ANESTHESIOLOGY

A Neurologic Examination for Anesthesiologists

Assessing Arousal Level during Induction, Maintenance, and Emergence

Edith R. Reshef, M.D., Nicholas D. Schiff, M.D., Emery N. Brown, M.D., Ph.D.

ANESTHESIOLOGY 2019; 130:462–71

ABSTRACT

Anesthetics have profound effects on the brain and central nervous system. Vital signs, along with the electroencephalogram and electroencephalogram-based indices, are commonly used to assess the brain states of patients receiving general anesthesia and sedation. Important information about the patient's arousal state during general anesthesia can also be obtained through use of the neurologic examination. This article reviews the main components of the neurologic examination focusing primarily on the brainstem examination. It details the components of the brainstem examination that are most relevant for patient management during induction, maintenance, and emergence from general anesthesia. The examination is easy to apply and provides important complementary information about the patient's arousal level that cannot be discerned from vital signs and electroencephalogram measures.

(ANESTHESIOLOGY 2019; 130:462–71)

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/130/3/462/385993/20190300_0-00025.pdf by guest on 09 April 2024

Since the mid-1980s in the United States, patient safety in anesthesiology has improved and malpractice premiums have been reduced by mandating continuous monitoring of basic physiology in all patients who receive anesthesia care.[1,2] These American Society of Anesthesiologists standards require monitoring of heart rate, oxygen delivery, end-tidal carbon dioxide, and body temperature. Such monitoring standards are in keeping with the American Society of Anesthesiologists motto of "vigilance." For the most part, vigilance has focused on paying careful attention to the physiology as displayed on standard monitors in the operating room. However, vigilance has been enhanced by use of the train-of-four monitor to track the level of muscle relaxation, pressure-volume displays to monitor the respiratory system, ultrasonography to assess and monitor cardiac function, and electroencephalogram-based indices to track level of unconsciousness.[3]

Interpretation of certain neurologic signs and symptoms antedates the use of electroencephalogram-derived indices in anesthesiology to assess a patient's anesthetic state. The most commonly used signs and symptoms are movements—in the absence of muscle relaxation—including the eyelash reflex, gaze, pupil size, and pupillary response to light. Guedel formalized the use of these eye signs and respiratory patterns to characterize the anesthetic state for ether, and ether used in combination with opioids.[4] Today, there is still sole use of ether-derived anesthetics, with or without opioids, in spontaneously breathing patients. However, balanced anesthetic techniques that use combinations of anesthetic drugs are far more common. Although Guedel's system no longer applies to anesthetic states created by modern techniques, anesthesiologists continue refer to the excitatory states seen at times on emergence or on induction as Guedel's stage two.[5]

Patients receiving general anesthesia are placed into and brought out of a pharmacologically induced coma.[6,7] This suggests that the parts of the neurologic examination that are commonly used by neurologists to assess level of arousal and integrity of brainstem and corticothalamic function in patients in coma, vegetative states, and minimally conscious states should be used to evaluate arousal levels in patients who receive general anesthesia or sedation. Use of the neurologic examination in anesthesia care would place assessments of level of unconsciousness within the same framework used by neurologists to track coma recovery. This article reviews the neuroanatomy and neurophysiology of selected components of the neurologic examination, and the principal findings from the examination in patients receiving general anesthesia or sedation. Because distinct parts of the brain and central nervous system are affected for different amounts of time during the administration of general anesthesia, the findings from the neurologic examination change with changes in the patient's anesthetic state. The components of the examination that are most relevant for given periods of general anesthesia are discussed, where the periods are divided into induction, maintenance, and emergence.

This article is featured in "This Month in Anesthesiology," page 5A.

Submitted for publication July 12, 2017. Accepted for publication October 31, 2018. From the Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts (E.R.R.); the Feil Family Brain and Mind Research Institute and the Department of Neurology, Weill Cornell Medical College, New York, New York (N.D.S.); the Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts (E.N.B); the Department of Brain and Cognitive Science, the Institute for Medical Engineering and Sciences, the Picower Institute for Learning and Memory, and the Institute for Data, Systems and Society, Massachusetts Institute of Technology, Cambridge, Massachusetts (E.N.B).

Copyright © 2019, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. All Rights Reserved. Anesthesiology 2019; 130:462–71

Copyright © 2018, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Induction

Physiologic Signs of Loss of Consciousness

Induction of general anesthesia is accomplished typically through administration of a hypnotic drug such as propofol, a barbiturate, or etomidate, given as an intravenous bolus over 5 to 10 s. During this time, several physiologic changes are commonly observed as the patient becomes unconscious within 10 to 30 s. When asked to count backwards from 100, the patient typically loses consciousness between 80 to 90, *i.e.* stops counting. The anesthesiologist can also monitor the transition to unconsciousness by using a task called smooth pursuit, whereby the patient is instructed to track with his or her eyes the course of the anesthesiologist's finger through space along a horizontal line.[6] As the patient's level of consciousness declines during smooth pursuit, the lateral excursions of the eyes decrease, blinking increases, and nystagmus may appear. The eyes eventually fix in the midline as the lids close. Almost simultaneously, the patient becomes unresponsive, atonic, apneic, and the oculocephalic (or more precisely vestibular-oculocephalic) (fig. 1A) and corneal (fig. 1B) reflexes are lost. The pupillary response (fig. 1C) to light may be absent or present. At this point, unresponsiveness is interpreted as unconsciousness. It must be acknowledged that a patient could be in a state of cognitive motor dissociation.[8] That is, conscious but unable to respond. Detecting this state would require imaging techniques and behavioral assessments not commonly used in clinical practice.[9]

To evaluate the oculocephalic reflex, the patient's head is turned from right to left. The reflex is present if the eyes move opposite the direction of the head motion. In an alert, unanesthetized patient with no neurologic deficits, this reflex is not present because voluntary eye movements can hide the reflex. After administration of the induction agent, the eyes fix in the midline and the reflex is lost.[10] Therefore, it is important to note that the absence of the oculocephalic reflex in the anesthetized patient suggests brainstem dysfunction whereas the absence of this reflex in a neurologically intact awake patient is normal. Horizontal rotation of the head activates the vestibular system, which projects through the eighth cranial nerve to the vestibular nucleus in the pons (fig. 1A). Projections from the vestibular nucleus synapse directly on the lateral rectus muscles of the eyes, the abducens (sixth cranial nerve) nucleus, the oculomotor (third cranial nerve) nucleus, and the trochlear (fourth cranial nerve) nucleus. The motor nucleus of the sixth cranial nerve is located in the upper pons whereas the motor nuclei of the third and fourth cranial nerves are located in the midbrain. Thus, failure to elicit an oculocephalic response reflects dysfunction at least along this expanse of brainstem.

