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## KEY POINTS

- Sleep is a dynamic neuronal and behavioral state that can be characterized using specific electroencephalographic, electrophysiologic, and behavioral findings.
- Characteristics of sleep can be quantified using questionnaires, actigraphy, or respiratory polygraphy. However, polysomnography, including electroencephalogram, electrooculogram, submental electromyogram, and analysis of breathing, is required to describe the cortical characteristics and immediate physiological consequences.
- Activation of hypothalamic sleep-promoting pathways including the ventrolateral preoptic nucleus and the median preoptic nucleus produces the physiological switch from wakefulness to sleep.
- Sleep and anesthesia can look similar. Although small doses of anesthetics can induce sleep by activating sleep-promoting pathways, surgical anesthesia and immobilization cannot be induced by sleep-promoting pathways.
- Control of breathing is altered during sleep and anesthesia, typically leading to a decreased drive to upper airway dilator and respiratory pump muscles.
- Persistent respiratory depressant effects of anesthetics and neuromuscular blocking drugs increase the risk of postoperative respiratory complications, particularly in patients with obstructive sleep apnea.
- Anesthesia and surgery, as well as treatment in the intensive care unit and opioids, affect sleep duration and sleep architecture, which may lead to impaired outcome.

Probably the earliest mention of “overpowering sleep” as a metaphor describing what possibly characterizes anesthesia can be found in Genesis 2:21: “And the Eternal God caused an overpowering sleep to fall upon the man and he slept. He took one of his ribs and shut in flesh instead thereof.” Although this “overpowering sleep” allegedly occurred by divine intervention and did not represent the drug-induced unconsciousness and immobility that characterizes anesthesia, the basic narrative is an example of antiquarian history that implicates the concept that deep sleep may be the only viable condition that allows a surgical procedure to be completed successfully.<sup>1</sup>

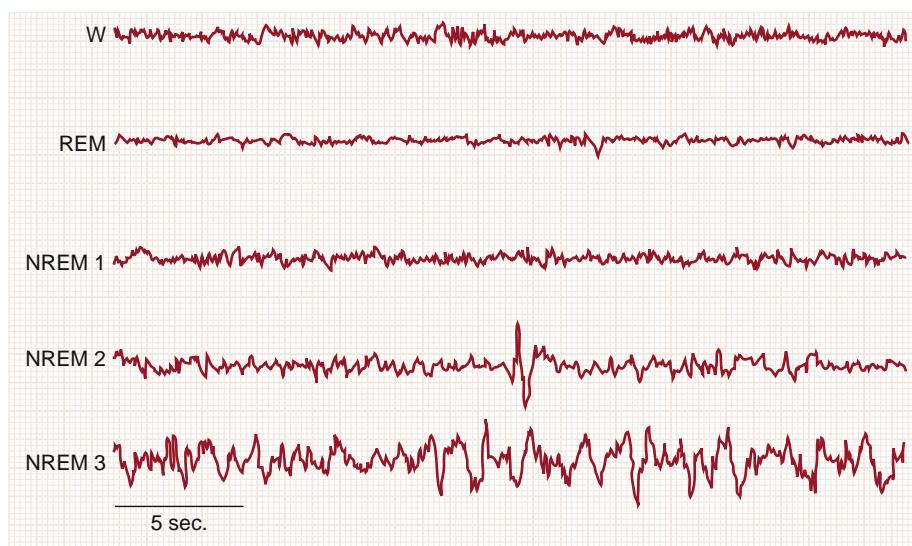
In the 21st century, an increasing body of knowledge has revealed the common ground between sleep and anesthesia, as well as their fundamental differences in clinical picture and underlying mechanisms.

Sleep is required for survival. Rats deprived of sleep will die within 2 to 3 weeks, a time frame similar to death due to starvation.<sup>2</sup> In humans, sleepiness can be deadly. Approximately 100,000 motor vehicle accidents each year result from drivers who are “asleep at the wheel.” In a survey of drivers in New York State, approximately 25% reported they had fallen asleep at the wheel at some time.<sup>3</sup> In addition, sleep deprivation impairs the psychomotor performance of night shift workers, specifically surgeons and residents. In patients, perioperative sleep deprivation occurs frequently, particularly in critically ill patients, and there may be consequences on patients’ outcomes. Among sleep disorders, obstructive sleep apnea (OSA) has probably the most meaningful consequences for perioperative treatment.<sup>4</sup>

Therefore, high-quality physiologic sleep is a key domain of public health that needs to be considered in perioperative medicine from both a provider and a patient perspective.

## Definition of Sleep

Sleep is the natural periodic suspension of consciousness during which the powers of the body are restored. A behavioral definition of sleep includes a species-specific posture and behavioral quiescence, as well as elevated arousal thresholds. However, sleep is much more than an absence of activity. The brain is highly active during sleep, especially during rapid eye movement (REM) sleep, during which atonia, phasic muscle movements (driven by different activation levels in distinct areas of the brain), and vivid dreaming occur. Sleep is not a simple electrophysiological phenomenon. At different stages of sleep, brain activities can be as distinct from each other as they are from wakefulness.<sup>5</sup> In humans and other vertebrates (see “Evolution”), sleep has two major stages: REM sleep and non-REM (NREM) sleep, with each of these further divided into substates. Most of sleep time is spent in NREM sleep, which is characterized by relatively low electroencephalographic (EEG) frequencies with higher amplitudes compared with awake EEG frequencies (Fig. 10.1). In the transition from wake to NREM sleep, the fast activity of waking disappears ( $\alpha$ - $\theta$  transition), and then in the deeper stages of NREM large, slow waves (i.e.,  $\delta$  waves) emerge. Thus deep NREM sleep is also referred to as *slow-wave sleep*. NREM sleep is associated with waxing and waning muscle tone, as well as decreased body



**Fig. 10.1** Representative electroencephalogram activity seen during different behavioral states. Electroencephalogram recordings of one patient during wakefulness (eyes closed; *W*), rapid eye movement sleep (REM), and non-REM (NREM) sleep stages 1 to 3.

temperature and heart rate. In contrast, REM sleep is characterized by muscle atonia, loss of slow waves in the EEG, and bursts of REMs that give this state its name.<sup>6</sup> Other prominent features of REM include marked irregularities of respiration and heart rate, as well as penile and clitoral erection. REM sleep is associated with the high likelihood of vivid dreaming. A distinct property of REM sleep is the operation of a system that suppresses motor activity, which is responsible for baseline atonia and suppression of motor commands that would otherwise result in acting out of dreams, a phenomenon known as *REM sleep behavior disorder*. This REM atonia system is not constant, as it periodically allows breakthrough muscle activity that comprises REM sleep and twitching of the extremities. REM sleep has therefore been subdivided into *tonic REM sleep* (i.e., a period with muscle atonia and without eye movements) and *phasic REM sleep*, which is interrupted by short phasic events of the eye and other movements.<sup>7</sup> The pattern and amounts of NREM sleep, REM sleep, and wakefulness throughout the night are referred to as *sleep architecture*, and there are many physiologic and pathophysiologic processes that can affect sleep architecture. For example, many antidepressant medications, benzodiazepines, and opioids selectively suppress REM sleep. A disease example is narcolepsy, in which individuals often transition rapidly from wake to REM, whereas normally REM is nearly always entered from a prolonged episode of NREM state.

## Physiology

### EVOLUTION

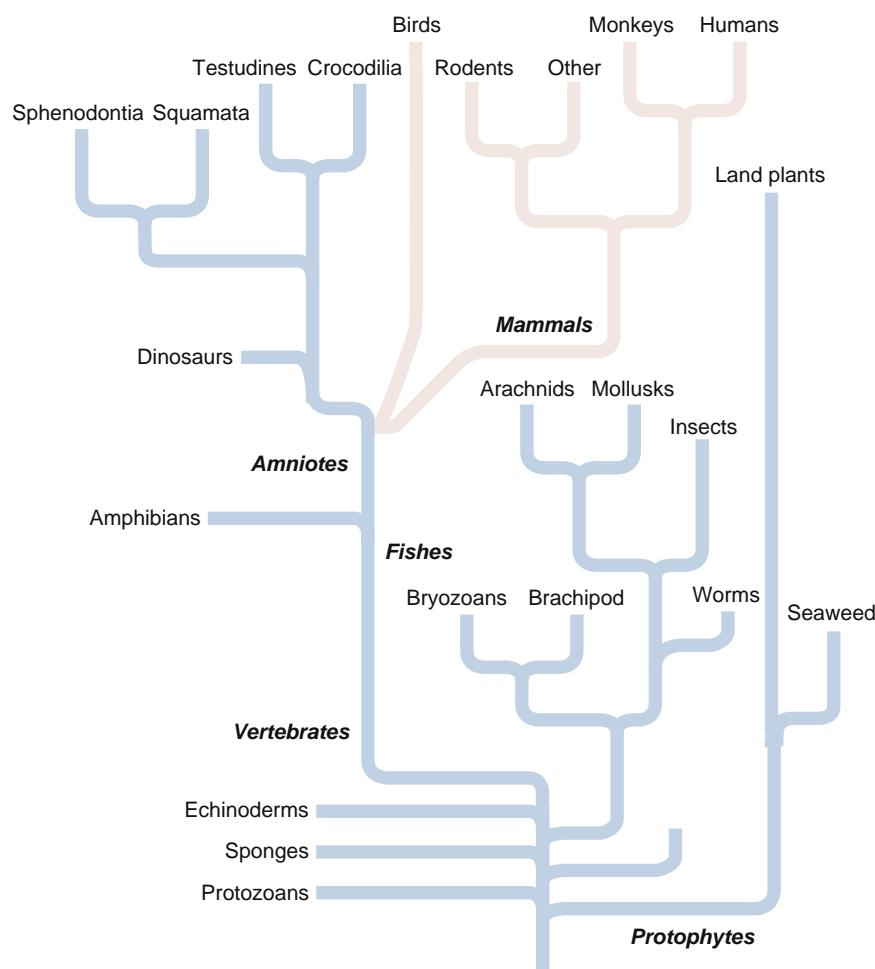
It is unknown why we sleep; however, one can imagine that evolutionary pressure would favor systems that are optimized for nature's rhythms.<sup>8,9</sup> In a rhythmic world, organisms must adapt to alternating changes in the environment, such as daily and seasonal rhythms in light intensity, ambient temperature, and humidity.

### CIRCADIAN RHYTHMS

Species-dependent temporal behavior can be adapted depending on the environmental conditions: behaviorally, anatomically, and physiologically. Circadian rhythms affect almost every aspect of the body's function, including activity and rest patterns, cognitive function (e.g., learning and memory), cardiovascular and endocrine physiology (e.g., heart rate, metabolism, and hormone secretion), and gene expression (15% of the genes in the human body show daily rhythms).

