.[54,55]

Propofol (2 mg/kg followed by a continuous infusion) increased wave I, III, and V latencies by less than 5%

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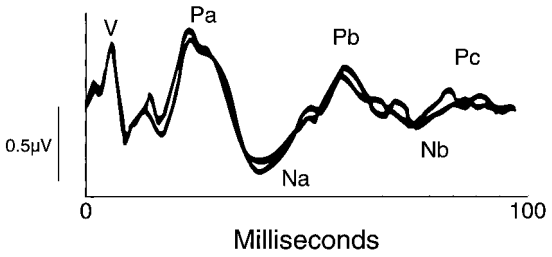

Fig. 7. Cortical midlatency auditory evoked potential recorded over the parietal cortex. Wave *V* of the brainstem auditory evoked potential can be seen in the first 10 ms, followed by the cortical peaks (P_a, N_a, P_b, N_b, and P_c). (Redrawn with permission from Albin MS: Textbook of Neuroanesthesia with Neurosurgical and Neuroscience Perspectives. New York, McGraw-Hill, 1997.)

without changing amplitude.[135,136] In volunteers exposed to stepped blood concentrations of propofol, wave V amplitude did not change, but latency was slightly prolonged.[137] In patients anesthetized with thiopental and nitrous oxide, etomidate infusions of 10–50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ had no effect on individual wave, interpeak latencies, or the amplitude of BAEP[138] (table 4), nor did 2 mg/kg ketamine.[139,140] Fentanyl,[141,142] alfentanil,[142] sufentanil,[143] morphine,[142,144] and benzodiazepines do not change the amplitude or latency of BAEP.[145] Likewise, BAEPs do not change in humans receiving chronic therapy with phenobarbital.[146]

Midlatency Auditory Evoked Potentials.

The midlatency auditory evoked potential (MLAEP) consists of waves (N_a, P_a, N_b, and P_1) occurring 10–80 ms after stimulation (fig. 7). It represents processing of the auditory stimulus by the primary auditory cortex and can be monitored when that area is at risk.[147] MLAEPs have a characteristic periodic waveform with a large peak-to-peak amplitude. The major energy of the power spectrum is in the 30- to 40-Hz frequency range, which is why they are sometimes referred to as "40-Hz potentials" (fig. 8).

Inhaled Anesthetics. Because BAEP signals are preserved with all volatile anesthetics, initial signal transduction remains intact, and auditory stimuli can be further processed rostral to midbrain level. Volatile anesthetic agents produce predictable dose-dependent increases in MLAEP latency and decreases in amplitude.[128–130] All volatile anesthetics suppress MLAEP components to a similar extent at equi-MAC.[119,121,122] At approximately 1 MAC, MLAEP components are markedly attenuated, indicating suppression of cortical auditory processing such as auditory perception, intraoperative wakefulness, and explicit or implicit recall of intraoperative events.[148–151]

Nitrous oxide decreases cortical auditory evoked potential wave amplitude in a progressive, dose-related manner.[133,134,152,153] The auditory EP changes may be

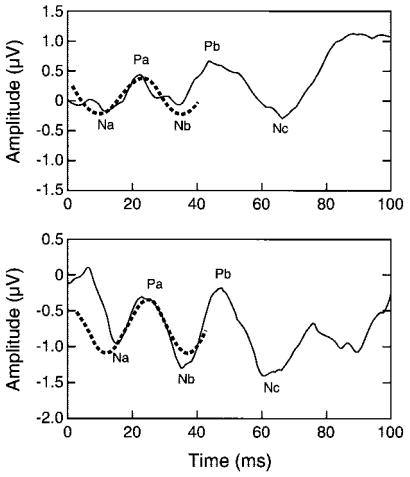

Fig. 8. Midlatency auditory evoked potential waveforms (*continuous line*) from two unmedicated subjects. Stimuli consist of 50-Hz tonebursts. Each trace is the average response to 3,000 stimuli. The *thick dashed line* is a segment of a 40-Hz sinusoid superimposed on the N_a, P_a, and N_b waves to illustrate that this portion of the midlatency auditory evoked potential contains substantial 40-Hz activity. (Redrawn with permission from Plourde G: Auditory evoked potentials and 40-Hz oscillations: An opportunity to study mechanisms of action of general anesthetics? ANESTHESIOLOGY 1999; 91:1187–9.)

the result of a nitrous oxide–induced increase in the auditory threshold.[133]