Anesthesiologists' use of the eyelash reflex is an approximation to the more precise corneal reflex (fig. 1B). The corneal reflex is evaluated by using either a wisp of cotton or a drop of sterile water to touch the cornea. Using sterile water is the preferred method because it is less likely to result in a corneal abrasion. If the eyes blink consensually, the reflex is intact. If only one eye blinks, the reflex is impaired, and if neither eye blinks, the reflex is absent. The ophthalmic branch of the fifth cranial nerve carries the afferent signal of the corneal reflex to the sensory nucleus of the fifth cranial nerve. The efferent component of the reflex emanates from the motor nucleus of the seventh cranial nerve. Both of these nuclei are located in the pons.

Absence of the oculocephalic reflex soon after anesthetic administration indicates that the anesthetic has affected the motor nuclei that control eye movements. Likewise, absence of the corneal reflex after anesthetic administration indicates that the anesthetic has affected the sensory and/or the motor nuclei of the eyes and face. The patient loses consciousness, and the oculocephalic and corneal reflexes at approximately the same time. The nuclei for the third, fourth, and sixth cranial nerves, which control the oculocephalic reflex, and the nuclei of the fifth and seventh cranial nerves, which control the corneal reflex, are adjacent to the brain's arousal centers in the midbrain, pons, and hypothalamus (fig. 2).[10] Because the cranial nerve nuclei that govern these reflexes are located close to the arousal centers, it can be inferred that loss of consciousness is partially due to the anesthetic effects on the arousal centers.[6,11] This statement is consistent with the neurophysiology of the brainstem and hypothalamic circuits and the pharmacology of the hypnotic agents.

Most commonly used hypnotic agents—propofol, etomidate, and the barbiturates—enhance γ-aminobutyric acid–mediated (GABAergic) inhibition.[6,7] The preoptic area of the hypothalamus sends GABAergic projections to nearly all of the arousal centers.[7] These anesthetics also act at GABAergic synapses in the ventral and dorsal respiratory groups of the pons and medulla, causing the apnea that commonly accompanies induction.[12] The circuits of the oculocephalic and corneal reflexes are also under inhibitory control by GABAergic interneurons.[13] Simultaneous action of the hypnotic agents at these GABAergic synapses explains why the changes in arousal level and apnea occur concomitantly with the loss of these brainstem reflexes.

The atonia observed on induction can be attributed to actions of the anesthetic at multiple GABAergic sites in the motor pathways running from primary motor cortex to through the brainstem to the spinal cord. However, sites of likely brainstem action are the reticular nuclei of the pons and midbrain; lesions in these nuclei, as occur with pontine strokes, are associated with cataplexy[14,15] and flaccid paralysis.[10]

The brainstem's neuronal and vascular anatomy suggest a simple explanation as to how on induction of general anesthesia, the component of loss of consciousness due to brainstem inactivation occurs concomitantly with loss of

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/130/3/462/385993/20190300_0-00025.pdf by guest on 09 April 2024