Virtually all species show circadian rhythms that regulate periodic changes in behavioral and physiologic parameters within a period of approximately 24 hours.<sup>10</sup> These rhythms can be characterized as a synchronization of activity to the external light-dark cycle in the majority of living creatures. Bacteria, plants, animals, and humans exhibit such a behavior that helps them stay in tune with the environmental light-dark cycles.<sup>11</sup> Our sleep timing preference, or chronotype, is a manifestation of our internal biological clock. Variation in chronotype has been linked to sleep disorders, cognitive and physical performance, and chronic disease.<sup>12</sup>

Clock genes generate endogenous clock pulses in most (if not all) cells of the body, synchronized by regulatory pathways across the body to a superior rhythm generator (a so-called master clock). Desynchronization of these rhythms seems to be involved in the pathogenesis of metabolic, psychiatric, and other disorders.<sup>11</sup> The superior rhythm generator in humans is located in the suprachiasmatic nucleus that receives external inputs about light and darkness from the retinal cells and synchronizes inputs of melatonin levels. While this master clock synchronizes the behavioral and biological rhythms of the human body to the changing demands of the environment during the solar day, sleep itself entrains circadian rhythms,<sup>11,13</sup> and the temporal organization of circadian rhythms and nocturnal sleep must be preserved to accomplish a restful and refreshing experience that fulfills the sleep needs produced by the



**Fig. 10.2** Evolutionary tree. Circadian rhythms are common among all living beings. However, only mammals and birds (red) have integrated sleep with different stages. Fish, reptiles, insects, and plants (blue) manifest circadian rhythms as periods of activity and rest.

second major regulatory factor, sleep homeostasis. During waking, “sleep pressure” continuously increases, leading to an increased likelihood for the transition from wakefulness to sleep.<sup>14</sup> Increasing homeostatic sleep pressure can be partly offset by a sufficient circadian wakening stimulus during the circadian wake phase, but the circadian wake stimulus disappears in the presence of an overwhelming sleep pressure.<sup>15</sup> In this situation, sleep sufficient in quantity and quality is needed to reestablish proper functioning.

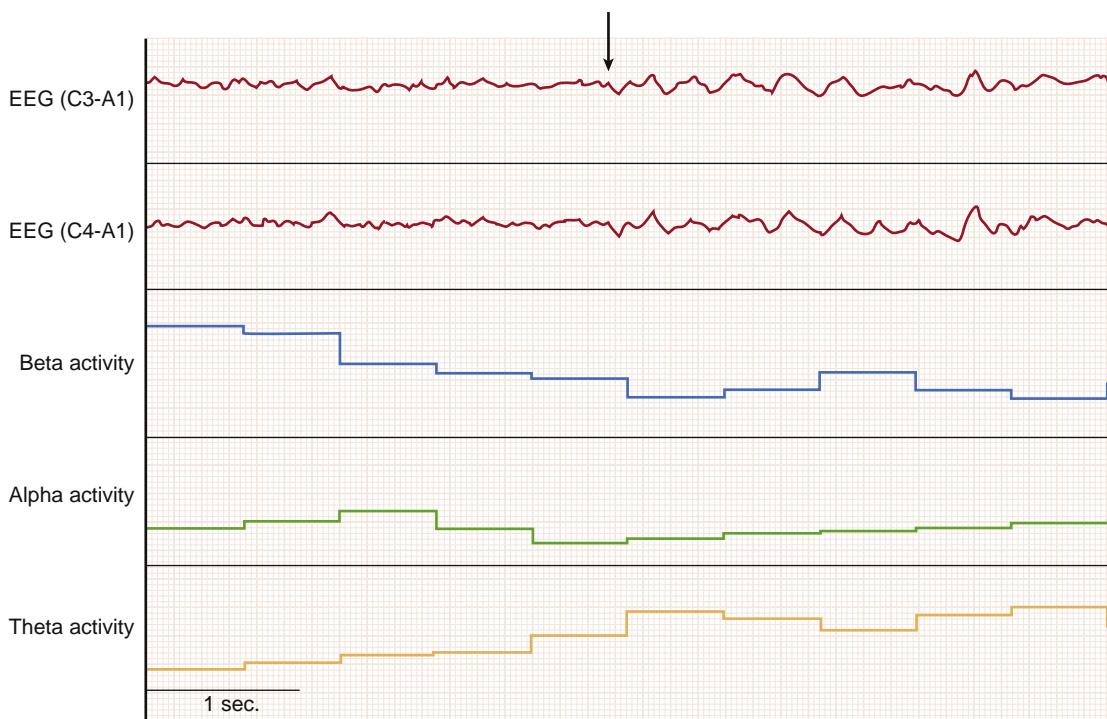
Although circadian and homeostatic regulation of sleep can be observed in almost all living organisms,<sup>16</sup> differentiation of sleep into NREM and REM sleep (“integrated sleep”) probably has developed during the last 300 to 350 million years because it appears only in birds and the majority of terrestrial mammals (Fig. 10.2).<sup>17,18</sup>

### Sleep Stages and Sleep Cycles

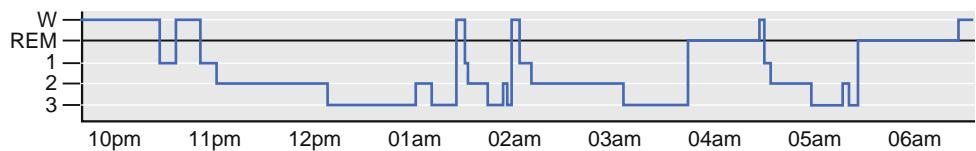
Sleep architecture—a structured temporal order of different sleep stages—is an important determinant of sleep quality. If tired individuals rest in their individual sleeping postures, the increasing level of drowsiness is paralleled by continuous EEG slowing from that seen during attention and cortical activation (16–30 Hz, “ $\beta$  activity”) to slower frequencies, predominantly between (7.5 and 11 Hz, “ $\alpha$  activity,” typically observed in subjects with reduced attention and closed eyes).

During this state of vigilance, the individuals do not sleep, and a full level of cognitive function can be established easily even without a strong sensory stimulus. The transition from  $\alpha$  state to sleep is paralleled by a further decrease in  $\alpha$  and  $\beta$  activity and an increase of EEG activity in the  $\theta$  band (4.5–7.5 Hz; Fig. 10.3).

This transition from  $\alpha$  to  $\theta$  activity is widely accepted as the EEG correlate of sleep onset.<sup>19</sup> At this transition from wakefulness to NREM sleep stage 1, heart rate and heat production decrease, resulting in a slight decrease in body temperature. Furthermore, respiration is regular and deep. As sleep deepens, EEG activity shows low amplitudes and  $\theta$  activity with intermittent sleep spindles and K-complexes. The latter represents an activation of brainstem and subcortical brain areas during sleep<sup>20,21</sup> for selective processing of unexpected sensory inputs (e.g., sounds) that might require complete arousal and restoration of consciousness to address a potential threat.<sup>22</sup> In accordance with that hypothesis, in comatose patients with brain injury, the presence of K-complexes in response to an acoustic stimulus during coma seems to be a marker of a better outcome compared with comatose patients with no evoked K-complexes.<sup>23</sup> With increasing depth of sleep, during NREM sleep, electrical activity of the cortex measured by EEG is dominated by slower frequencies and high amplitudes, also referred to as *slow-wave sleep*.



**Fig. 10.3** Electroencephalogram recording during sleep onset (arrow). The two top rows show bipolar electroencephalogram (EEG) signals from left (C3-A1) and right (C2-A1) frontal leads. Rows 3 to 5 show the relative amount (EEG power) of  $\beta$ ,  $\alpha$ , and  $\theta$  activity calculated using fast Fourier transformation.



**Fig. 10.4** Hypnogram of a night of physiologic sleep. During one night (time on x axis) of sleep, humans transition repetitively from one sleep stage to another with short episodes of occasional wakefulness (indicated on y axis). REM, Rapid eye movement sleep; W, awake; 1, non-REM sleep stage 1; 2, non-REM sleep stage 2; 3, non-REM sleep stage 3 (slow wave sleep).

REM sleep, or paradoxical sleep, is associated with an alteration of homeostatic regulation, such as increased heart rate variability, irregular respiration, and impaired body temperature control. Brain metabolism increases while EEG recordings show similarities to wakefulness with low-voltage and mixed-frequency power spectra. Prominent  $\theta$  waves generated by the hippocampus occur. These waves are not apparent in the scalp EEG recording from humans, but in rodents, in which the hippocampus is larger and closer to the brain surface, the EEG is dominated by  $\theta$  during REM. This sleep state is associated with a decreased tone in skeletal muscles (except for extraocular muscles that control eye movement). Dreaming is a typical experience during REM sleep,<sup>24</sup> but can also happen during NREM sleep.<sup>25</sup> During physiologic sleep, an individual typically switches back and forth across sleep stages, interrupted by occasional arousals from sleep (Fig. 10.4).

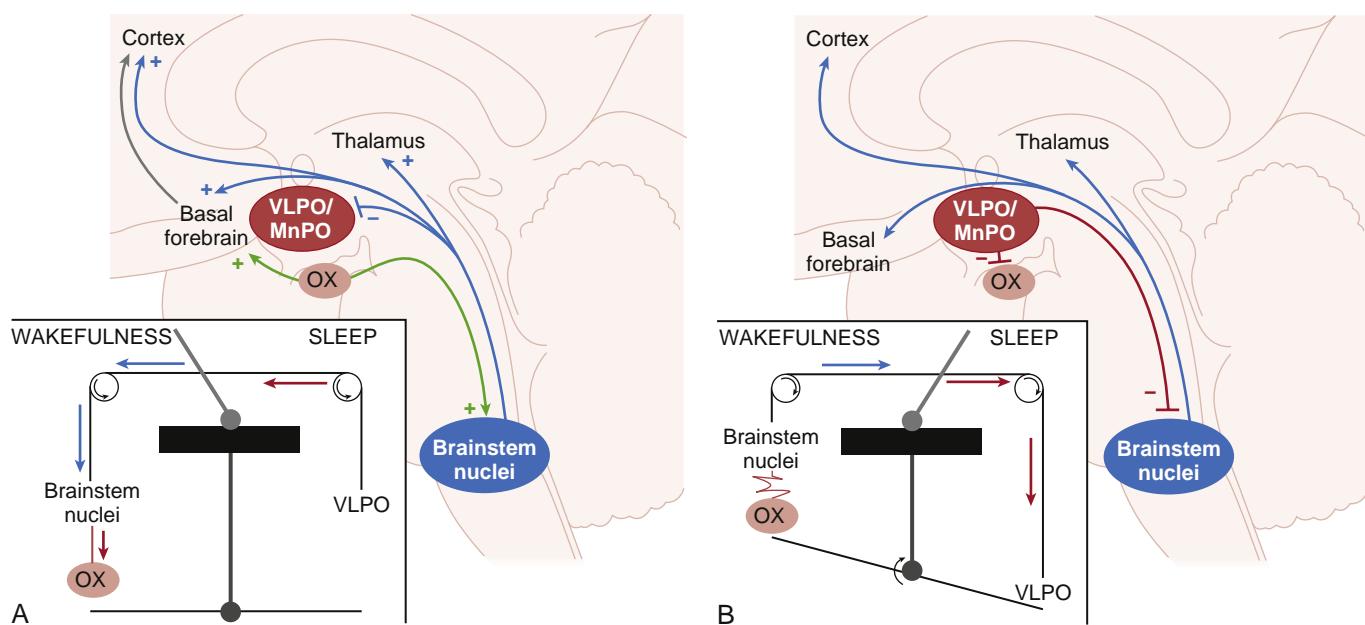
## NEUROANATOMY OF SLEEP

### Sleep-Promoting and Arousal Pathways

Several neuronal pathways have evolved to maintain cortical activation and behavioral arousal during normal waking, and others have evolved to promote and maintain sleep

(Fig. 10.5). It is the balance between these two systems that determines whether one is awake or asleep.