Intravenous Anesthetics. Induction of anesthesia with barbiturates, propofol[135,136,154] and etomidate,[138,155] but not with benzodiazepines[145,156] (see next paragraph) causes complete suppression of MLAEPs. Amplitudes and latencies of MLAEP returned to the awake values 4–6 min after thiopental induction as motor signs of wakefulness appeared.[157] Etomidate caused dose-dependent decreases in amplitude and increases in latency of the P_a and N_b waves. Maintenance of anesthesia with propofol at a dose of 3–5 $mg \cdot kg^{-1} \cdot h^{-1}$ caused MLAEP latency prolongation and amplitude reduction that was comparable to 0.4–0.8% isoflurane.[154] Stepwise increases in the dose of propofol caused graded changes in MLAEP (decrease in P_a and N_b amplitude and increase in latency), which correlated well with the level of sedation. The addition of alfentanil decreased the mean propofol concentration required for the same endpoint.[137] P_a and N_b latency had the best correlation with propofol concentration and sedation level[137] (fig. 9).

Induction of anesthesia with midazolam (0.2–0.3 mg/kg), diazepam (0.3–0.4 mg/kg), or flunitrazepam (0.03–0.04 mg/kg) did not affect waves N_a, P_a, N_b, and P_1 of the MLAEP, except for an isolated 15% increase in P_1 latency with midazolam and a 40% decrease in N_a/P_a amplitude with flunitrazepam.[145] Maintenance of anesthesia with flunitrazepam and fentanyl preserved MLAEP latency and amplitude and was associated with a high incidence of motor signs of wakefulness.[155] Induction doses of racemic ketamine (2 mg/kg) or *S*(+)-ketamine (1 mg/kg) likewise did not affect the MLAEP[140] Primary cortical

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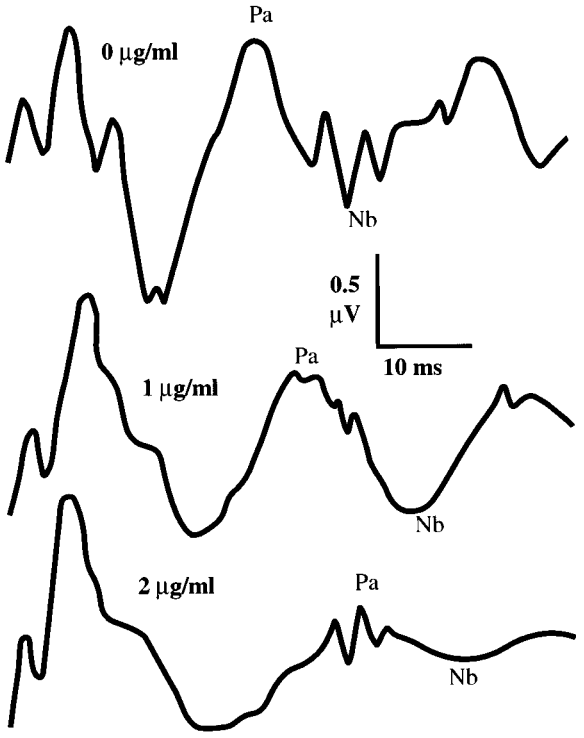

Fig. 9. Typical changes in the midlatency auditory evoked potential in a volunteer given 0-, 1-, and 2-μg/ml target concentrations of propofol who lost consciousness at a target propofol concentration of 2 μg/ml. Each point represents one assessment. (Redrawn with permission from Iselin-Chaves IA, El Moalem HE, Joo Gan TJ, Ginsberg B, Glass PS: Changes in the auditory evoked potentials and the Bispectral Index following propofol or propofol and alfentanil. ANESTHESIOLOGY 2000; 92:1300–10.)

processing of auditory stimuli therefore seems to be preserved with ketamine[140] and benzodiazepine[145] "anesthesia."

Opioids produce partial suppression of the MLAEP without a clear dose dependence. Even at the highest opioid doses, early cortical MLAEPs (waves N_a and P_a) are only slightly suppressed. Induction of anesthesia with alfentanil (100–500 μg/kg), fentanyl (10–50 μg/kg), or morphine (1–3 mg/kg) produced no changes in the (early) N_a wave latency or N_a/P_a and P_a/N_b amplitudes. However, P_a, N_b, and P_1 latencies were prolonged by 5–25%, and the (later) N_b/P_1 amplitude was reduced by 50–75%.[142] With sufentanil, 1–5 μg/kg, N_a latency increased 10%, while P_a, N_b and P_1 latencies increased 20–33%.[143] N_b/P_1 amplitude decreased 60% after 3–5 μg/kg sufentanil.[143] In contrast to other opioids, remifentanil's effects on MLAEP showed mild dose dependence.[76] Remifentanil combined with 0.4 MAC isoflurane produced a 20% increase in P_a and N_b amplitude at a low dose (1-μg/kg bolus and 0.2-$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion). The medium dose (2.5 μg/kg and 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) left amplitude unchanged, while the high dose (5 μg/kg and 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) decreased P_a and N_b amplitude by 10–20%.[76]