Copyright © 2018, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

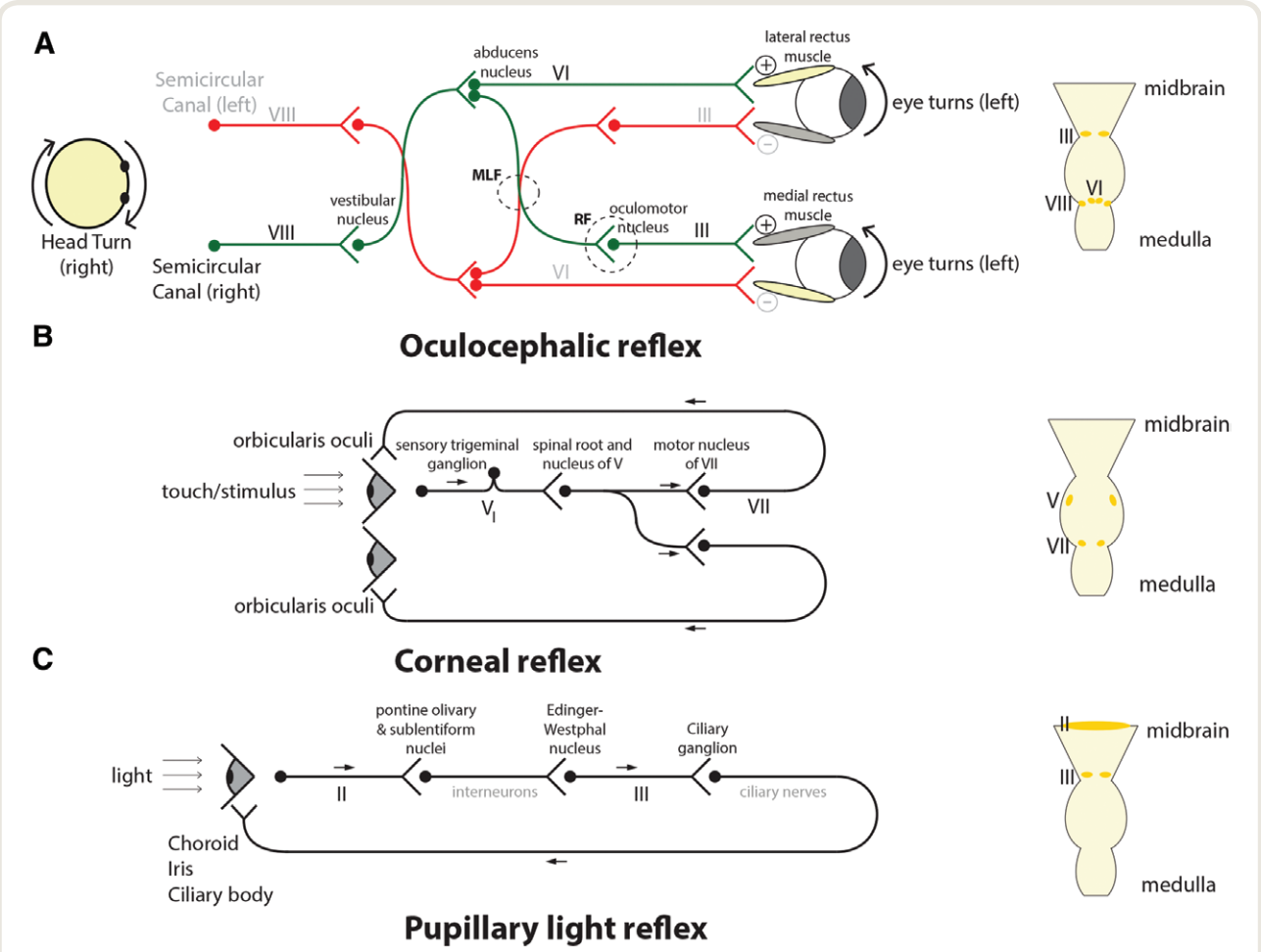

Fig. 1. Neural circuit mechanisms for brainstem reflexes. (*A*) Oculocephalic reflex. Manual head turn elicits eye movements that counter the head movement. For example, during a right head turn, activity in the right semicircular canal excites the right vestibulocochlear nerve (cranial nerve VIII) that innervates the ipsilateral vestibular nucleus. Excitatory projections decussate and synapse on the contralateral abducens nucleus, which has two outputs. The abducens nerve (cranial nerve VI) propagates the excitatory signal causing the left (contralateral) lateral rectus muscle to contract. In addition, an excitatory projection crosses the midline and ascends through the medial longitudinal fasciculus (MLF) to the oculomotor nucleus within the reticular formation (RF). From there, excitatory projections of the oculomotor nerve (cranial nerve III) cause the medial rectus of the right (ipsilateral) eye to contract. Inhibitory projections beginning from the left semicircular canal follow the same pathway, causing the right (contralateral) medial rectus muscle and the left (ipsilateral) lateral rectus muscle to relax. (*B*) Corneal reflex. The physical stimulus applied to the cornea is sensed by the sensory trigeminal nerve (cranial nerve V) that projects to the spinal root and nucleus of cranial nerve V. From there, the efferent signal is carried to the motor nuclei of the facial nerves (cranial nerve VII) that synapse onto the orbicularis oculi of the left and right eyes, causing bilateral blink. (*C*) Pupillary light reflex. Light enters the eye and travels through the optic nerve (cranial nerve II) to the pontine olivary and sublentiform nuclei. Interneurons project to the Edinger–Westphal nucleus, and from there, the oculomotor nerve (cranial nerve III) propagates the signal to the ciliary ganglion. Ciliary nerves synapse on the choroid, iris and ciliary body, causing the iris to constrict.

the oculocephalic and corneal reflexes, atonia and apnea. After the hypnotic agent is administered intravenously, it rapidly reaches all parts of the brain. In particular, the agent travels through the two vertebral arteries, which fuse to form the basilar artery, the principal blood supply to the brainstem.[11] Many penetrating arteries arise from the basilar artery, travel to the brainstem nuclei carrying the induction agent where it induces the observed physiologic and behavioral changes.

Electroencephalogram Markers of Loss of Consciousness

Electroencephalogram-derived indices are often used to monitor changes in level of consciousness during induction of general anesthesia. As an induction agent takes effect, the electroencephalogram indices typically change from the high values that are associated with wakefulness, to lower values indicative of sedation or unconsciousness.

Copyright © 2018, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/130/3/462/385993/20190300_0-00025.pdf by guest on 09 April 2024

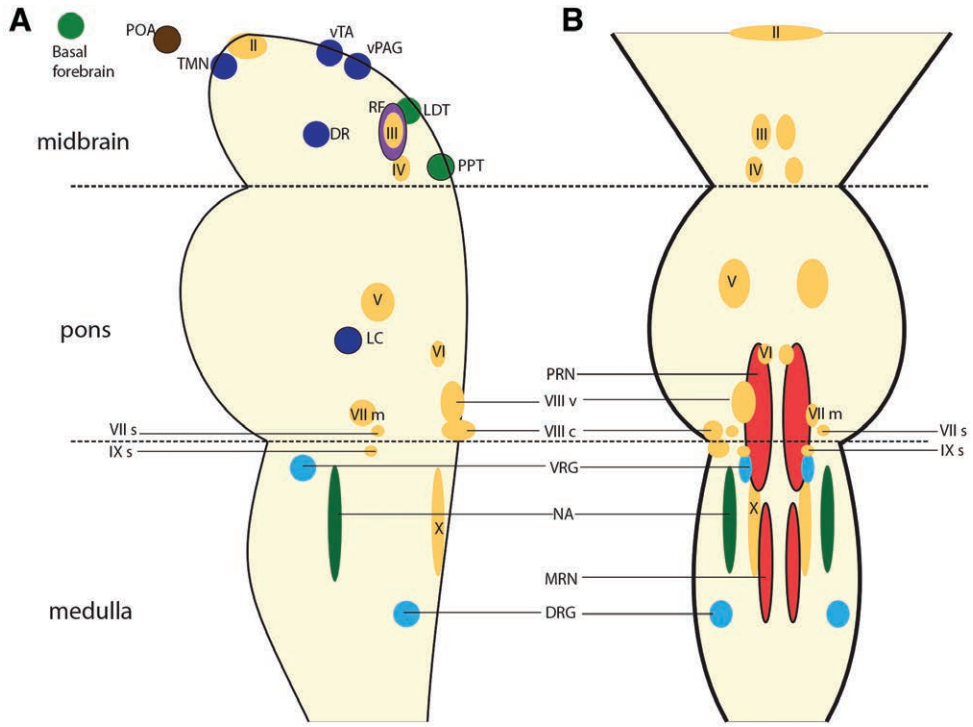

Fig. 2. Anatomy of the brainstem arousal and cranial nerve nuclei. (*A*) Sagittal and (*B*) coronal sections of brainstem showing the relationship between the arousal centers and the cranial nerve nuclei. The close proximity between the arousal centers and cranial nerve nuclei is why loss of and recovery of function in the brainstem examination (cranial nerve examination) may be used to infer changes in arousal state. Color legend: *brown* indicates hypothalamus; *dark blue*, monoaminergic arousal centers; *green*, cholinergic arousal centers; *light blue*, respiratory centers; *purple*, reticular formation; *red*, motor relay nuclei; *yellow*, cranial nerve nuclei. II optic nerve nucleus; III oculomotor nucleus and Edinger-Westphal nucleus; IV, trochlear nucleus; V, principal sensory trigeminal nucleus; VI, abducens nucleus; VII m, facial motor nucleus; VII s, superior salivatory nucleus; VIII c, cochlear nucleus; VIII v, vestibular nucleus; IX s, inferior salivatory nucleus; X, dorsal motor nucleus of vagus; DR, dorsal raphe nucleus; DRG, dorsal respiratory group; LC, locus ceruleus; LDT, laterodorsal tegmental group; MRN, medullary reticular nucleus; NA, nucleus ambiguus; POA, preoptic area of the hypothalamus; PPT, pedunculopontine tegmentum; PRN, pontine reticular nucleus; RF, reticular formation; TMN, tuberomanmilary nucleus; vPAG, ventral periaqueductal gray; vTA, ventral tegmental area; VRG, ventral respiratory group.