**Ascending Arousal System.** The ascending arousal system (AAS) is the main wakefulness-mediating network in the brain. Main pathways within the network receive cholinergic, monoaminergic, dopaminergic, and glutamatergic inputs. Cholinergic inputs originate from pedunculopontine and laterodorsal tegmental nuclei, innervate the lateral hypothalamus, prefrontal cortex, basal forebrain, and thalamic relay nuclei (i.e., medial and lateral geniculate nuclei; mediodorsal nucleus; pulvinar; anterior, ventral, and lateral thalamic cell groups).<sup>26,27</sup> Glutamatergic neurons that provide inputs to the AAS are mainly located within a small area just ventral of the locus ceruleus (LC), the preceruleus area, as well as in the parabrachial nuclei that mainly project to the basal forebrain and the lateral hypothalamus.<sup>28,29</sup> Monoaminergic inputs mainly come from noradrenergic neurons within the LC, histaminergic neurons of the tuberomammillary nuclei (TMN), serotoninergic neurons of the median and dorsal raphe nuclei,<sup>30,31</sup> as well as dopaminergic neurons adjacent to dorsal raphe nuclei.<sup>24,32</sup> Beside projections to the basal forebrain, multiple inputs are sent to the thalamus, mainly the interlaminar



**Fig. 10.5** Flip-Flop switch ensuring rapid transitions between wakefulness and sleep. During wakefulness (A), brainstem nuclei of the ascending arousal system (AAS) directly and indirectly provide excitatory input to the thalamus, basal forebrain, and the cerebral cortex, while they inhibit the ventrolateral (VLPO) and median (MnPO) preoptic nuclei (switch flips to wakefulness). The excitatory, wake-promoting stimulus is enforced by additional excitatory input of orexinergic neurons (OX) to the BF and the AAS. During sleep (B), neurons of VLPO and MnPO inhibit the brainstem and orexinergic neurons of the AAS (switch flops to sleep). (Modified from Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. *Nature*. 2005;437:1257–1263; and Saper CB, Fuller PM, Pedersen NP, Lu J, Scammell TE. Sleep state switching. *Neuron*. 2010;68:1023–1042.)

and reticular nuclei, as well as the amygdala and cerebral cortex. Furthermore, noradrenergic neurons of the LC project mainly to the posterior part of the lateral hypothalamus. In return, the latter area of the lateral hypothalamus projects to the LC and to the TMN.

Some neurons of the posterior hypothalamus produce orexin A and B, also known as hypocretin (HCRT) 1 and 2. These neurons project to the basal forebrain and the amygdala and cerebral cortex and other important arousal areas, and they are essential for stabilizing the waking state.<sup>32</sup> Orexin deficiency causes narcolepsy (severe daytime sleepiness) with cataplexy (abrupt loss of muscle tone),<sup>33</sup> a disorder showing some characteristics of REM sleep (i.e., REM sleep atonia during wakefulness [discussed later]).

**Orexin System.** Orexin and its cognate receptors ( $OX_1R$  and  $OX_2R$ ) play a key role in sleep/wake regulation. This neurotransmitter system has a crucial involvement in the pathogenesis of narcolepsy, a disorder associated with chronic excessive daytime sleepiness, sleep attacks, and rapid transitions between vigilance states and sleep in humans.<sup>34</sup> Studies in mice recapitulating the narcolepsy phenotype by targeted mutagenesis of the HCRT gene encoding the prepropeptide precursor of orexin neuropeptides,<sup>35</sup> or the less pervasive phenotype of  $OX_2R$  knockout mice,<sup>36</sup> not only demonstrated the role of orexin signaling in sleep/wake regulation but also demonstrated biological proof of concept for the development of orexin receptor antagonists for the treatment of insomnia. In contrast, the activation of orexin pathways, either by exogenous administration of orexin receptor agonists or by optogenetic activation of orexinergic neurons in the lateral hypothalamus, increases arousal.<sup>37,38</sup> Orexinergic neurons are counteracted by inhibitory  $\gamma$ -aminobutyric acid (GABA)-ergic

neurons originating from the ventrolateral preoptic nucleus (VLPO).  $OX_2R$  is expressed exclusively in the histaminergic TMN, whereas  $OX_1R$  is expressed preferentially in the noradrenergic LC, and both receptors are present in cholinergic pedunculopontine and laterodorsal tegmental nuclei.<sup>38,39</sup> Orexinergic tone at these hypothalamic and brainstem nuclei contributes to cortical arousal.<sup>40</sup> TMN, the predominant source of histamine in the brain responsible for cortical arousal, receives a prominent projection from orexinergic neurons<sup>40,41</sup> mediated predominantly by  $OX_2R$ . Orexin receptor antagonists promote sleep mainly via inhibition of the  $OX_2R$  receptor.<sup>42–45</sup>

**Non-Rapid Eye Movement Sleep-Promoting Pathways.** About 100 years ago during the epidemic of encephalitis lethargica, it was observed that lesions in the preoptic region around the rostral end of the third ventricle were associated with profound insomnia,<sup>46</sup> which was confirmed in neuroanatomic experiments (lesion studies) in rats and cats.<sup>47,48</sup> Neurons in the preoptic area are active during sleep.<sup>49–51</sup> Two key nuclei within this area are the VLPO as well as the median preoptic nucleus. VLPO neurons fire at a higher frequency during sleep compared with wakefulness.<sup>52</sup> Anatomically, the VLPO consists of a dense core of sleep-active, galanin-positive neurons innervating the TMN (which is part of the AAS) while being surrounded dorsally and medially by a more diffuse population of sleep-active, galanin-positive neurons that project to the dorsal raphe and LC.<sup>53</sup> Physiologically, the VLPO neurons constitute a sleep-promoting pathway that inhibits many components of the arousal system during sleep. Likewise, parts of the arousal system such as the laterodorsal tegmental nucleus and the pedunculopontine tegmental nucleus, as well as the LC, the parabrachial nucleus, the dorsal raphe nucleus, the PC,

the ventral periaqueductal gray, and the TMN, are capable of inhibiting the VLPO. The mutually inhibitory relationship of the arousal and sleep-promoting pathways produces the conditions of a flip-flop switch, which can generate rapid and complete transitions between waking and sleeping states (see Fig. 10.5).<sup>53,54</sup> It also makes simultaneous activation of arousal and sleep circuits highly improbable.

Because animal experiments showed that even large lesions of the VLPO substantially reduce but do not completely erase sleep, other brain areas beside this nucleus are likely involved in promoting sleep.<sup>55</sup> Several basal forebrain areas,<sup>49,51</sup> as well as some GABA-ergic interneurons across the cerebral cortex,<sup>56</sup> have been implicated to function as sleep-active neurons. Nevertheless, the role of these brain regions in the promotion or regulation of sleep remains unclear.

**Rapid Eye Movement Sleep-Promoting Pathways and Non-Rapid Eye Movement–Rapid Eye Movement Transition.** During normal sleep that presents at onset as a sharp  $\alpha$ - $\theta$  EEG activity transition, a similar sharp transition from NREM to REM sleep can be observed. Two groups of mutually inhibitory neurons located in the pons are involved in mediating the switch between NREM and REM sleep.<sup>28</sup> The first group consists of REM active inhibitory neurons of the sublaterodorsal nucleus and the PC region.<sup>29,54,57</sup> These neurons inhibit but are also inhibited by a second group of neurons that are located in ventrolateral periaqueductal gray and adjacent lateral pontine tegmentum. This mutually inhibitory relationship produces a REM-NREM flip-flop switch, promoting rapid and complete transitions between sleep states.<sup>54</sup>

Within the sublaterodorsal nucleus and PC, glutamatergic neurons are mixed within the population of REM-on GABAergic neurons. The glutamatergic sublaterodorsal nucleus neurons project to the spinal cord and are important for REM sleep atonia; the glutamatergic PC neurons activate forebrain pathways driving EEG desynchronization and hippocampal  $\theta$  rhythms—characteristic EEG signs of REM-sleep.<sup>58</sup>

## How to Assess Sleep

The complexity of signs and symptoms of sleep suggests that different instruments need to be applied to capture all the important elements of sleep.

### QUESTIONNAIRES

Several questionnaires are used for the assessment of sleep duration, sleep quality, and the related physiologic and pathophysiologic consequences. Quality of sleep is a frequent target of generic health surveys for measuring patient-reported outcomes. Other questionnaires quantify the consequences of sleep deprivation, specific sleep disorders, or both (Table 10.1). The most commonly used instrument in sleep medicine is probably the Epworth Sleepiness Scale, a short questionnaire to assess symptoms of daytime sleepiness, expressed as intolerance to monotony. The questionnaire asks the subject to rate the probability of falling asleep on a scale of increasing probability from 0 to 3 for eight different situations, such as such as watching TV, reading, lying down in the afternoon, and so on.<sup>59</sup> Despite the fact that the Epworth Sleepiness Scale

**TABLE 10.1** Sleep Questionnaires: Questionnaires Commonly Used for Clinical and Research Purposes and Their Focus

Questionnaire*	Focus	References
<i>Pittsburgh Sleep Quality Index (PSQI)</i>	Sleep and sleep disorders	60,61
Sleep Quality Scale (SQS)	Sleep quality	66
Functional Outcome of Sleep Questionnaire (FOSQ)	Impact of daytime sleepiness on daily living	12,67
Pediatric Sleep Questionnaire	Sleep and SDB in children	68
Child Sleep Habits Questionnaire (CSHQ)	Sleep	69
<i>Epworth Sleepiness Scale (ESS)</i>	Daytime sleepiness	59,62,63
<i>Sleep Diaries/Sleep Logs</i>	Sleeping times, sleep duration	70,71
<i>Morningness-Eveningness Questionnaire</i>	Sleeping times, sleep duration, circadian rhythm	72
Loughborough Occupational Impact of Sleep Scale (LOISS)	Sleep quality	73
Insomnia Sleep Questionnaire (ISQ)	Insomnia	74
Berlin Questionnaire	SDB in surgical patients	66
<i>STOP/STOP-Bang Questionnaire</i>	Obstructive sleep apnea	75,76
Brief Insomnia Questionnaire (BIQ),	Insomnia	77
<i>International Restless Legs Syndrome Study Group Rating Scale (IRLS)</i>	Restless leg syndrome	78
<i>Clinical Global Impression (CGI) Scale</i>	Restless leg syndrome	67
<i>Richard–Campbell Sleep Questionnaire</i>	Sleep assessment in the ICU	79

\*Recommended questionnaires are italicized.

ICU, Intensive care unit; SDB, sleep-disordered breathing; STOP, snoring, tiredness, observed apneas, and high blood pressure.

is reliable for detection of daytime sleepiness,<sup>60,61</sup> the instrument does not determine the mechanism of daytime sleepiness.<sup>62,63</sup>

Other clinically useful questionnaires that focus on the detection of signs and symptoms of sleep disorders are available,<sup>59-79</sup> which is important because the prevalence of sleep pathologies typically varies in a wide range across populations (see Table 10.1).

An effective process for clinical assessment of sleep-related diseases is a stepwise assessment using a screening tool first (e.g., Epworth Sleepiness Scale), followed by a more specific questionnaire that helps identify individual mechanisms or consequences of sleepiness.

A special form of sleep questionnaires comes in the form of sleep diaries and “morningness-eveningness” questionnaires that evaluate daily sleep habits, including sleep time, sleep duration, number of nocturnal awakenings, and subjective sleep quality.<sup>80</sup>

Although questionnaires allow a quick and easy screening for daytime symptoms of sleep disturbances, they do not quantify sleep architecture. Subjective methods of assessing sleep are influenced by the spectrum of disease within a tested group, actual clinical change over time, the testing conditions, and recall bias.<sup>80</sup> Clearly, a questionnaire cannot replace a medical history or objective assessment for sleep disorders. However, sleep questionnaires are important tools for measuring health improvement or decline, predicting medical expenses, assessing treatment effects, or comparing disease burden across populations.