The inability of opioids to suppress the MLAEP indicates that perception, processing, and, possibly, the explicit or implicit encoding of auditory information do not cease completely during opioid anesthesia.[142,143] Opioids, even in very large doses, are less reliable in suppressing consciousness and sensory information processing than are volatile anesthetics.[142,158,159] This is consistent with clinical reports of intraoperative awareness and perception of auditory stimuli if opioids are used exclusively for general anesthesia. Dexmedetomidine did not influence the suppressant action of volatile anesthetics on MLAEP.[87] Succinylcholine activated the MLAEP during isoflurane–nitrous oxide anesthesia, as evident from its ability to enhance N_a and N_b amplitudes by 50%, possibly through increased neuronal traffic from muscle afferents.[160]

Implications for Perioperative Monitoring. Brainstem auditory evoked potential waves I–V can be adequately monitored under deep volatile anesthesia, even exceeding 1 MAC, whether in the presence or absence of nitrous oxide.[125] BAEP monitoring can also be successfully performed during deep levels of intravenous anesthesia, even at electroencephalogram burst suppression,[54,55] and does not impose limitations on anesthetic technique.

The MLAEP is affected by anesthetic agents in a manner similar to the cortical SSEP. Therefore, monitoring the MLAEP to assess the integrity of cortical brain areas requires modification of the anesthetic technique. In particular, the use of benzodiazepines, opioids, or ketamine and volatile anesthetics at less than 0.5 MAC would preserve MLAEPs for IOM. Current evidence suggests that MLAEPs are a sensitive indicator of residual cortical information processing and cognitive function during general anesthesia.[148,149] They may be useful for recognizing periods of insufficient anesthesia and intraoperative awareness.[148] The auditory evoked potential$_{Index}$, a mathematical derivation from the MLAEP waveforms, has been used successfully as the input signal in a closed-loop system to control the administration of propofol[161] and volatile anesthetic[162] anesthesia. The auditory brainstem response has been used to differentiate brainstem anesthesia from other states affecting consciousness.[163]

Visual Evoked Potentials

Anatomic and Electrophysiologic Considerations. The visual pathway includes the retina, optic nerve, optic chiasm (where half the fibers cross to the contralateral side), optic tracts, lateral geniculate nucleus in the thalamus, optic radiation, and occipital visual cortex. Stimulating the retina produces an evoked electrical response in the occipital cortex, which may change with impairment of the visual apparatus and associated neural pathways. VEPs are recorded from scalp electrodes placed over the occipital, parietal, and

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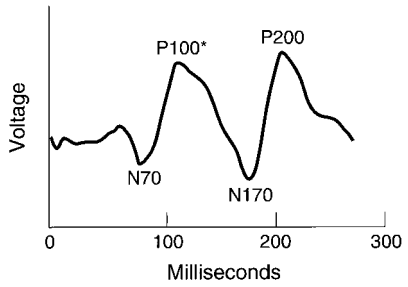

Fig. 10. Normal visual evoked potential obtained by flash stimulation *via* light emitting diodes. P-100 is the wave used for intraoperative monitoring. *Some authors use the designation P-89.

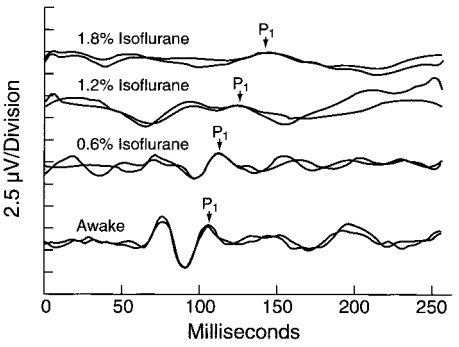

Fig. 11. Visual evoked potential recording obtained from one patient at different end-expiratory isoflurane concentrations in 100% oxygen. Two separate tracings obtained during each condition have been superimposed. (Redrawn with permission from Chi OZ, Field C: Effects of isoflurane on visual evoked potentials in humans. ANESTHESIOLOGY 1986; 65:328–30.)

central areas.[1] They are cortical near-field potentials with long latencies. In anesthetized patients, flashes of red light are delivered through closed eyelids using light-emitting diodes.[121] The characteristic waves of the flash VEP are a negative wave with 70-ms latency (N-70) and a positive wave with 100-ms latency (P-100). In the VEP waveform complex, the P-100 wave has been evaluated for IOM (fig. 10).