As the patient becomes sedated, the unprocessed electroencephalogram shows beta oscillations (13 to 25 Hz). The beta oscillations are believed to represent primarily the effects of the induction agent on GABAergic circuits in the cortex.[16] With unconsciousness, the unprocessed electroencephalogram shows profound slow (0.1 to 1 Hz) and delta (1 to 4 Hz) oscillations. The neurophysiology of these slow-delta oscillations is consistent with the anesthetics acting in the brainstem, thalamus, and cortex to decrease excitatory activity in the cortex, and hyperpolarizing thalamic and cortical circuits.[17,18] The slow-delta oscillations may precede or appear at the same time as alpha (8 to 12 Hz) oscillations. Because the alpha oscillations most likely represent hypersynchronous activity between the thalamus and frontal cortex,[16,19] the simultaneous appearance of the slow-delta and alpha oscillations indicates that propofol is acting simultaneously in the brainstem, thalamus, and cortex to induce loss of consciousness. The slow-delta and alpha oscillations may also evolve into burst suppression, which is a more profound state of brain inactivity characterized by periods of slow-delta and alpha oscillations or bursts, interspersed with isoelectric, flat electroencephalogram periods termed suppressions.[18] Rapid appearance of burst suppression on induction, is common in elderly patients.[18]

Table 1 summarizes the principal neurologic examination and electroencephalogram findings observed at loss of consciousness during a propofol induction.

Maintenance

During maintenance of general anesthesia, a combination of physiologic signs, established anesthetic pharmacology and practice habits are used to track the anesthetic state. This section reviews the neurophysiology and

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/130/3/462/385993/20190300_0-00025.pdf by guest on 09 April 2024

Copyright © 2018, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Table 1. Summary of Findings at Loss of Consciousness during Propofol Induction

Neurologic Examination Findings	Electroencephalogram Findings
• Patient stops backward count and becomes unresponsive to voice commands • Loss of oculocephalic reflex • Loss of the corneal reflexes • Apnea • Decrease/loss of muscled tone	• With sedation, appearance of beta oscillations (13–25 Hz) • With loss of conscious, appearance of slow-delta oscillations (0.1–4 Hz); slow-delta oscillations with alpha oscillations (8–12 Hz); burst suppression

neuroanatomy of these paradigms and suggests some further clinical correlations.

Physiologic Responses and the Nociceptive Medullary Autonomic Pathway

Tracking increases in blood pressure, increases in heart rate, and movement remain the most frequently used methods to monitor changes in anesthetic state during maintenance of general anesthesia.[3,20] If there is an inadequate level of general anesthesia (level of antinociception and unconsciousness) for a given level of surgical stimulation, the patient's heart rate and blood pressure can rise rapidly. The nociceptive medullary autonomic circuit—consisting of the spinoreticular tract, the nucleus of the tractus solitarius in the medulla, and the sympathetic and parasympathetic efferents from the medulla—can explain these physiologic changes that arise in response to a nociceptive stimulus such as surgery (fig. 3).[6,21] Similarly, neurologists often assess level of arousal in brain injury patients by applying nociceptive stimuli—nail bed pinches, body pinches, or sternal rubs—to activate the nociceptive medullary autonomic circuit.[10,22,23] It is imperative that anesthesiologists understand the nociceptive medullary autonomic circuit because tracking activity in this pathway is the most common method used in clinical practice to track patients' levels of antinociception and unconsciousness.

For example, consider the case in which a patient is under general anesthesia and shows an abrupt increase in heart rate and blood pressure in response to the surgical incision. It is reasonable to assume that these changes can be attributed to inadequate antinociception provided that there are no respiratory, hemodynamic, or arousal issues. The anesthesiologist can determine whether this is this case by quickly checking the patient's ventilation, oxygen saturation, oxygen delivery, and signs of bleeding to rule out any cardiopulmonary and/or hematologic derangements, and electroencephalogram indicators to assess changes in level of unconsciousness. If there is no change in the electroencephalogram indicator to suggest a decrease in the level of arousal, then an inadequate level of antinociception is likely the case, and the anesthesiologist can administer more analgesic. If there is a decrease in the level of arousal then, an additional dose of a hypnotic or an increase in the dose of the inhaled ether may also be required. Similarly, if movement is associated with the changes in vital signs, recovering control of nociception may be sufficient prevent further movement; however, muscle relaxation may also be needed.

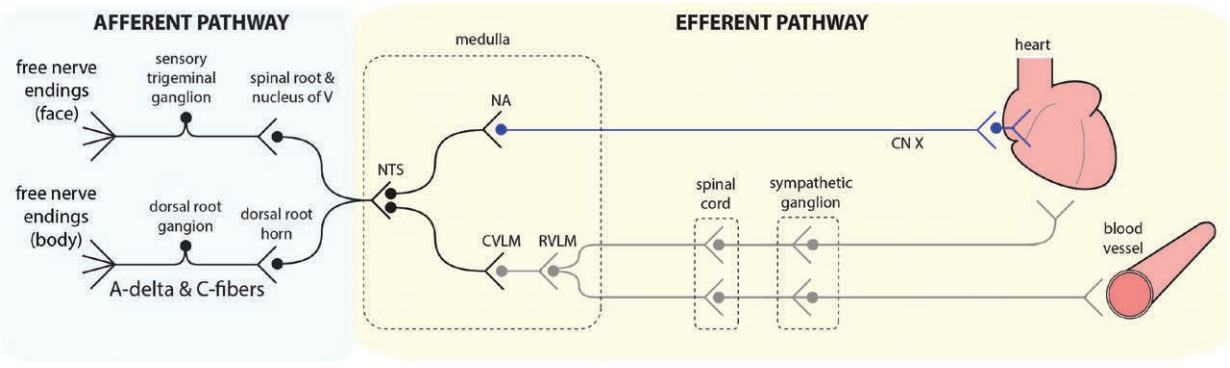

Fig. 3. Nociceptive medullary autonomic circuit. A-delta and C peripheral afferents carrying somatic nociceptive information from the body synapse on the dorsal root horn. Free nerve endings from the face synapse at the spinal root and nucleus of the trigeminal nerve (cranial nerve V). Projection neurons from both the dorsal root horn and the nucleus of cranial nerve V synapse at the nucleus tractus solitarius (NTS) of the medulla. The sympathetic response is propagated from the nucleus tractus solitarius to the caudal ventral lateral medulla (CVLM) and the rostral ventral lateral medulla (RVLM). Pre-ganglionic fibers project to post-ganglionic fibers in the sympathetic ganglia that innervate the heart and peripheral blood vessels. The parasympathetic response to the nociceptive information from the face and body is mediated by the nucleus ambiguous (NA). The vagus nerve (cranial nerve X) projects from the NA to a post-ganglionic fiber that synapses onto the sinoatrial node of the heart.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/130/3/462/385993/20190300_0-00025.pdf by guest on 09 April 2024