## ACTIGRAPHY

Actigraphy is used to study sleep-wake patterns by detecting motion of the wrist with linear accelerometers in single or multiple axes. Based on movement-derived data, predictions of the time spent during sleep and wakefulness can be made, and even assumptions on sleep staging are made. Actigraphy can be used conveniently in a patient's home for several nights, weeks, or longer,<sup>81</sup>

but its validity for detecting transitions from wakefulness to sleep has been debated, especially in patients with high levels of sleep fragmentation.<sup>81,82</sup> In the clinical setting, actigraphy has been used to evaluate sleep patterns in patients with insomnia, for diagnosis of circadian rhythm disorders (including shift work), and in evaluating sleep in individuals who are less likely to tolerate polysomnography (PSG), such as infants and demented elderly. However, its accuracy is limited for patients with reduced mobility, such as nursing home or intensive care unit (ICU) patients. Actigraphy allows for convenient follow-up measurements to evaluate the effects of treatments designed to improve sleep architecture and circadian rhythm disorders.<sup>83</sup> In more recent years, an increasing number of wearable devices for the detection and analysis of activity and rest have been marketed. Although some have claimed to detect sleep accurately, as well as some sleep stages (mainly REM sleep),<sup>84</sup> none of the current models are yet approved or validated for clinical use.

## RESPIRATORY POLYGRAPHY

Home respiratory polygraphy (RP) can be a cost-effective alternative to PSG for the diagnosis of sleep apnea-hypopnea syndrome. RP usually calculates airflow through nasal pressure changes taken via nasal cannulae. Thoracic and abdominal movements are measured by piezoelectric bands, which also measure body position and blood oxygen saturation by pulse oximetry. Using these parameters, RP can identify apnea and hypopnea, and categorize the pathophysiology of apnea into obstructive versus central. Furthermore, similar to actigraphy, RP provides some analysis of sleep duration and time spent awake, using its body position and light sensors. However, the quality of the latter can be more precisely evaluated by a combination of sleep diary and actigraphy. Nevertheless, EEG is required to decide whether a subject was awake or sleeping (Table 10.2).

**TABLE 10.2** Pros and Cons of Different Methods of Sleep Evaluation

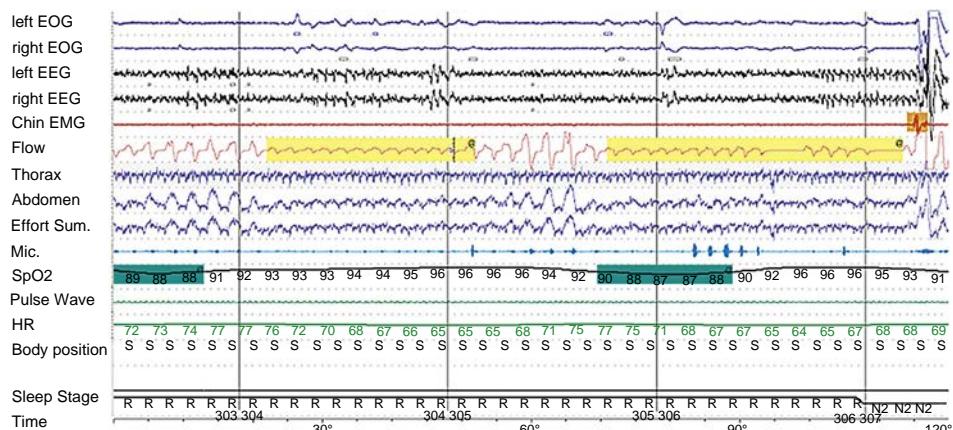
Method	Pros	Cons	Recommendation
Sleep questionnaire	Low cost Good compliance Easy to use	Recall bias Limited reliability in some populations Limited validity	Should be combined with interview
Sleep diary	Less recall bias  Easy to administer  Low cost Documentation of daily variability	Lower compliance compared with other questionnaires  Biased by daily mood and expectations on sleep	Should be combined with other measurement of sleep duration (e.g., actigraphy)
Actigraphy	Provides objective information about daily variability and sleep duration  Provides information on sleep habits at home Not influenced by patient expectations, recall bias, or memory impairments Lower cost than laboratory polysomnography	Limited assessment of sleep stages and sleep onset latency  Higher cost than questionnaires	Should be combined with other measurement of sleep duration (e.g., sleep diary)

*Continued*

**TABLE 10.2** Pros and Cons of Different Methods of Sleep Evaluation—cont'd

Method	Pros	Cons	Recommendation
Polygraphy	Lower cost than laboratory polysomnography Objective assessment of respiratory events Provide information on sleep habits at home	Limited assessment of sleep Higher cost than questionnaires Limited assessment of sleep disorders other than sleep-disordered breathing	Should be accompanied by questionnaires and clinical interview
Laboratory polysomnography	Objective assessment of sleep, sleep stages, and sleep disorders	High cost  First-night effect Limited capacity No information about sleep habits at home	Should be last step in sleep evaluation with previous questionnaires and ambulatory screening (e.g., polygraphy)
Out-of-center polysomnography	Objective assessment of sleep, sleep stages, and sleep disorders  Less first-night effect Lower cost than laboratory polysomnography Can provide information about sleep habits at home	Limited observation may lead to decreased recording quality	Good patient education mandatory  If possible, surveillance recording preferred

Adapted in part from Martin JL, Hakim AD. Wrist actigraphy. *Chest*. 2011;139(6):1514–1527.



**Fig. 10.6** Polysomnographic recording. Left and right electrooculogram (EOG), two electroencephalogram (EEG) channels, and mental electromyogram (Chin EMG) allow scoring of sleep stage (REM sleep [R] with typical eye movements in the electrooculogram channels). Additional channels (e.g., respiratory flow [Flow], respiratory effort of thorax [Thorax] and abdomen [Abdomen], microphone [Mic.], oxygen saturation [SpO<sub>2</sub>]) allow diagnosis of sleep disordered breathing. In this patient, apneas (yellow boxes) led to oxygen desaturation (blue boxes) and finally to arousal (far right, brown box).

## POLYSOMNOGRAPHY

PSG is the only method that can precisely determine the actual sleep stage and is a reference diagnostic tool (i.e., gold standard) that is required for the diagnosis of several sleep disorders.<sup>85</sup> PSG measurements include EEG, electrooculography for the measurement of eye movements, and at least electromyographic measurement of muscle activity of the chin.<sup>86</sup> These three measurements are typically supplemented by other channels for the detection of sleep-disordered breathing (SDB), such as a nasal sensor to detect apneas and hypopneas, oximetry, inductance plethysmography for respiratory effort of the chest and abdomen, and a body position sensor and leg electromyogram<sup>87</sup> to identify periodic limb movement syndrome or REM sleep behavior disorder, respectively.<sup>88</sup> A typical PSG recording is shown in Fig. 10.6.

## Sleep Laboratory Testing

For several decades, PSG was performed only within a sleep laboratory. Sleep laboratory PSG is attended by a trained technician and is analyzed by a clinician trained in sleep medicine according to the published guidelines.<sup>87,89-91</sup> However, the high cost and requirement of an overnight stay can present socioeconomic challenges that affect the accessibility of this method. In-center PSG provides only a momentary view of the patient's sleep, and the measurements themselves can impair patients' sleep (the so-called first-night effect) and does not provide information about sleep at home. Multiple repeated measurements to tailor treatment over time are challenging or even impossible from a logistic and healthcare economics perspective. Therefore, an increasing number of out-of-center devices

**TABLE 10.3** Polysomnographic Characteristic of the Different Behavioral States

EEG and EOG Characteristics		AASM
Wakefulness	α rhythm (8-13 Hz) present in more than 50% of an epoch	W
Non-REM sleep stage 1	Lower amplitudes and activity in range of 4-7 Hz (vertex sharp waves,* slow eye movements*)	N1
Non-REM sleep stage 2	EEG of sleep stage 1 with additional a sleep spindles and K-complexes; slow waves not fulfilling the criteria for sleep stage 3	N2
Non-REM slow wave sleep	20%-50% of slow wave activity (0.5-2 Hz)	N3
REM sleep	EEG of low amplitude and mixed frequencies, low chin electromyogram activity, rapid eye movements	R

\*Not necessary but may be present.

AASM, American Academy of Sleep Medicine criteria (see reference 87); EEG, electroencephalography; EOG, electrooculogram; N1, non-REM sleep stage 1; N2, sleep stage 2; N3, sleep stage 3; R, REM-sleep; W, wakefulness.

are now available, offering the possibility of recording PSG in almost every environment, such as at the patient's home, within the hospital or nursing home room, and even within the recovery room or ICU.

### Out-of-Center Testing

Portable out-of-center PSG sleep monitors are a reasonable, reliable, and effective method for diagnosing OSA<sup>92</sup> compared with PSG recording performed within a sleep laboratory, when applied in preselected population at risk of moderate-to-severe OSA.<sup>92-94</sup> The Portable Monitoring Task Force of the American Academy of Sleep Medicine (AASM) supports the use of these devices in subjects for clinical and research purposes and indicates a comparable quality of PSG data.<sup>92</sup>

### Scoring of Sleep and Sleep Disordered Breathing

More than 40 years ago, Rechtschaffen and Kales<sup>86</sup> standardized the method of scoring PSG recordings—the R&K criteria. Since then, major innovations in technology have transformed the science and clinical practice of sleep medicine. The latest criteria of the AASM<sup>87,95</sup> capture the full potential of innovations resulting from computerization of data, including automation of sleep scoring, recognition of disorders that occur during sleep, and integration with other procedures, such as positive airway pressure titration. Although the R&K criteria are still sufficient for clinical and research purposes, they are less commonly used in sleep centers around the world.

According to these criteria, the arousal states are categorized based on the EEG activity recorded from three different scalp locations and divided into wakefulness (W), REM sleep (R), and three NREM sleep stages (Table 10.3 and see Fig. 10.1).

Respiratory events during sleep are defined as follows:

1. *Apnea* with a decrease in respiratory flow of 90% or more from baseline for at least 10 seconds, whereas a minimum of 90% of the event duration has to meet the criteria of respiratory flow reduction
2. *Hypopneas*, in which the signal of respiratory flow measurement decreases at least 30%, whereas oxygen saturation ( $SpO_2$ ) decreases by 4% or more compared with pre-event baseline for at least 90% of the duration (minimum of 10 seconds). Hypopneas can also be defined as a decrease in respiratory flow measurement of at least 40% with a decrease in  $SpO_2$  of only 3%.

3. *Respiratory event-related arousal* is defined as a series of breaths not meeting the criteria for apnea or hypopnea lasting at least 10 seconds characterized by increasing respiratory effort or flattening of the nasal pressure waveform leading to an arousal from sleep.
4. *Hypoventilations* are defined as an increase of 10% or more in arterial carbon dioxide tension ( $PaCO_2$ ).

Although the AASM 2007 criteria<sup>87</sup> are commonly used in many sleep centers for clinical and research purposes all over the world, questions about whether the new criteria should be used in children<sup>96</sup> and the scoring of some respiratory events are still unanswered.