Inhaled Anesthetics. In general, all volatile anesthetics markedly prolong VEP latency and decrease amplitude in a dose-dependent manner[164,165] (table 5). At 1.5 MAC, the VEP could not be interpreted (fig. 11). Nitrous oxide alone severely attenuates VEP amplitude,[132,166] and its addition to volatile anesthetics can make waveforms unrecordable.[27]

Intravenous Agents. Induction doses of thiopental decrease the amplitude and prolong the latency of VEP waves,[167] while etomidate produces a small increase in latency with no change in amplitude[168] (table 5). However, etomidate transiently decreased amplitude by as much as 50% when administered to patients already anesthetized with fentanyl and nitrous oxide. An induction dose of fentanyl (10–60 μg/kg) produced a 30% amplitude reduction beyond that associated with premedication[169] and was independent of dose.

Implications for Intraoperative Monitoring. Visual evoked potentials are very sensitive to the effects of anesthetics and physiologic factors because they represent polysynaptic cortical activity. Because flashlight stimulation activates both temporal and nasal parts of the retina and the nasal fibers cross to the contralateral side at the level of the optic chiasma, retrochiasmatic lesions cannot be monitored.[170] In addition, VEPs are highly dependent on appropriate stimulation of the retina and

Table 5. Anesthetic Effect on Visual Evoked Potentials

Anesthetic Drug	Dose/Concentration	Latency of P-100	Amplitude
Halothane[165]	1 MAC	≈10% ↑	Inconsistent
Isoflurane[27,164]	0.5 MAC	10% ↑	40% ↓
	1.0 MAC	20% ↑	66% ↓
	1.5 MAC*	30% ↑	80% ↓
	1.0 MAC + 70% N_2O	Abolished	Abolished
	1.5 MAC + 70% N_2O	Abolished	Abolished
Sevoflurane[37]	0.5 MAC + 66% N_2O	5–10% ↑	20% ↓
	1 MAC + 66% N_2O	Abolished	Abolished
	1.5 MAC + 66% N_2O	Abolished	Abolished
	1.4–1.7 MAC	Abolished	Abolished†
Nitrous oxide[132,163,244]	10–50%	No effect	25–80% ↓ ‡
Propofol[171]	2 mg/kg + 10 mg · kg^{-1} · h^{-1}	Negligible	≈20% ↓
Thiopental[167]	3 mg/kg	< 10% ↑	No change
	6 mg/kg	Abolished	Abolished
Etomidate[168]	0.3 mg/kg	< 10% ↑	No change
Fentanyl[169]	10–60 μg/kg	<10% ↑	30% ↓
Ketamine[171]	1 mg/kg + 2 mg · kg^{-1} · h^{-1}	Negligible	≈60% ↓
Morphine scopolamine (premedication)[169]	0.2 mg/kg morphine + 0.4 mg scopolamine	No change	≈20% ↓
Neuroleptanalgesia[245]		10% ↑	No change
Fentanyl, droperidol nitrous oxide			

All data are from humans.

* In a substantial fraction of patients, waveforms were not recordable at this concentration. † During electroencephalogram suppression; visual evoked potentials reappeared during electroencephalogram bursts.[246] ‡ Some report a 40% increase in N-70–P-100 amplitude[171]. (Fig. 10).

MAC = minimum alveolar concentration; N_2O = nitrous oxide; ↑ = increase; ↓ = decrease.

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may be unduly affected by narcotic-induced pupillary constriction.[169]

The available data indicate that opioid and ketamine or propofol-based anesthetic techniques, as well as regimens using low-dose volatile anesthetics without nitrous oxide, allow intraoperative recording of VEPs. Although satisfactory intraoperative recordings can be obtained in the majority of patients, clinical observations suggest a high incidence of false-positive and false-negative results.[170] Anesthetic technique can affect the incidence of false-positive VEP changes. A propofol–nitrous oxide technique was associated with a 10–15% incidence of false positives compared to none with ketamine.[171] Up to 80% of intraoperative changes in VEP are not followed by postoperative neurologic deficits.[172,173] VEP monitoring has been largely abandoned for intraoperative applications because of these many limitations. However, VEPs have been recently used to assess the safety of peribulbar and retrobulbar blocks for regional anesthesia of the orbit.[174]

Physiologic Influences on Sensory Evoked Potentials

Temperature

In clinical practice, cooling to 33°–34°C may occur passively or represent a protective strategy for patients at risk of neurologic injury who at the same time may be undergoing IOM of EP (*e.g.*, during thoracic aortic aneurysm repair). Even lower temperatures may occur during cardiopulmonary bypass. A clear understanding of the effects of hypothermia on EP is therefore necessary for the appropriate interpretation of the intraoperative SEPs.