Copyright © 2018, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

The afferent branch of the nociceptive medullary autonomic circuit begins with peripheral A-delta and C fibers that carry nociceptive information to the dorsal horn of the spinal cord where they synapse on to projection neurons (fig. 3).[24] The projection neurons travel in the anterolateral fasciculus and synapse in several brainstem sites, including the nucleus of the tractus solitarius in the medulla.[6,21] From the face, nociceptive information is transmitted through the trigeminal ganglia and the nucleus of the fifth cranial nerve, and then, onto the nucleus of the tractus solitarius and other brainstem sites. The nucleus of the tractus solitarius mediates the body's sympathetic output to the blood vessels and the heart *via* the rostral and caudal portions of the ventral lateral medulla, which project to the thoracolumbar sympathetic ganglia. This pathway initiates the sympathetic response seen after a nociceptive stimulus.[6] Furthermore, the parasympathetic outputs from the nucleus of the tractus solitarius project to the nucleus ambiguus and the dorsal motor nucleus of the vagus which, in turn, projects *via* the vagus nerve to the heart's sinoatrial node.[6] Finally, the nucleus tractus solitarius sends projections to both the periventricular and the supraoptic nuclei of the hypothalamus which release vasopressin.[25] Hence, the nociceptive stimulus of making the incision in a patients with an inadequate level of antinociception activates the nociceptive medullary autonomic circuit, causing an increase in the sympathetic activity and a simultaneous decrease in parasympathetic activity that manifest as rapid increases in blood pressure and in heart rate.

It is logical that anesthesiologists use changes in nociceptive medullary autonomic activity to detect rapidly inadequate antinociception because this circuit is a critical part of the "fight or flight" response.[26] The nociceptive medullary autonomic circuit allows anesthesiologists to detect, almost immediately, nociceptive stimuli that may trigger stress and/or arousal responses.

The level of nociceptive medullary autonomic activity can be used along with electroencephalogram activity to determine whether a patient receiving an apparently adequate dose of a hypnotic or an inhaled ether to produce unconsciousness may still have an inadequate level of antinociception. This situation would be indicated by increases in heart rate and blood pressure in the absence of any changes in electroencephalogram activity or in electroencephalogram-based indices suggestive of increased arousal. The nociceptive stimulus is therefore sufficient to activate the nociceptive medullary autonomic pathway, but not the arousal circuits. This situation, in the setting of an otherwise stable physiologic condition, would suggest a need to administer analgesics. On the other hand, if there are increases in blood pressure and heart rate, and also electroencephalogram activity changes suggestive of increased arousal, then increasing the dose of the hypnotic or the inhaled ether along with administering the analgesics may be required. Given the importance of the nociceptive medullary autonomic circuit, indices of antinociception derived from heart rate variability and nerve stimulation are now appearing in clinical use.[27,28]

Other markers of inadequate antinociception include other indicators of increased sympathetic and decreased parasympathetic activity such as perspiration, pupil dilation, and tearing, along with return of muscle tone, return of breathing, and movement.[20] The latter three markers are unlikely if a muscle relaxant has also been administered. Although not widely used in clinical practice, changes in electrodermal activity has been proposed as another method of detecting inadequate antinociception.[29]

Electroencephalogram Markers of Unconsciousness during Maintenance

During general anesthesia maintained with GABAergic agents (inhaled ethers, propofol) the electroencephalogram shows strong alpha and slow-delta oscillations patterns. In older patients (greater than 55 yr), the frequency range of the alpha oscillations tends to be lower and more narrow, and the amplitude tends to be diminished relative to young adults.[18,30] In children (6 to 17 yr), the opposite is observed. The frequency range of the alpha oscillations tends to be higher and broader, and the amplitude is increased relative to young adults.[18,31] That patients are unconscious when the alpha and slow-delta oscillations are present in the electroencephalogram has been well documented.[18,19,32] The electroencephalogram markers of unconsciousness can be used to help distinguish between a nociceptive stimulus that produces just an autonomic response and one that produces an autonomic and an arousal response.

Emergence

Physiologic Signs of Return of Consciousness

During emergence, the patient's state of consciousness can be tracked by using changing physiologic signs. These signs correlate with the return of specific brainstem functions (fig. 4).[6]

By linking these predictable physiologic signs to their associated brainstem foci, the anesthesiologist can gain an informed understanding of how the brainstem returns during emergence from general anesthesia.

Soon after the reversal of muscle relaxation, the patient regains the ability to breathe unassisted. Most patients typically begin breathing spontaneously once there is a sufficient amount of carbon dioxide in the cerebral circulation, as indicated by the end-tidal carbon dioxide level. Often the patient's respiratory pattern is first irregular and tidal volumes are small. Within a short period of time, the pattern becomes more regular with larger tidal volumes.[6] Return of spontaneous respiration signals return of function of the

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/130/3/462/385993/20190300_0-00025.pdf by guest on 09 April 2024