## Sleep and Breathing

### RESPIRATORY REGULATION DURING SLEEP

Sleep puts breathing at risk. The upper airway dilator muscle activity is decreased during sleep compared with wakefulness, particularly at sleep onset and during REM sleep. Furthermore, the ventilatory response to hypoxia can be impaired, such that critical hypoxia levels can occur during sleep that can be offset only by arousal from sleep.

The major determinant of minute ventilation during wakefulness and sleep is  $PaCO_2$ . In contrast to wakefulness, where  $PaCO_2$  is maintained close to 40 mm Hg, the chemo sensitivity to  $CO_2$  decreases during sleep, as does the chemo sensitivity for oxygen. This leads to  $PaCO_2$  values of 45 mm Hg commonly occurring during stable sleep, while ventilatory demand is decreased and the arousal threshold varies with sleep stages.

Accordingly, the changes in respiratory muscle activity, ventilatory demand, and arousal threshold observed from wakefulness to sleep and across sleep stages challenge ventilatory control and can lead to instability in breathing. A structured approach to evaluating breathing instabilities is the loop gain. This engineering term is used to describe the stability of a feedback-controlled system (in this case, the chemical feedback loop controlling an individual's ventilation). In the setting of ventilatory control, loop gain reflects the propensity of an individual to develop periodic (unstable) breathing. Patients with a high loop gain caused by a more sensitive respiratory controller (i.e., high controller gain), more effective  $CO_2$  excretion (i.e., high plant gain), or

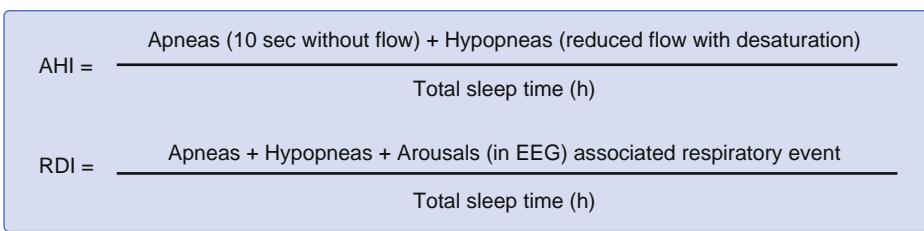


Fig. 10.7 Definition of apnea hypopnea index (AHI) and respiratory disturbance index (RDI).

an increased delay because of slowed CO<sub>2</sub> distribution from peripheral tissues to the central chemoreceptors based on, for example, reduced blood circulation (i.e., mixing gain) may be more vulnerable to disturbances of the feedback system, such as slight hypoventilation that occurs as a consequence of decreased upper airway dilator muscle activity during the transition from wakefulness to sleep.

High loop gain may contribute to severity of OSA. Moreover, subjects with a high loop gain have been shown to be more likely to develop breathing instabilities such as Cheyne-Stokes respiration (CSR; see “Central Sleep Apnea”).

## SLEEP-DISORDERED BREATHING

SDB refers to the respiratory signs and symptoms associated with sleep-associated respiratory dysfunction and is defined by the occurrence of respiratory events, which are cessations in breathing rhythm (apneas) or momentary or sustained reduction in the amplitude of respiratory flow (hypopnea) during the sleeping state, leading to arterial hypoxemia.<sup>97</sup> They are usually caused either by increases in upper-airway resistance due to reduction in intraluminal airway diameter (obstructive event), marked reduction or cessation of brainstem respiratory motor output (central event), or both. A specification of SDB into obstructive or central sleep apneas (CSA) is made based on the predominant type of respiratory events. The severity of SDB is usually quantified by the number of respiratory events per hour of sleep. This is necessary because a low number of short apneas and hypopneas can occur up to about five times per hour in healthy subjects. Two measures can be used for this purpose: the apnea hypopnea index (AHI) and the respiratory disturbance index (RDI). Typically the AHI (number of hypopneas and apneas per hour of sleep; Fig. 10.7, top) and RDI (number of hypopneas, apneas, and arousals related to respiratory events per hour of sleep; see Fig. 10.7, bottom) are used to quantify the severity of SDB.

### Obstructive Sleep Apnea

**Definition.** OSA is the most common type of SDB and is diagnosed in patients with more than 15 predominantly obstructive events per hour of sleep, or with fewer respiratory events (i.e., 5–15 per hour) if daytime symptoms (i.e., sleepiness) or comorbidities such as hypertension or atrial fibrillation are present. These cutoff values have been used as an indication for treatment by clinicians based on the clinical guidelines and the international classification of sleep disorders.<sup>87,88</sup> The severity of sleep apnea is further characterized as mild in patients with less than 15 events per hour of sleep, as moderate with 15 to 30 or less events per hour of sleep, and as severe sleep apnea with 30 or more events per hour of sleep (Table 10.4).<sup>88,90</sup>

**TABLE 10.4** Severity of Sleep Apnea Based on Respiratory Disturbance Index or Apnea Hypopnea Index

	RDI (Events Per Hour)	AHI (Events Per Hour)
No sleep apnea	<5	<5
Mild sleep apnea*	≥5 to <15	≥5 to <15
Moderate sleep apnea	≥15 to <30	≥15 to <30
Severe sleep apnea	≥30	≥30

\*Only diagnosed if comorbidities like hypertension, atrial fibrillation of daytime sleepiness are present.

A respiratory disturbance index (RDI) less than 5 per hour is physiologic and found in healthy humans. Sleep apnea is mild with RDI between 5 and 15 per hour, moderate with RDI between 15 and 30 events per hour, and considered severe with an RDI of 30 and greater per hour of sleep. Equal cutoff values are similar for severity based on the apnea hypopnea index (AHI).

**Epidemiology.** OSA with daytime symptoms affects 0.3% to 5% of the general population.<sup>98,99</sup> As obesity is one of the major risk factors for OSA, the prevalence might continue to increase with higher rates of obesity in the general population.<sup>100–102</sup> The prevalence of SDB without daytime symptoms is even higher, with rates of up to 9% in women and 24% in men between the ages of 30 and 60 years, and is often unrecognized.<sup>103,104</sup>

Furthermore, the prevalence of OSA varies widely between different populations. Individuals with a high susceptibility to OSA include the obese, the elderly, and those with specific comorbidities (e.g., stroke, myocardial infarction). Depending on methodology, the rates of OSA in patients following surgery is between 45%<sup>105</sup> and 75%.<sup>106</sup> A recent study in patients undergoing bariatric surgery revealed an incidence of OSA of as high as 77.5% in this population,<sup>107</sup> while another study showed OSA to be prevalent in 50% of women undergoing gynecologic oncology surgery.<sup>108</sup>

**Clinical Symptoms.** Approximately one-third of patients with OSA complain of typical signs and symptoms occurring during wakefulness. Waking with dry mouth or headache in the morning, daytime sleepiness, falling asleep during monotonous situations (e.g., watching television), as well as subjective impairment of cognitive function are frequently reported. This combination of OSA with daytime symptoms is usually referred to as OSA syndrome.<sup>109,110</sup>

Sleep-associated signs and symptoms of OSA include witnessed pauses in breathing or snoring, and a high number of nocturnal awakenings, mostly reported as pseudo-nocturia. Patients with OSA occasionally complain of tachycardia

or respiratory distress upon nocturnal awakening (choking sensation) and other symptoms (Box 10.1).

**Consequences and Comorbidities.** OSA is associated with serious medical consequences, such as hypertension, myocardial infarction, stroke,<sup>109,111,112</sup> diabetes, diabetic neuropathy, as well as cognitive dysfunction resulting in occupational difficulties and motor vehicle accidents.<sup>113,114</sup> The development of cognitive impairment in patients with OSA<sup>115</sup> is associated with atrophy of brain structures relevant for cognition and memory (hippocampal areas)<sup>116</sup> that can be partially reversed by adequate treatment.<sup>117</sup> Whether the negative effects of OSA are due to impaired sleep architecture or effects of intermittent hypoxia remain unclear,<sup>118</sup> because data investigating the effect of intermittent hypoxia without other symptoms in OSA patients are limited. Nevertheless, recent findings suggest that even asymptomatic OSA might be associated with cardiovascular effects, such as altered daytime autonomic regulation (i.e., heart rate variability).<sup>119</sup>

### BOX 10.1 Symptoms of Obstructive Sleep Apnea

#### Nighttime Symptoms

- Frequent awakening during the night (e.g., pseudo-nocturia)
- Awaking from own snoring with choking sensation
- Tachycardia
- Sleep that is not restorative

#### Daytime Symptoms

- Awaking with dry mouth
- Dull headache in the morning
- Daytime sleepiness
- Falling asleep during monotonic situations (e.g., watching television)
- Subjective impairment of cognitive function

#### Symptoms Reported by Bed Partner

- Snoring, especially when loud and arrhythmic
- Observed pauses in breathing during sleep

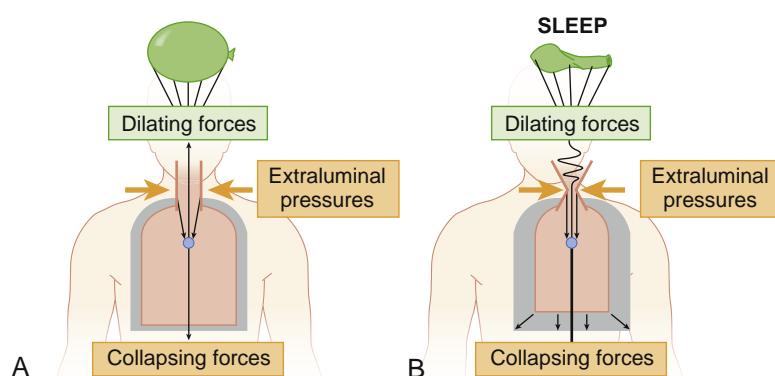
Given the frequent rate of complications associated with OSA, it is not surprising that OSA leads to increased socio-economic costs because of significantly more frequent rates of health-related contacts and medication use, and even higher rates of unemployment.<sup>120</sup>

**Risk Factors.** Predisposing factors for OSA are obesity,<sup>121</sup> age,<sup>121,122</sup> male sex,<sup>121</sup> factors leading to swelling of the superficial tissue of the upper airway (smoking),<sup>123</sup> allergic rhinitis,<sup>124</sup> and decreased muscle tone of upper airway dilator muscles (e.g., central nervous system) caused by respiratory depressants.<sup>125</sup>

**Pathophysiology.** Respiratory events during OSA are characterized by decreased respiratory flow with persisting respiratory effort due to reduced intraluminal diameter of the upper airway up to complete pharyngeal airway collapse (see Fig. 10.6). The muscles involved in respiration are morphologically and functionally skeletal muscles and can be classified into two groups: upper airway dilator muscles and respiratory pump muscles.