General Physiologic Considerations: Hypothermia. Mild hypothermia (33°–34°C) may produce cerebral stimulatory effects as reflected by arousal phenomena, increased EP amplitude, and hyperresponsive reflexes.[175] It is associated with increased amplitude and duration of nerve action potential but decreased conduction velocity,§ brought about by enhanced neurotransmitter release leading to higher miniature endplate potentials.[176] Resting electroencephalogram at 33°C is characterized by a small shift to lower frequencies without changes in amplitude. These general electrophysiologic observations explain the small increase in EP latency and inconsistent effect on amplitude seen with mild hypothermia.

Neuronal function is decreased at temperatures less than 32°C (moderate hypothermia) because of reduced neurotransmitter release and impaired synaptic transmission.[177–179] Electrophysiologic changes are characterized by decreased resting membrane potential, decreased amplitude, increased nerve action potential duration, and decreased nerve conduction velocity. The slowing of axonal conduction has been linked to decreases in resting membrane potential and increases in sodium–potassium channel activation time across the membrane.[180] Synaptic transmission is more sensitive to the effects of hypothermia than axonal propagation.[178,181,182] Both peripheral and central conduction are significantly delayed by hypothermia decreasing by 5%[183] and 15%[184] per degree Celsius, respectively. The effects of temperature on the axon and synapse are additive, compounding temperature effects on multisynaptic pathways. For example, the more pronounced effect of hypothermia on cortical than on spinal SSEP is attributed to the additional suppression of synaptic transmission in the lemniscal–thalamic pathway.[185] Similarly, hypothermia progressively depresses both the resting electroencephalogram and late cortical SSEP components that involve an increasing number of interposed synapses.[183]

Effect of Temperature on SSEP. *Hypothermia.* The site of temperature monitoring is important in assessing the relation between SSEP waves and body temperature. In patients undergoing hypothermic cardiopulmonary bypass, posterior tibial nerve SSEP latency correlated best with nasopharyngeal temperature.[186] Local extremity hypothermia also delays conduction along peripheral nerves in anesthetized patients,[187] but cortical SSEP amplitude and CCT are not affected by extremity temperature.[188] In acquired poikilothermia, hypothermia to 33.5°C decreased central and peripheral nerve conduction velocities.[189] SSEP latencies and CCT increased by 10–20%. The latency of the first cortical SSEP wave increased by 9–12% for every degree Celsius decrease in temperature in humans[186] as well as rats.[183] During hypothermic cardiopulmonary bypass, all SSEP components could be consistently recorded at esophageal temperatures as low as 19°C.[186] This level of hypothermia results in cessation of cortical electrical activity and, hence, electroencephalogram silence.[190] Cooling to a nasopharyngeal temperature of 27°C was associated with a linear increase in the latency of cortical and subcortical SSEP components. Latency to the first positive cortical median nerve SSEP peak N-20 increased by 1.5 ms/°C (or approximately 15%/°C) in nasopharyngeal temperature. Posterior tibial nerve SSEP latencies increased with nasopharyngeal temperature by 1.05 ms/°C for the subcortical P-27 peak and by 1.47 ms/°C for the cortical P-40 peak (approximately 4%/°C).[191] Human central conduction time increases linearly by 8–12% per degree reduction in temperature from 37–28°C.[186,187] Other authors have found an exponential relation between CCT[28,192] or median nerve SSEP latency[28] and

§ The velocity of conduction in human nerve fibers varies from 5 to 100 m/s. It is directly proportional to myelinated fiber diameter and exponentially related to unmyelinated fiber diameter. A decrease in conduction velocity results in a proportionately increased latency of the EP wave. EP latency can be affected to a greater extent than conduction velocity if the corresponding latency assesses a neural pathway with multiple synapses.

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temperature during hypothermic cardiopulmonary bypass.