Copyright © 2018, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

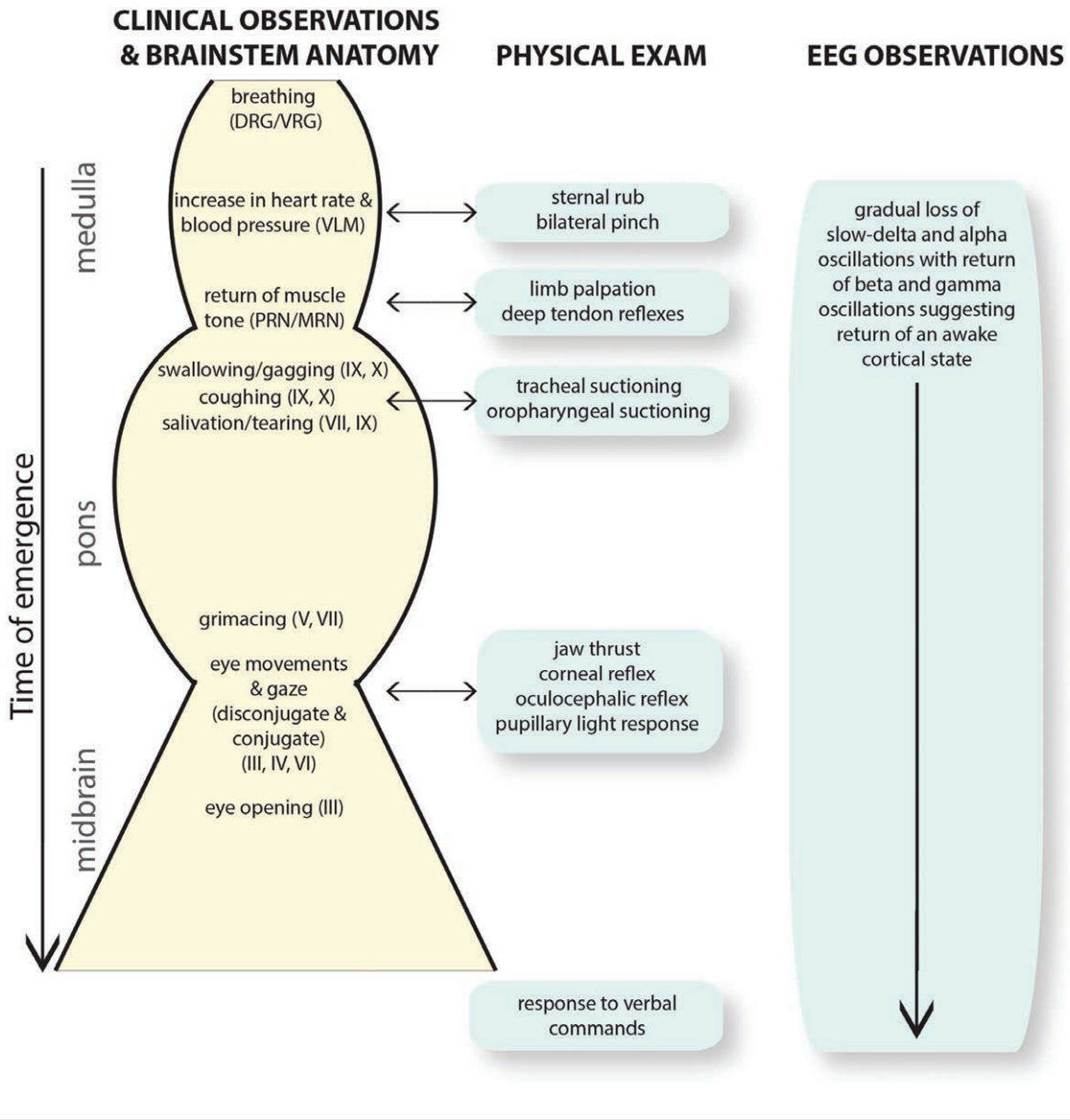

Fig. 4. The clinical observations and neurologic examination findings can be used to assess return of brainstem function on emergence from general anesthesia. The clinical observations depicted correlate approximately with return of brainstem function and with time of emergence in a caudal to rostral direction. As patients emerge from general anesthesia, the anesthesiologist should interpret these clinical observations as indications of return of function in specific brainstem sites. If they are not present, the anesthesiologist can perform the suggested neurologic examination maneuvers to actively assess brainstem function.

ventral and dorsal respiratory groups situated respectively in the caudal pons and medulla.[12]

Swallowing, gagging, salivation, tearing, and grimacing often return either concomitant with spontaneous breathing, or a few minutes thereafter (fig. 4). Each of these signs indicates return of function of specific brainstem centers. Swallowing and gagging occur because the endotracheal tube becomes a noxious stimulus as the antinociceptive and hypnotic effects of the anesthetics recede. These two signs indicate returning medullary function, particularly in the motor nuclei of ninth and tenth cranial nerves, as well as the associated sensory afferents that carry the nociceptive signals from the trachea, larynx, and pharynx.[24] Return of salivation and tearing represents parasympathetic activity coming from the inferior and superior salivatory nuclei in the medulla and pons respectively, as well as activity of seventh and ninth cranial nerves, which carry the efferent signals.[24] Grimacing indicates function in the pons, specifically the motor nucleus of the seventh cranial nerve which innervates the muscles of facial expression.[24] Finally, return of the patient's muscle tone indicates return of function in motor circuits including the primary motor tracts, the basal ganglia, the reticulospinal tract, and the spinal cord.[6]

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/130/3/462/385993/20190300_0-00025.pdf by guest on 09 April 2024

Copyright © 2018, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Return of these physiologic signs suggests that there is adequate return of airway control and motor function. Therefore, as long as other vital signs are stable, the patient may be extubated even without the ability to respond to commands.

The corneal reflex may return soon after or as grimacing occurs (fig. 4).[6] Recovery of this reflex indicates recovery of function in the ophthalmic branch afferents of the fifth cranial nerve that project to the fifth nerve sensory nucleus, as well as in the motor efferents originating from the seventh nerve motor nucleus. Both the fifth and seventh cranial nerve nuclei lie in the pons. A consensual blink in response to corneal stimulation in one eye suggests bilateral recovery of both the motor and sensory components in the corneal reflex.

Recovery of the oculocephalic reflex reflects a recovery of function of the third, fourth, sixth, and eighth (vestibular) cranial nerve nuclei which are responsible for eye movements.[10] Because an awake patient may not show an oculocephalic reflex because voluntary control of the eyes has resumed, the best way to assess the function of these cranial nerve nuclei is to ask the patient to track the anesthesiologist's finger in a smooth pursuit maneuver as described in the Induction section. The ability to move the eyes by voluntarily tracking the anesthesiologist's finger indicates recovery of function in both the midbrain and pons, as well as certain cortical, cerebellar, and basal ganglia circuits. Moreover, visual tracking in the form of recovery smooth pursuit is an unambiguous sign of conscious awareness; for assessment of patients with disorders of consciousness, it is one of the most reliable signs distinguishing vegetative state from minimally conscious state in terms of nonreflexive movements.[23] Recovery of function in these brain stem nuclei indirectly offers evidence that the arousal centers in the midbrain, pons, and hypothalamus have likely also recovered function (fig. 2).[6]

The pupillary light reflex may be variable as the patient recovers from general anesthesia.[10] This reflex can remain intact even when a patient is deeply unconscious under general anesthesia. In contrast, the pupillary light reflex can be diminished in a patient who received a large opioid dose, yet the patient may be conscious. Therefore, the pupillary light reflex may not necessarily reflect changes in a patient's level of consciousness during emergence. Pupillary activity measured using infrared pupillometry can track nociception. However, these measurements require special equipment, are intermittent and are not recommended for use by anesthesiologists without up-to-date knowledge of rare pupillary syndromes.[33] All in all, return of brainstem function during emergence from general anesthesia follows an approximate caudal-rostral progression, *i.e.* return of spontaneous ventilatory drive, grimacing/corneal reflexes, integrative oculomotor function, and finally, volitional demonstrations of conscious awareness.