Upper airway dilator muscles counterbalance the negative inspiratory pressure generated by the pump muscle to permit airflow during inspiration. Respiratory pump muscles are the collection of muscles responsible for generating inspiratory and expiratory forces in the thorax across the breathing cycle (Fig. 10.8). The patency of the upper airway is maintained by balancing dilating forces (generated by the upper airway dilator muscles) and collapsing forces (i.e., negative intraluminal pressure generated by the respiratory pump during inspiration and compressive extraluminal forces from the surrounding tissues).<sup>126</sup>

**UPPER AIRWAY DILATOR MUSCLES.** The most extensively studied of the upper airway dilating muscles are the genioglossus and the tensor palatini (Table 10.5). The genioglossus receives a variety of inputs, including phasic (inspiratory) and tonic (noninspiratory) drives, which are distributed differentially across the hypoglossal motoneurons.<sup>127</sup> In response to negative pharyngeal pressure created by the respiratory pump during inspiration, the



**Fig. 10.8** Relationship of upper airway patency and respiratory pump activation. (A) During wakefulness, the force of the upper airway dilator muscles (green balloon, dilating forces) counterbalance the collapsing forces imposed on the upper airway by extraluminal pressures and negative inspiratory pressure generated by the respiratory pump muscles (represented by the orange counterweight [collapsing forces]). In obstructive sleep apnea, (B) sleep onset (blue needle) leads to decreased upper airway patency by reducing the dilating forces. (Modified from Sasaki N, Meyer MJ, Eikermann M. Post-operative respiratory muscle dysfunction: pathophysiology and preventive strategies. *Anesthesiology*. 2013;118:961–978.)

**TABLE 10.5** Some Muscles of the Upper Airway Relevant for Upper Airway Stability

Muscle	Tonic Activity	PHASIC ACTIVITY	
		Insp.	Exp.
Tensor palatini <sup>153</sup>	+	+	-
Levator palatine <sup>153</sup>	+	+	-
Genioglossus <sup>154</sup>	+	+	-
Geniohyoid <sup>155</sup>	+	-	+
Thyrohyoid	X	X	X

+, Present; -, absent; X, insufficient data. Major muscles of the upper airway and their activity during breathing. Tonic activity, as well as inspiratory (Insp.) and expiratory (Exp.) muscle activity.

genioglossus reflexively stabilizes the upper airway in animals and humans.<sup>128,129</sup> This reflex is likely a product of signaling from inspiratory modulated motor units. Whereas the genioglossus responds to phasic input on top of its tonic activation, the tensor palatini is considered a tonic muscle with consistent tone throughout the respiratory cycle.<sup>130</sup>

**ANATOMIC VULNERABILITY TO COLLAPSING FORCES.** The soft tissues of the pharynx are enclosed and stabilized by bony structures, such as the mandible and the spine, and complete collapse of the pharyngeal airway ordinarily requires extraluminal forces, such as hematoma, edema, peripharyngeal masses, or an airway trauma, for instance, as a consequence of prolonged endotracheal intubation.<sup>131</sup> Pharyngeal manifestation of obesity compresses the airway.<sup>132</sup> Craniofacial abnormalities can further increase the collapsing effects of excessive pharyngeal extraluminal soft tissue in obese patients.<sup>133</sup> The extraluminal soft tissue, as well as size and shape of the bony enclosure, are determinants of the extraluminal pressure that need to be antagonized by the upper airway dilator muscle contraction during inspiration, to avoid an upper airway obstruction-related apnea.<sup>133</sup> In addition, the upper airway is more vulnerable to collapse in the supine position than in the lateral or sitting positions, due to gravitational effects.<sup>134,135</sup>

Excessive intravenous fluid administration can affect upper airway patency. In awake, healthy volunteers, the inflation of antishock trousers displaced fluid from the lower extremities to increase neck circumference,<sup>136</sup> so that the upper airway had a lower threshold to collapse.<sup>137</sup> This concept is reinforced in studies of subjects with lower extremity venous insufficiency<sup>138</sup> and congestive heart failure (CHF).<sup>139</sup> These studies have shown nocturnal redistribution of fluid from the lower extremities into the neck increases upper airway collapsibility<sup>138</sup> and the severity of central apnea and OSA.<sup>139</sup> Similar effects may increase the risk for OSA during pregnancy and early after delivery.<sup>139</sup>

Another important component of airway patency is the interplay between lung volume and upper airway collapsibility. Higher end-expiratory lung volumes are associated with a decrease in upper airway resistance to airflow in awake healthy humans,<sup>140</sup> and an increase in upper airway lumen dimensions in subjects with and without OSA.<sup>141</sup> The mechanism for the interaction between upper airway patency and lung volume is thought to lie in the generation of longitudinal traction forces in the trachea.<sup>142,143</sup> Upon inspiration, the

lung inflates and effectively forces the carina into a more caudal position, creating stretching forces on the fixed trachea.<sup>142</sup> These forces are transferred to the side walls of the upper airway.<sup>143</sup> Effectively, tracheal traction allows the respiratory pump muscles to contribute to upper airway opening.

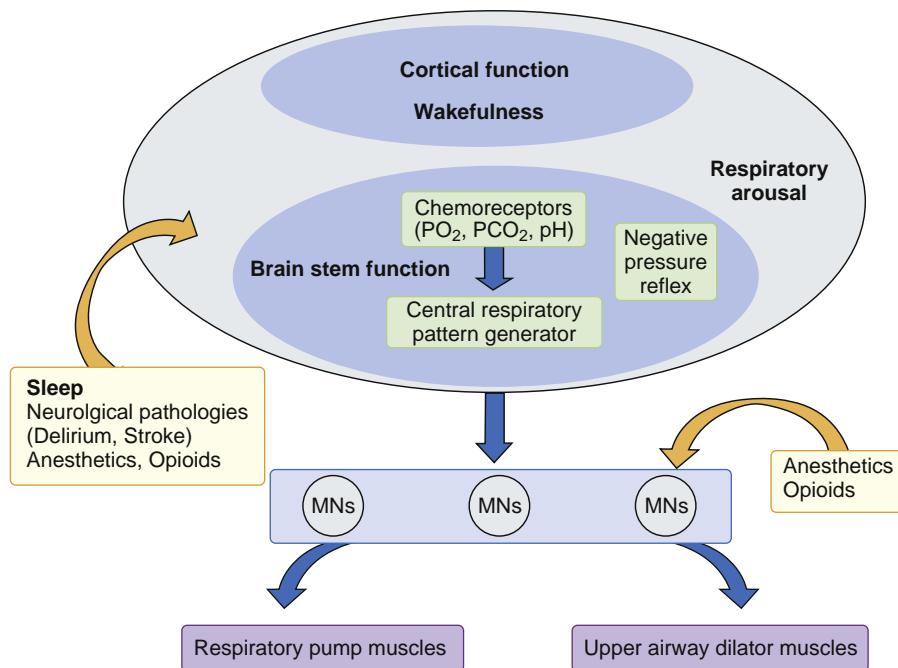
**COLLAPSING INTRALUMINAL PRESSURE.** The respiratory pump is the motorized action driving inspiration and expiration. It is the force that broadens the thoracic cavity and creates negative intrathoracic pressure to draw a breath in, and when needed, positive intrathoracic pressure to exhale rapidly. Inspiratory pump muscles are an anatomically diverse group, with the most studied being the intercostal muscles and the diaphragm. The diaphragm accounts for 60% to 70% of lung volume change during quiet respiration.<sup>144</sup> During inspiration, the volume of the thoracic cavity increases as a result of contraction of the diaphragm and the external intercostal muscles. The lungs expand secondarily to the increased negative intrathoracic pressure generated by these phasic actions of the inspiratory pump muscles. The negative intrathoracic pressure translates into a negative intraluminal pressure in the upper airway, forcing the airway to collapse as soon as this pressure drops below a critical value.<sup>145</sup>

Although this critical airway pressure (Pcrit) is typically negative (approximately  $-5$  cm H<sub>2</sub>O) in healthy controls, the upper airway in patients with OSA during sleep may even collapse at a positive Pcrit. Positive intraluminal pressure is required for reopening the paralyzed airway in patients with OSA.<sup>146</sup> Under normal conditions, the two compressing factors, (1) negative intraluminal pressure and (2) positive extraluminal pressure, need to be actively compensated by muscular activity of the upper airway dilator muscles to maintain airway patency.<sup>97</sup>

**WAKEFULNESS STIMULUS AND SLEEP.** Excitatory inputs to the upper airway motoneurons (e.g., hypoglossal motoneurons) include those from serotonergic and noradrenergic neurons that fire predominantly during wakefulness,<sup>147-150</sup> resulting in a “wakefulness stimulus” that increases the activity of upper airway dilator muscles during this arousal state. With onset of sleep, this arousal-dependent neuronal input (active while awake versus less active, or inactive when asleep) disappears, leading to a decrease in upper airway muscle activity and causing increased upper airway resistance in healthy controls and airway collapse in patients with OSA.<sup>151-153</sup> The resulting retropalatal obstruction of the upper airway is reported to be the most common pathophysiological mechanism in OSA.<sup>146</sup>

**ONE WAY VALVES IN THE UPPER AIRWAY.** Observing the respiratory flow tracings in patients with OSA, one can find some respiratory events that do not show the characteristic progressive flow limitation ultimately resulting in complete upper airway occlusion, typically seen as a result of “collapsible tube pathophysiology” with variable compliance. In these cases, the flow tracings show normal expiratory flow and sudden reduction/cessation before reaching maximum inspiratory flow. This “rapid obstruction” only during the inspiratory phase occurred in approximately 20% to 30% of OSA patients.<sup>154</sup> Recent findings suggest that there are two one-way valves in the pharynx. While the epiglottic valve closes during inspiration, the soft palate may function as a second one-way valve limiting flow during expiration.<sup>155</sup>

Similar to the epiglottis, the soft palate hangs from the hard palate like a peninsula in the oropharynx and might



**Fig. 10.9** Effects of respiratory arousal on upper airway dilator and respiratory pump muscles. Respiratory arousal is composed of three primary inputs: central respiratory pattern generator processing peripheral and central chemoreceptor afferents, reflex responsiveness to the magnitude of negative pressure in the airway generated by the respiratory pump muscles, and strength of the wakefulness stimulus. Different factors can impair respiratory arousal, such as sleep and neurologic pathologies, anesthetics, and opioids. Blue arrows indicate excitatory effect; yellow arrows indicate inhibitory effect. MN, Motor neuron. (Modified from Sasaki N, Meyer MJ, Eikermann M. Postoperative respiratory muscle dysfunction: pathophysiology and preventive strategies. *Anesthesiology*. 2013;118:961–978.)

occlude the upper airway during expiration.<sup>156</sup> A recent study found that sudden reduction of expiratory airflow immediately after peak expiratory flow occurs more often in OSA patients under positive pressure ventilation.<sup>157</sup> Similar expiratory flow limitation pattern was also reported in spontaneously breathing OSA patients, suggesting that this phenomenon is not unique to positive pressure ventilation.<sup>158</sup>

These findings may point to a second, slightly different mechanism underlying OSA than the pure collapsible tube pathophysiology in some OSA patients, which should be particularly important during anesthesia. Correct identification of the closure site in each OSA patient will enable the clinician to provide an individualized OSA treatment.<sup>155</sup>

**RESPIRATORY AROUSAL.** Respiratory arousal is arousal from sleep owing to cumulative and progressive increases in stimuli related to breathing (hypoxia, hypercapnia, and respiratory effort).<sup>159</sup>

Three primary inputs contribute to arousal-related restoration of breathing following an apnea (Fig. 10.9):

1. Peripheral and central chemoreceptors sensitive to partial pressures of oxygen and carbon dioxide<sup>160</sup>
2. Sensors in the upper airway responsive to negative pressure generated by the respiratory pump<sup>128,129</sup>
3. Cortical inputs directly related to state of consciousness or wakefulness<sup>161</sup>

Any of these inputs can restore respiratory muscle tone if the magnitude of stimulation is sufficient. Cortical awakening from sleep, identified by EEG signs of wakefulness, is an adequate stimulus for ventilation. However, obstructive apneas, such as upper airway collapse in OSA, can be terminated by an increased drive to the respiratory muscles

not involving cortical arousal.<sup>162</sup> For example, hypercarbia resulting from sustained hypopnea<sup>160</sup> and elevated upper airway negative pressure<sup>128,129</sup> can independently restore tone to the respiratory muscles. The level of drive provided to the respiratory muscles depends on the summation of stimuli in the central respiratory pattern generator output, including peripheral and central chemo-responsiveness, reflex responsiveness to the negative airway pressure, and strength of the wakefulness drive.