Hypothermia-induced SSEP changes return to baseline after 30 min of rewarming.[186] However, a hysteresis exists in the relation between temperature and EP latency,[193] indicating that cooling and rewarming curves should be considered separately.[184] In one report, the latency of the primary cortical N-20 response increased by 1.7ms/°C during cooling but decreased by only 1 ms/°C during rewarming. The CCT increased linearly by 0.85 ms/°C during cooling and decreased by 0.46 ms/°C during rewarming.[183]

While hypothermia-induced changes in SSEP latency are well defined, amplitude behaves unpredictably,[189,191] with reports of no change, decreased amplitude, and even increases in amplitude.[194] In one study, N-20 and N-13 amplitudes decreased by 3.5% and 1.3%, respectively, for each 1°C temperature reduction[195]

Hyperthermia. Raising body temperature from 37.5° to 40.5°C produced a decrease in latency and increase in conduction velocity of rat spinal and cortical SSEP.[185] Compared with 37°C, mild hyperthermia to 39°C caused human cortical and subcortical SSEP latencies to decrease by 5–7%, with no changes in amplitude.[185] Further increases in temperature prolong SSEP latency. Hyperthermia beyond the temperature at which reversal of latency changes occurs (41.4°–42.1°C) alters rat SSEPs permanently, shortens survival time, and is associated with histologic evidence of neuronal damage.[196] For example, SSEP amplitude decreased to 15% of baseline[194] at 42°C.

Effects of Temperature on BAEP. *Hypothermia.* Brainstem auditory evoked potentials are more resistant than SSEPs to the effects of mild hypothermia. In humans undergoing cardiopulmonary bypass, BAEP latency was prolonged by 33% at 29°C and returned to baseline with rewarming.[197] Wave V was the most affected, while wave I showed the least change. As is the case with SSEPs, hysteresis exists in the temperature-*versus*-latency relation of the BAEP.[198]

Brainstem auditory evoked potential amplitude is variably affected by hypothermia. In some studies, amplitude increased during progressive hypothermia, reaching a maximum at 28°–32°C.[189,199] At lower temperatures, BAEP amplitude decreased (as is the case with other EPs) until the waves disappeared at 20°–23°C. Other studies report a decrease in BAEP amplitude with progressive cooling without an initial increase.[197] This discrepancy may be related to differences in stimulus intensity, rate of temperature change, or both. Hypothermia-related amplitude increases were observed at stimulus levels of 75–90 dB but not with stimuli of lower intensity, which is at the high end of the stimulus-intensity range for IOM.[200] BAEP amplitude has also been shown to increase initially when temperature decreased rapidly but to decrease steadily with the slow and gradual development of hypothermia.[201]

Hyperthermia. Several animal studies demonstrated that increases in temperature from 36° to 40°C to decrease BAEP amplitude, latency, and IPL.[202–204] Persistence of hyperthermia beyond a critical level was associated with increases in latency, further decreases in amplitude, loss of waves V and VI, and the appearance of new abnormal peaks. These changes likely indicate damage to neural tissue in the brainstem region. In rats, exposure needed to produce injury was 60 min at 41°C, 30 min at 42°C, and 15 min at 42.5°C.[202] Therefore, changes in BAEP during hyperthermia may serve as a noninvasive indirect estimate of regional brainstem temperature. Because BAEPs reflect the functional state and integrity of the brainstem, BAEP monitoring may have potential clinical utility in guiding the use of hyperthermic therapy of malignant diseases of the CNS, especially brainstem gliomas.

Effects of Temperature on VEP. In conscious humans, VEP latency is 10–20% longer at 33°C than at 37°C.[203] Russ *et al.*[204] reported progressive latency prolongation and amplitude reduction of VEP with hypothermia leading to complete loss of waves at 25°–27°C. With faster cooling, VEP disappeared at a higher temperature than with slower cooling.

Carbon Dioxide. Clinically relevant levels of induced hypocapnia (arterial carbon dioxide tension [Pa_{CO_2}] 20–25 mmHg) do not compromise SSEP monitoring but shorten SSEP latencies by 2–4% in isoflurane-anesthetized patients[205] and awake volunteers.[206] In contrast to the 70% cortical amplitude enhancement seen in hyperventilating awake volunteers,[206] no changes in amplitude occurred in anesthetized hypocapnic patients.[205] The hypocapnia-related decrease in latency reflects an increase in conduction velocity, perhaps attributable to changes in pH, ionized calcium concentrations, and ionic equilibrium across neural membranes leading to enhanced neuronal excitability. It does not seem to be related to changes in anesthetic depth.[206]

Hypercapnia to a Pa_{CO_2} of more than 100 mmHg was associated with an increase in feline SSEP latency by 15–30% and a decrease in amplitude by 60–80%.[188] Hypercapnia to a Pa_{CO_2} of 50 mmHg had no effect on human SSEPs.[207]