When the patient begins responding correctly to verbal commands, this indicates that the patient has regained integrative function between the brainstem, thalamus, and cortex.[6,34,35] Moreover, this transition marks a significant shift in demonstrated level of consciousness. Collectively, the full sequence of stimulus and response requires a functional eighth cranial nerve to carry the auditory stimulus to the eighth nerve nucleus in the pons, as well as functional auditory pathways from the pons to the thalamus and cortex, and relevant motor tracts to carry out the response as well as frontal cortical regions and their connected basal ganglia nuclei to organize the behavioral set. The ability to respond appropriately to commands is a criterion used often by anesthesiologists to evaluate the patient's overall recovery from general anesthesia, and therefore, readiness to be extubated. According to the criteria that neurologists use to assess patients recovering from coma, a patient that follows motor commands inconsistently is in a minimally conscious state (fig. 4).[22,23,36]

Spontaneous eye opening is often one of the last signs observed as a patient emerges from general anesthesia (fig. 4). It is possible that a patient has substantially regained motor function and is reliably responding to verbal commands, but has not yet opened his or her eyes.[6] Even when patients have regained consciousness, they frequently keep their eyes closed. In contrast, a patient recovering from coma may open his or her eyes spontaneously.[6]

Electroencephalogram Markers of Return of Consciousness during Emergence

Sufficient return of activity in intracortical, thalamocortical, brainstem–thalamic, and brainstem–cortical communication pathways is required in order for the patient to regain consciousness.[19,35,37–39] At present, these changes can be tracked indirectly with electroencephalogram monitoring.[3,18] On emergence from general anesthesia maintained by GABAergic anesthetics, the electroencephalogram shows transition from alpha to beta to gamma oscillations, with a concomitant decrease in and eventual loss of slow-delta oscillations.[18] On the spectrogram, this transition of power across frequencies appears like a zipper opening.[18] Disappearance of the slow-delta oscillations correlates with return of the brainstem functions mentioned above. The transition from, alpha to beta to gamma oscillations correlates with dissipation of thalamocortical hypersynchrony and with the patient transitioning from unconsciousness, to sedation and on to being arousable.[6,16,18,19] The appearance of muscle artifact as muscle tone returns may make it difficult to read the electroencephalogram arousal patterns.

Conclusion and Summary

General anesthesia is a reversible coma that is induced pharmacologically. Neurologists regularly perform neurologic examinations on patients in pathologic comas to assess the degree of injury and to track recovery. This discussion has shown how the elements of the neurologic examination that focus on the brainstem can be used to assess loss of

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/130/3/462/385993/20190300_0-00025.pdf by guest on 09 April 2024

Copyright © 2018, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

consciousness, level of unconsciousness, and recovery of consciousness in patients receiving general anesthesia and sedation. When used with other parts of the physical examination, vital signs, and electroencephalogram assessments, the neurologic examination can provide the anesthesiologist with more informed picture of a patient's state of arousal during general anesthesia and sedation. One of the authors (E.N.B.) uses the neurologic examination described here as part of regular practice in the operating room.

The neurologic examination is helpful for confirming when a patient has lost consciousness on induction and is helpful in assessing level of unconsciousness when a waking event is suspected during general anesthesia. The examination is especially useful for tracking emergence from general anesthesia. The vital signs provide information about residual effects of the anesthetics on the nociceptive and autonomic nervous system, whereas the electroencephalogram dynamics offer a picture of recovery of cortical function and the extent to which normal interactions between cortex and subcortical structures have been reestablished. The neurologic examination provides information about the degree of brainstem recovery. Therefore, together, the vital signs, electroencephalogram dynamics, and the neurologic examination findings provide real-time insight into how the brainstem and cortex are recovering from general anesthesia.

The neurologic examination is also helpful for assessing the arousal state of a patient following extubation. For example, an extubated patient who follows simple verbal commands, and in particular, performs smooth pursuit, is in a much higher arousal state than a patient who only follows simple verbal commands. At extubation, return of the electroencephalogram to an awake pattern, return of muscle tone, partial return of the corneal reflex and absence of the oculocephalic reflex is not uncommon even though the patient may follow simple commands. The corneal and oculocephalic reflexes may not have returned prior to leaving the operating room. This observation suggests that a component of the sedative state observed in patients in the recovery room is a residual effect of the anesthetic on the brainstem arousal centers. This residual effect may contribute to postoperative cognitive dysfunction. The neurologic examination, along with the electroencephalogram, is also useful in helping to understand whether a prolonged emergence from general anesthesia is due to the residual anesthetic effects or to a new neurologic event.

Anesthesiologists, like other physicians, learn the neurologic examination during their neurology rotations in medical school. Despite the fact that anesthetics have profound effects on the brain and central nervous system, anesthesiologists do not use the examination to assess these effects on patients' levels of arousal. Unlike learning to use a new technology such as ultrasonography, the exciting part about incorporating the neurologic examination into anesthesia care is that it involves review of already learned materials. We hope that this review will encourage anesthesiologists to make daily use of this already acquired knowledge.

Research Support

Supported by grant Nos. DP1-OD003646 and R01-GM104948 from the National Institutes of Health (Bethesda, Maryland; to Dr. Brown) and funds from the Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts.

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Brown: 55 Fruit Street, Grey/Jackson, 444, Boston, Massachusetts, 02114. enb@neurostat.mit.edu. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

References

1. Eichhorn JH, Cooper JB, Cullen DJ, Maier WR, Philip JH, Seeman RG: Standards for patient monitoring during anesthesia at Harvard Medical School. JAMA 1986; 256:1017–20
2. Gaba DM: Anaesthesiology as a model for patient safety in health care. BMJ 2000; 320:785–8
3. Brown E, Solt K, Purdon P, Akeju O. Monitoring brain state during general anesthesia and sedation. Miller's Anesthesia 8th ed. Phildelphia, PA: Elsevier; 2015.
4. Douglas BL: A Re-evaluation of Guedel's Stages of Anesthesia: With particular reference to the ambulatory dental general anesthetic patient. J Am Dent Soc Anesthesiol 1958; 5:11–4
5. Guedel AG: Third stage ether anesthesia: A subclassification regarding the significance of the position and movement of the eyeball. American Journal of Surgery 1920; 34 (Suppl.):53–57
6. Brown EN, Lydic R, Schiff ND: General anesthesia, sleep, and coma. N Engl J Med 2010; 363:2638–50
7. Brown EN, Purdon PL, Van Dort CJ: General anesthesia and altered states of arousal: a systems neuroscience analysis. Annu Rev Neurosci 2011; 34:601–28
8. Schiff ND: Cognitive Motor Dissociation Following Severe Brain Injuries. JAMA Neurol 2015; 72: 1413–5
9. Fernández-Espejo D, Rossit S, Owen AM: A thalamocortical mechanism for the absence of overt motor behavior in covertly aware patients. JAMA Neurol 2015; 72:1442–50