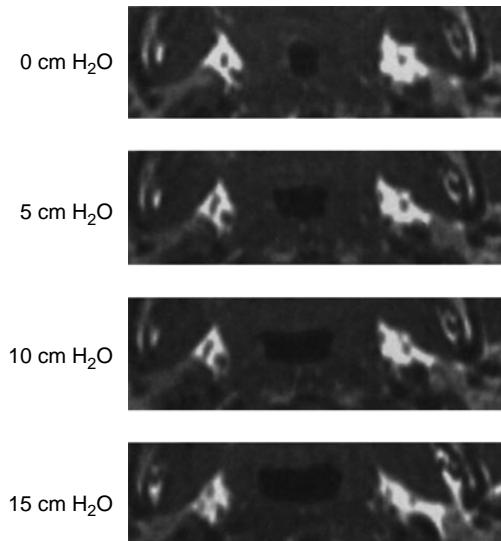
**Treatment.** Adequate treatment of OSA improves nocturnal oxygen saturation as well as duration and quality of sleep, which translates to reduced daytime sleepiness, improvement of daytime functions, and improved quality of life. Successful treatment of OSA reduces cardiovascular risk, improves insulin sensitivity, and increases neurobehavioral performance.<sup>163–165</sup> Therefore, all patients with a diagnosis of OSA should be offered treatment as soon as the diagnosis of OSA has been established and its severity has been determined by objective testing (i.e., PSG).<sup>88</sup> Although different treatment options for OSA have been developed during the last decades (Table 10.6), continuous positive airway pressure (CPAP) dose dependently increases upper airway diameter and is still the most effective treatment for OSA of all severities.<sup>166–168</sup> However, a recent study has questioned if CPAP treatment is able to prevent the long-term adverse cardiovascular events in OSA.<sup>169</sup>

**POSITIVE AIRWAY PRESSURE TREATMENT.** CPAP as a treatment for SDB is typically applied continuously with a nasal or oronasal mask, and can dose dependently reverse any sleep-associated upper airway obstruction, as outlined in Fig. 10.10. The CPAP level needed for treatment of OSA

**TABLE 10.6** Treatment Possibilities for Obstructive Sleep Apnea

Treatment	Procedure/Device	Recommendation	References
Weight reduction	Reduction of body weight Weight-loss surgery (improves success of weight loss)	Medium to high, SU	170,171
Medication	Drug-based treatment (e.g., tricyclic antidepressants, serotonin reuptake inhibitors, cholinergic agonists, carbonic anhydrase inhibitors)	NR, ID	90
Surgical	Nasal surgery Palatal surgery and implants Tongue base surgery	Low, SU Low, MC Low, MC	172,173
Increase of muscle activity	Muscle training Hypoglossal nerve stimulation	ID ID	174
Nonsurgical	Oral appliance Positive airway pressure	High, AT High, GS	175 175

AT, Alternative treatment if positive airway pressure is not tolerated; GS, gold standard; ID, data not sufficient for recommendation; MC, may be concerned in carefully selected patients if conservative treatment fails; NR, not recommended; SU, supportive treatment.



**Fig. 10.10** Magnetic resonance imaging of the human upper airway during different levels of continuous positive airway pressure. Magnetic resonance imaging of the upper airway during continuous positive airway pressure of 0, 5, 10, and 15 cm H<sub>2</sub>O shows a dose-dependent increase in upper airway diameter. (Obtained from Schwab RJ, Pack AI, Gupta KB, et al. Upper airway and soft tissue structural changes induced by CPAP in normal subjects. *Am J Respir Crit Care Med*. 1996;154[4 pt 1]:1106–1116.)

varies mostly between 5 and 20 cm H<sub>2</sub>O. However, home RP and titration of CPAP might be similarly effective in some but not all patients with suspected OSA.<sup>176,177</sup> After titration, the prescribed treatment pressure is applied continuously throughout the night. Although this treatment is efficient in reversing the underlying pathology, the impact of CPAP on outcome is limited by patient adherence,<sup>112,178</sup> mostly because of local side-effects at the nose or face, or discomfort caused by the mask.<sup>179</sup> When applied with high pressure, the amount of airflow can prevent the patient from falling asleep while using the treatment device. Some treatment devices offer a ramp or delay function that gradually increases treatment pressure from

a low starting pressure to the prescribed pressure over a period of 5 to 45 minutes, allowing the patient to fall asleep more easily. Some patients report difficulties exhaling against high CPAP. To avoid this problem, bilevel treatment with reduced expiratory positive airway pressure and a sufficiently high inspiratory positive airway pressure can be used.

In some cases, one CPAP pressure level is not sufficient to treat sleep apnea. CPAP devices with dynamic pressure levels can improve treatment success, particularly in patients with a variable severity of sleep disordered breathing during different sleep stages. These automatic positive-airway pressure or auto-tiltrating devices measure different variables associated with hypopnea, such as oropharyngeal wall vibration, snoring, and inspiratory flow limitation, and increase the airway pressure until these signs and symptoms of hypopnea disappear. In addition, it is not entirely clear whether CPAP treatment is able to prevent the increased cardiovascular risk inherited by OSA.

CPAP is sufficient in the treatment of most patients with OSA. However, some patients may need different treatment methods. For example, patients with mixed apneas (obstructive and central) or predominantly central apneas need a more controlled (frequency or time controlled), noninvasive ventilation (NIV) with predefined minimal respiratory frequency or respiratory timing that automatically induces the next inspiration (ventilation) if the patient does not induce the next breath within preset parameters.

**ALTERNATIVE TREATMENT OPTIONS.** Oral appliances (OAs) are possible treatment options in patients with mild to moderate OSA who do not tolerate CPAP therapy. Two major designs are currently used clinically: (1) mandibular repositioning appliance, which holds the mandible in an advanced position (a protrusion of at least 50% of the maximal possible extension is recommended for effective treatment),<sup>179</sup> and (2) tongue-retaining devices, leading to repositioning of the tongue into a forward position without any protrusion of the mandible. A multidisciplinary

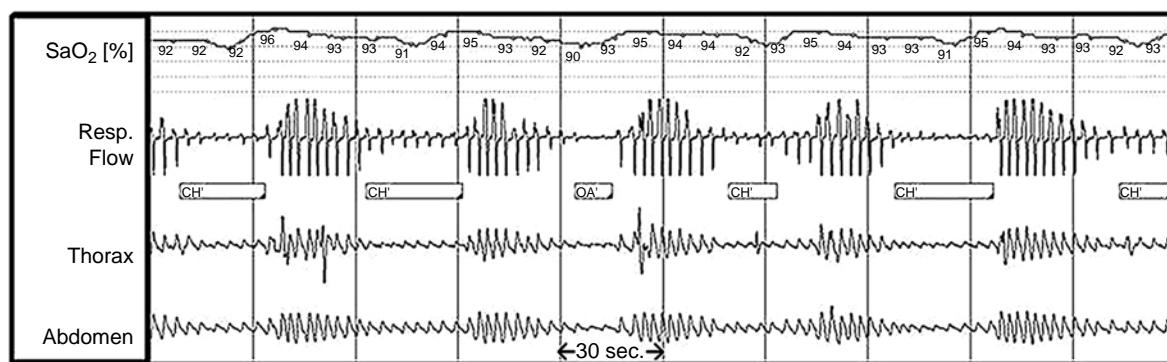


Fig. 10.11 Polysomnographic recording of an episode of Cheyne-Stokes respiration. CH, Central hypopnea; OA, obstructive apnea.

approach including a sleep physician and a dental technician experienced in OAs has been recommended for this purpose, because both factors are crucial for patient adherence and outcome from OA treatment.<sup>109</sup> OAs are recommended in patients with mild to moderate OSA who do not tolerate,<sup>179</sup> do not respond to, fail, or are not appropriate candidates for CPAP treatment.<sup>88</sup>

Historically, surgical treatment methods were the only approach to treatment of OSA, but the effectiveness of most of the nasopharyngeal surgical approaches for severe OSA remains unclear. However, tonsillectomy is beneficial in adult patients with OSA from tonsillar hypertrophy, and adenotonsillectomy is recommended in children with OSA and adenotonsillar hypertrophy.<sup>180</sup> Repeated sleep testing before and following surgery is recommended to ensure sufficient long-lasting therapeutic effects.<sup>88,179,181</sup>

Electrical stimulation of the upper airway muscles has been explored recently as a new approach to treatment of OSA. Hypoglossal nerve stimulation induces genioglossus muscle contractions, which dose dependently increase inspiratory airflow during OSA,<sup>182</sup> but the invasiveness of the procedure, the cost of the device, and the requirement for preimplantation endoscopy during anesthesia limit its use as a first-line treatment of OSA.<sup>149</sup>

While pharyngeal fat deposits led to a decrease in pharyngeal patency, underlining the risk factor of obesity,<sup>183,184</sup> weight loss leads to a reduction in Pcrit and the severity of OSA<sup>145,171</sup> and is recommended as adjunctive treatment in all overweight patients with OSA.<sup>185</sup> Because long-term weight reduction is more effective when accompanied by weight loss surgery, bariatric surgery may be considered as an adjunctive therapy in very obese patients (body mass index [BMI]  $\geq 40$  kg/m<sup>2</sup>), as well as in those with important comorbidities and BMI of 35 kg/m<sup>2</sup> or greater and in whom dietary attempts at weight control have been ineffective.<sup>88</sup>

Oxygen is currently not recommended as primary treatment of OSA, but may be used as an adjunctive treatment in some patients, particularly in the postoperative period.<sup>88,186</sup>

Although OSA is more common in the older population, it occurs in children with a peak in the incidence between 2 and 5 years of age. Obesity predicts snoring and other signs of obstructive respiratory events in children.<sup>109</sup> Tonsillar and adenoidal hypertrophy is another important cause of OSA in children and can be treated surgically.<sup>187</sup>

### Central Sleep Apnea

CSA impairs quality of life<sup>188</sup> and is associated with adverse outcome in heart failure patients.<sup>189,190</sup> CSA is defined as cessation of air flow without respiratory effort,<sup>188</sup> which separates it from OSA, where respiratory effort is maintained or even increased during an apnea. In clinical sleep apnea, considerable overlap between OSA and CSA occur that need to be identified and subsequently treated.<sup>191</sup>

CSA can be found in older patients and in patients with severe comorbidities such as CHF, stroke, or other neurologic disorders (e.g., amyotrophic lateral sclerosis). In a southern Pennsylvania cohort, CSA (AHI  $\geq 20$ /hour) was found in 5% of men aged 65 years and older, but it was not found in younger men or in women of any age. For an AHI of 2.5 per hour and greater, the prevalence estimates in men younger than 45 years remains negligible, while CSA was found in 1.7% of men between 45 and 64 years, and 12% in men older than 65 years,<sup>192</sup> or 9% in individuals between 40 and 97 years, respectively.<sup>193</sup>