Enflurane-induced increases in BAEP latency are mildly ($< 5\%$) potentiated by hyperventilation to a Pa_{CO_2} of 25–30 mmHg.[208]

Hypoxia. Mild hypoxemia (to an end-tidal pressure of oxygen [P_{ETO_2}] of 48 mmHg) does not affect human[206] SSEPs. Severe progressive hypoxia[209] or cerebral ischemia[210] is associated with a decrease in SSEP amplitude and an increase in latency, eventually resulting in complete loss of cortical SSEP waves.[102] Grundy *et al.*[211] reported a decrease in SSEP amplitude as a manifestation of intraoperative hypoxemia in patients. Cortical SSEPs are more sensitive to hypoxia than the electroencephalogram.[212] Because SSEP changes due to hypoxia corre-

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late with reductions in brain high-energy phosphate concentrations, changes in SSEP may represent an indicator of CNS ischemia. Cortical evoked responses also seem to be more sensitive to hypoxia than spinal and subcortical responses, presumably because the latter are more tolerant of hypoxia than the cerebral cortex, because of their lower metabolic rate.[213] Early responses to ischemia or hypoxia can manifest as a transient *increase* in SSEP amplitude ("injury potential") before the occurrence of amplitude reduction and latency prolongation.[102] This may be related to the phenomenon of anoxic activation, which is attributed to the early loss of function by inhibitory cortical interneurons.[214]

No changes in BAEP were observed with arterial oxygen tension (Pao_2) values ranging from 60 to 570 mmHg.[141] In sleep apnea patients, BAEP did not change with mild hypoxemia (arterial oxygen saturation as low as 45%).[215] However, acute severe hypoxemia (Pao_2 20–30 mmHg) depressed the feline BAEP.[216,217] Rabbit peak and interpeak latencies increased before the complete loss of BAEP waves.[218] With normal mean arterial pressure, severe hypoxemia depressed BAEP waves but left cortical EPs unaffected. Early hypoxia-induced changes in BAEP result from failure of the cochlear mechanism and not from brainstem dysfunction, suggesting that the cochlea is exquisitely sensitive to hypoxia.[216,217] Hypoxia to Pao_2 of 20 mmHg results in a transient increase followed by a decrease in feline VEP amplitude.[212]

Hypotension. A decrease in mean arterial pressure (MAP) to levels below the autoregulatory threshold progressively decreased SSEP amplitude without changing latency. Such changes, which may be reversible or irreversible (in the case of permanent tissue injury),[219] likely reflect reduced oxygen delivery to neural tissues. A rapid decrease in MAP within the autoregulatory range is also associated with transient changes in SSEP that resolve despite the persistence of hypotension, presumably reflecting autoregulation at work to restore blood flow. The rapid reduction of MAP from 140 mmHg to 50 mmHg decreased canine SSEP amplitude to 58% of control. Within 15 min, SSEP recovered to 70% of control, and by 60 min, the amplitude had recovered to baseline despite continued hypotension.

Hemorrhagic shock has been associated with a transient increase in the amplitude of SSEP probably related to the phenomenon of anoxic activation followed by reduced amplitude and loss of SSEP.[220]

Clinically encountered levels of hypotension have little effect on BAEP. Animal studies have shown the BAEP to be well preserved with profound levels of induced hypotension (MAP of 20–40 mmHg).[221] In children, the BAEP became abnormal with a reduction in cerebral perfusion pressure to less than 30 mmHg.[222] Concomitant hypotension and hypoxemia, on the other hand, severely depressed all EP modalities.[217]

Hemodilution. In primates, acute isovolemic hemodilution to a hematocrit of 11–15% for 1 h was associated with decreased SSEP amplitude, which recovered when the hematocrit was restored to baseline.[199,223] In another study, SSEP and VEP amplitude increased at a hematocrit of 16–20%, as seen with anoxic activation. A hematocrit less than 10% decreased amplitudes even more, an effect that reversed at a hematocrit of 22%. Hematocrit below 15% also prolonged the latencies of SSEP and VEP.

Concomitant Hypotension and Hemodilution. Simian cortical SSEP amplitude was attenuated to 25–50% of control by the combined effect of hypotension (to a MAP of 25 mmHg) and hemodilution (to a hematocrit of 14%).[199] Latency was not affected. None of the surviving monkeys that maintained an SSEP amplitude greater than 60% of baseline had neurologic damage. The probability of brain injury was greater than 50%[199] if the SSEP amplitude decreased below 60% of baseline. SSEP may be useful as an intraoperative monitor to avoid neurologic injury under conditions of combined hypotension and hemodilution.