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/130/3/462/385993/20190300_0-00025.pdf by guest on 09 April 2024

Copyright © 2018, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

10. Posner J, Saper C, Schiff N, Plum F. Plum and Posner's Diagnosis of Stupor and Coma Oxford University Press; 2007
11. Coté CJ, Goudsouzian NG, Liu LM, Dedrick DF, Rosow CE: The dose response of intravenous thiopental for the induction of general anesthesia in unpremedicated children. Anesthesiology 1981; 55:703–5
12. Feldman JL, Del Negro CA: Looking for inspiration: New perspectives on respiratory rhythm. Nat Rev Neurosci 2006; 7:232–42
13. Che Ngwa E, Zeeh C, Messoudi A, Buttner-Ennever JA, Horn AK: Delineation of motoneuron subgroups supplying individual eye muscles in the human oculomotor nucleus. Front Neuroanat. 2014; 8:2
14. Fernandez JM, Sadaba F, Villaverde FJ, Alvaro LC, Cortina C: Cataplexy associated with midbrain lesion. Neurology 1995; 45:393–4
15. Stahl SM, Layzer RB, Aminoff MJ, Townsend JJ, Feldon S: Continuous cataplexy in a patient with a midbrain tumor: The limp man syndrome. Neurology 1980; 30:1115–8
16. Ching S, Cimenser A, Purdon PL, Brown EN, Kopell NJ: Thalamocortical model for a propofol-induced alpha-rhythm associated with loss of consciousness. Proc Natl Acad Sci U S A 2010; 107:22665–70
17. Pavone KJ, Akeju O, Sampson AL, Ling K, Purdon PL, Brown EN: Nitrous oxide-induced slow and delta oscillations. Clin Neurophysiol 2016; 127:556–64
18. Purdon PL, Sampson A, Pavone KJ, Brown EN: Clinical electroencephalography for anesthesiologists: Part I: Background and basic signatures. Anesthesiology 2015; 123:937–60
19. Purdon PL, Pierce ET, Mukamel EA, Prerau MJ, Walsh JL, Wong KF, Salazar-Gomez AF, Harrell PG, Sampson AL, Cimenser A, Ching S, Kopell NJ, Tavares-Stoeckel C, Habeeb K, Merhar R, Brown EN: Electroencephalogram signatures of loss and recovery of consciousness from propofol. Proc Natl Acad Sci U S A 2013; 110:E1142–51
20. Prys-Roberts C: Anaesthesia: A practical or impractical construct? Br J Anaesth 1987; 59:1341–5
21. Price DD: Psychological and neural mechanisms of the affective dimension of pain. Science 2000; 288:1769–72
22. Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, Kelly JP, Rosenberg JH, Whyte J, Zafonte RD, Zasler ND: The minimally conscious state: Definition and diagnostic criteria. Neurology 2002; 58:349–53
23. Giacino JT, Kalmar K, Whyte J: The JFK Coma Recovery Scale-Revised: Measurement characteristics and diagnostic utility. Arch Phys Med Rehabil 2004; 85:2020–9
24. Purves D, Augustine GJ, Hall WC, Lamantia A, McNamara JO, White LE. Neuroscience. 4th ed. Sunderland, Massachusetts: Sinauer Associates, Inc.; 2008
25. Freeman R: Clinical practice. Neurogenic orthostatic hypotension. N Engl J Med 2008; 358:615–24
26. Pfaff D. Brain Arousal and Information Theory: Neural and Genetic Mechanisms. Cambridge: Harvard University Press; 2005
27. Boselli E, Jeanne M: Analgesia/nociception index for the assessment of acute postoperative pain. Br J Anaesth 2014; 112:936–7
28. Lichtner G, Hösl TM, Jakuscheit A, Jurth C, von Dincklage F: Optimizing nociceptive flexion reflex (NFR) scoring criteria by adjusting for noise and reflex properties and sampling rate. Clin J Pain 2016; 32:773–83
29. Storm H: Changes in skin conductance as a tool to monitor nociceptive stimulation and pain. Curr Opin Anaesthesiol 2008; 21:796–804
30. Purdon PL, Pavone KJ, Akeju O, Smith AC, Sampson AL, Lee J, Zhou DW, Solt K, Brown EN: The ageing brain: Age-dependent changes in the electroencephalogram during propofol and sevoflurane general anaesthesia. Br J Anaesth 2015; 115 Suppl 1:i46–57
31. Akeju O, Pavone KJ, Thum JA, Firth PG, Westover MB, Puglia M, Shank ES, Brown EN, Purdon PL: Age-dependency of sevoflurane-induced electroencephalogram dynamics in children. Br J Anaesth 2015; 115 Suppl 1:i66–76
32. Lewis LD, Weiner VS, Mukamel EA, Donoghue JA, Eskandar EN, Madsen JR, Anderson WS, Hochberg LR, Cash SS, Brown EN, and Purdon PL: Rapid fragmentation of neuronal networks at the onset of propofol-induced unconsciousness. Proc Natl Acad Sci U S A 2012; 109:E3377–86
33. Larson MD, Behrends M: Portable infrared pupillometry: A review. Anesth Analg 2015; 120:1242–53
34. Alkire MT, Hudetz AG, Tononi G: Consciousness and anesthesia. Science 2008; 322:876–80
35. Hudetz AG: General anesthesia and human brain connectivity. Brain Connect 2012; 2:291–302
36. Hirschberg R, Giacino JT: The vegetative and minimally conscious states: Diagnosis, prognosis and treatment. Neurol Clin 2011; 29:773–86
37. Långsjö JW, Alkire MT, Kaskinoro K, Hayama H, Maksimow A, Kaisti KK, Aalto S, Aantaa R, Jääskeläinen SK, Revonsuo A, Scheinin H: Returning from oblivion: Imaging the neural core of consciousness. J Neurosci 2012; 32:4935–43
38. Mhuircheartaigh RN, Rosenorn-Lanng D, Wise R, Jbabdi S, Rogers R, Tracey I: Cortical and subcortical connectivity changes during decreasing levels of consciousness in humans: A functional magnetic resonance imaging study using propofol. J Neurosci 2010; 30:9095–102
39. Breshears JD, Roland JL, Sharma M, Gaona CM, Freudenburg ZV, Tempelhoff R, Avidan MS, Leuthardt EC: Stable and dynamic cortical electrophysiology of induction and emergence with propofol anesthesia. Proc Natl Acad Sci U S A 2010; 107:21170–5

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/130/3/462/385993/20190300_0-00025.pdf by guest on 09 April 2024

Copyright © 2018, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.