Brainstem auditory evoked potentials were unchanged in monkeys that survived the stress of combined hemodilution (hematocrit of 16%) and hypotension (MAP of 30 mmHg). However in the nonsurviving monkeys, BAEPs recorded before death were diminished substantially or abolished, indicating the occurrence of extensive brainstem damage, which may have contributed to the mechanism of death.[199] BAEP alone may not be a useful predictor of impending brainstem injury during combined hemodilution and hypotension because of the absence of early warning criteria.

Implications for Intraoperative Monitoring. Somatosensory evoked potentials may be recorded reliably at temperatures as low as 20°C and can be useful as indicators of neurologic function during a variety of surgical procedures that require hypothermic cardiopulmonary bypass and circulatory arrest (*e.g.*, basilar aneurysm clipping). The relation between the latency of SSEP and temperature assists in SEP interpretation during cardiopulmonary bypass. Pathologic prolongation of SSEP latency can be presumed if latencies lengthen substantially beyond the level predicted by temperature changes (1.5 ms/°C for the early cortical SSEP), particularly if asymmetric changes are detected. This assumes that sufficient time for equilibration of SSEP latency is available and hysteresis-related uncertainty about latency changes is eliminated. The latter may be especially an issue if there is repeated cooling and warming because the direction of temperature manipulation determines the expected SSEP change concomitant with the magnitude of the temperature difference. This is analogous to the problems encountered with electroencephalogram interpretation during rapidly occurring temperature fluctuations.[224] Acute, dramatic, unilateral changes in SSEP amplitude may therefore be a more reliable indicator of

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intraoperative stroke in patients undergoing hypothermic cardiopulmonary bypass.[225]

Somatosensory evoked potential waves disappear at different temperatures in individual patients, which argues against using a fixed temperature endpoint as an indicator of optimal cooling depth. Presence of the P-14 wave implies persistence of brainstem metabolic activity. Disappearance of the P-14 wave (which represents brainstem activity) has been used as the criterion for reaching satisfactory deep hypothermia.[226]

Only severe hypercapnia degrades SSEP waveforms,[188] whereas the effects of hypocapnia are clinically insignificant. Cortical but not subcortical SSEPs are quite sensitive to hypoxemia.[213] BAEP are not a reliable warning sign for intraoperative brainstem hypoxemia because early hypoxia-induced changes in BAEP result from failure of the cochlear mechanism, not from brainstem dysfunction.[216,217]

Transient SSEP changes in response to blood pressure reduction presumably reflect slow adaptation of cerebral blood flow autoregulation. Changes in SSEP after spinal distraction have resolved in some instances when the MAP was raised above the patient's normal blood pressure range. Therefore, during surgical manipulations, a degree of hypotension otherwise considered safe could result in spinal cord ischemia.[227] Monitoring of SSEP may help to determine the safe limits of hypotension in individual patients. During hypotension or hemodilution, cerebral oxygen delivery is maintained by compensatory cerebral vasodilation. The compensatory vasodilatory reserve is exhausted at higher perfusion pressures if hemodilution is combined with hypotension.[228] The exact safe thresholds for blood pressure and hematocrit during combined elective hypotension and isovolemic hemodilution (as used during scoliosis surgery) cannot be precisely defined but should probably be higher than they would be if either hypotension or hemodilution were used alone. Synergistic adverse effects of hemodilution and hypotension are evident in SSEP waveforms.[199] Hence, IOM of SSEP but not BAEP in this setting may be helpful in determining whether neuronal tissue oxygen demands are being met. An SSEP amplitude reduction greater than 40% from baseline may be cause for alarm in the setting of combined hypotension and hemodilution.[199]

Conclusion

The known effects of anesthetics and anesthetic adjuvants on the major SEP modalities used for IOM have been reviewed, along with the influences of body temperature, blood gas tensions, blood pressure, and hematocrit. Practical conclusions are summarized that reflect the relative importance of these effects on the ability to reliably monitor neurologic pathways at risk during the perioperative period.

The authors thank Tanya Callaway (Secretary, Department of General Anesthesiology, The Cleveland Clinic Foundation, Cleveland, Ohio) for her excellent work in manuscript preparation and Nadia Kolta, M.B.A., M.L.I.S. (Librarian, Program Coordinator, Department of General Anesthesiology, The Cleveland Clinic Foundation, Cleveland, Ohio), for her expert assistance with library resources.

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