CSA mechanisms can be categorized into those with high and low loop gain. The most common subtype of CSA with an increased loop gain is CSR and is commonly seen in patients with CHF and left-ventricular systolic dysfunction. CSR is defined as a crescendo-decrescendo pattern of hyper-ventilation between 20 and 30 seconds in duration, followed by 10 to 40 seconds of hypopneas or apneas (Fig. 10.11), usually occurring during NREM sleep stage 1 and 2.<sup>194</sup> Nevertheless, CSR can also occur during exercise or wakefulness. Nearly one out of two patients with CHF shows CSR.<sup>195</sup> CSR is more common in men and worse in the supine body position.<sup>161</sup>

Potential respiratory therapies of CSR include oxygen, respiratory stimulants (e.g., CO<sub>2</sub>, theophylline, and acetazolamide), and NIV such as bilevel positive airway pressure. The effectiveness of CPAP as therapy is controversial. Optimization of medical therapy is the best treatment, because CSR will often resolve with adequate treatment of CHF (cardiac resynchronization therapy and surgical treatment, such as heart transplant).<sup>194</sup>

**Other Forms of Central Breathing Disorders.** The term *periodic breathing* refers to altitude-induced breathing instability that occurs in subjects transferred to a high altitude, where ambient hypoxia caused by low barometric pressure leads to an increase in controller gain.<sup>97</sup> Idiopathic CSA,

which is a relatively uncommon disorder at sea level, occurs more likely in individuals with an elevated hypercapnic ventilatory response (high controller gain) that leads to hypocapnia and respiratory control instability during sleep. Patients with idiopathic CSA tend to have low  $\text{PaCO}_2$  levels, even during wakefulness.<sup>196</sup>

### Obesity Hypoventilation Syndrome

*Alveolar hypoventilation* is defined as insufficient ventilation leading to hypercapnia (increased  $\text{PaCO}_2$ ). Mechanisms of alveolar hypoventilation include central hypoventilation, chest wall deformities, neuromuscular disorders, chronic obstructive pulmonary disease, as well as severe obesity (obesity hypoventilation syndrome [OHS]). OHS is defined as the combination of nocturnal and daytime hypoventilation, usually leading to hypercapnia in obese subjects ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ), in the absence of other causes of hypoventilation.

The prevalence of OHS is estimated to be up to 50% in obese patients with OSA. It can occur in up to 50% of patients with a  $\text{BMI}$  of  $50 \text{ kg/m}^2$  or more,<sup>197</sup> compared with 0.15% to 0.3% in the general adult population. Ninety percent of patients with OHS also suffer from OSA.<sup>198,199</sup> OHS often remains undiagnosed, and the true prevalence remains unclear.

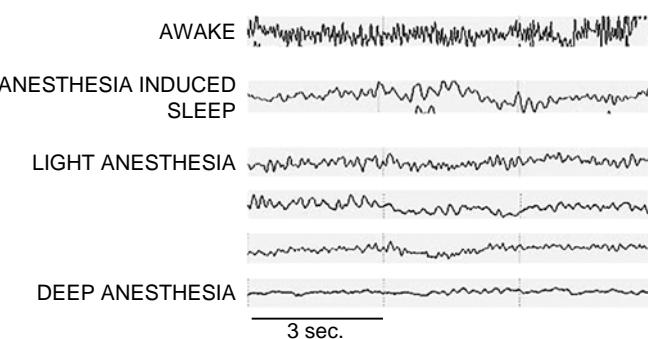
Severe obesity is associated with an increase in respiratory drive that helps maintain eucapnia in the presence of the abnormal chest wall mechanics and high work of breathing.<sup>200,201</sup> In OHS, this compensatory mechanism is abolished,<sup>201,202</sup> which in part might be explained by leptin resistance.<sup>203-205</sup> Typically, OHS manifests as a reduced lung capacity, vital and functional residual capacity, expiratory reserve volume, respiratory system compliance, and inspiratory muscle strength, whereas response to  $\text{CO}_2$  might be reduced or normal. In addition, there is an increase in serum bicarbonate and alveolar  $\text{PCO}_2$ , as well as in the work of breathing and leptin levels.<sup>205,206</sup>

Impairment of the effectiveness of respiratory pump muscle function in patients with OHS can be explained by the effects of low lung volume because of central fat distribution, leading to a cranial displacement of the diaphragm when lying supine.<sup>206,207</sup> In addition, diaphragmatic myopathy might be a contributing factor of OHS.<sup>205</sup> Treatment options include weight loss and NIV.<sup>207,208</sup>

## Sleep and Anesthesia: Two Unequal Twins Influencing Perioperative Medicine

### CLINICAL PICTURE OF SLEEP AND ANESTHESIA

Although physiologic sleep and anesthesia share some clinical features (loss of consciousness and a modulation of brainstem autonomic function), major differences can be found when closer observations of both behavioral states are undertaken. In contrast to anesthesia, sleep shows spontaneous generation and termination, ready reversibility by noxious stimuli, and homeostatic regulation. Anesthesia does not share the stage-wise structure seen during physiologic sleep. In addition, functional imaging studies underline the fundamental differences during onset of anesthesia and wakefulness-sleep transition.



**Fig. 10.12** Electroencephalographic recording during sedation and loss of consciousness induced by propofol. Compared with physiologic sleep (see Fig. 10.1), sedation shows electroencephalographic (EEG) traces comparable to slow wave sleep, indicating the sleep-inducing effect of anesthetics. Anesthesia-induced loss of consciousness (lower four traces), shows different EEG activity with reduced amplitudes and burst suppression. (Burst suppression is not shown in these traces.)

Although there are similarities in the EEG patterns between slow-wave sleep and anesthesia-induced unconsciousness, the EEG patterns during sleep and anesthesia are different,<sup>209</sup> with different frequencies and types of activation in EEG recorded during physiologic sleep and the uniform EEG picture observed during anesthesia-induced unconsciousness (Fig. 10.12).<sup>210</sup>

During anesthesia induction, the level of consciousness continuously decreases from fully awake through states of reduced response to external stimuli up to a completely unresponsive state.<sup>211</sup> This is in contrast to the sharp  $\alpha$ - $\theta$  EEG transitions seen while an individual proceeds from wakefulness to sleep without any transient stages. Individuals in a steady state of physiologic sleep can be aroused with sufficient stimulation, whereas drug-induced unconsciousness needs at least some drug elimination to occur before individuals can be aroused.<sup>212</sup>

### ACTIVATION OF SLEEP-PROMOTING PATHWAYS DURING ANESTHESIA

The role of the endogenous sleep-promoting system in the mechanism of action of general anesthetics has recently received much attention. This hypothesis is attractive because of the similarities of sleep and anesthesia and some evidence that anesthetically induced sleep could meet some of the homeostatic need for sleep.<sup>213,214</sup> It is even more attractive because, despite the large database of the molecular effects of anesthetics, how loss of consciousness occurs is still not explained. An important discovery is that some of the neurons that are active during sleep in the VLPO are also activated by certain anesthetics.<sup>213-216</sup> A second key observation is the inhibition of the arousal nuclei, the TMN, contributes to anesthesia.<sup>215</sup> This effect also implicates activation of VLPO because it provides the major source of inhibition of the TMN. The idea has emerged that anesthesia-induced loss of consciousness is mediated by effects of the anesthetics on the flip-flop switch centered in the VLPO that is responsible for the sharp transition from wakefulness to sleep and back (see earlier section).<sup>212,217,218</sup> However, there are a number of problems with this theory, including that rats and mice with complete lesions of the VLPO can still be anesthetized.<sup>216,219</sup> Although lesions of VLPO lead to a

transient resistance to volatile anesthetics,<sup>216</sup> if some time elapses following a VLPO lesion, the animals show increased sensitivity to isoflurane anesthesia attributable to increased homeostatic sleep drive.<sup>216,219-221</sup> Another problem with the VLPO-TMN circuit hypothesis of anesthesia is that direct inhibition of the TMN produces sedation but not anesthesia.<sup>215</sup> Animals without VLPO neurons have profound insomnia. Therefore, interaction of anesthetics with these sleep-promoting nuclei alone is not sufficient to produce unconsciousness during anesthesia. During recent years, several studies provided evidence to extend the scientific framework of general anesthetics modulating sleep-promoting regions by the anesthetic depression of arousal-promoting nuclei, including the LC, GABAergic neurons of the pontine reticular formation, the pedunculopontine and laterodorsal tegmentum, the ventral tegmental area, as well as the perifornical area, the tuberomammillary nucleus, and the basal forebrain.<sup>222,223</sup> This “bottom-up” hypothesis of anesthesia-induced unconsciousness may be the result of the simultaneous interaction with the brainstem and diencephalic regions, including the AAS and endogenous sleep circuitry. Although, these mechanisms show similarities with sleep-promoting neuronal interactions, they are unlikely to be the only correlate of anesthesia-induced unconsciousness. Sleep, but not anesthesia, is easily reversed or prevented by real or perceived environmental threats. While interaction with sleep-promoting neurons work by inhibiting these arousal pathways, other neuronal networks crucial for consciousness (e.g., thalamocortical networks) remain active during sleep.<sup>224</sup> However, the finding that many anesthetics engage sleep pathways is still important and meaningful, as this is undoubtedly an important mechanism by which these classes of anesthetics promote sleep. Nevertheless, this effect does not and cannot prevent arousal to sufficient external stimuli. The unique property of anesthesia to do so has to be mediated by an additional mechanism.

## PERIOPERATIVE INTERACTIONS BETWEEN ANESTHESIA AND SLEEP

Anesthesia and painful surgical procedures affect sleep and circadian rhythms<sup>225-227</sup> for as long as 6 months, depending on the complexity of the procedure performed.<sup>228</sup> A substantial decrease in REM sleep occurs on the first night after surgery and anesthesia, followed by a profound REM rebound phenomenon on the second to fourth postoperative nights, when REM sleep increases in both intensity and amount.<sup>225,227</sup> Although most anesthetics can lead to an impairment of sleep architecture, such as REM depression and reduced sleep quality during the early postoperative period, the extent of this impairment probably depends on the pharmacokinetics and pharmacodynamics of the anesthetics and opioids used,<sup>229,230</sup> which affect the duration of REM sleep,<sup>231,232</sup> as well as surgery-induced stress.

The effect of propofol on sleep architecture and REM sleep is complex and dose dependent. In long-term ventilated, critically ill patients, propofol sedation abolishes REM sleep and diminishes sleep quality,<sup>233</sup> whereas with low-dose propofol, REM sleep is possible. The effects of ketamine sedation on sleep architecture have not been studied in detail, although it may have rather mild effects on REM duration.<sup>234</sup>

Anesthetics have strong effects on GABA and NMDA receptors, both of which are linked with circadian control. As a result, anesthetics may interfere with entrainment of the circadian rhythm; however, preclinical and human data show inconsistent results. A recent trial in honeybees suggested an anesthetically induced circadian shift. Inside the laboratory with no outdoor cues, daytime anesthesia disturbed the usual activity patterns in the hive for the next several days. In addition, cycles of clock gene activity showed a delay,<sup>235,236</sup> and inhibition of the period circadian protein (per)-2 gene expression (one of the core clock genes) was observed during anesthesia.<sup>237</sup> Of note, psychotropic nonanesthetics, such as opioids, have been shown to affect melatonin secretion indirectly, independent of the behavioral state anesthesia in a pig model.<sup>238</sup> Previous work in humans has shown that 3 hours of anesthetic exposure does not affect the circadian phase of the body temperature rhythm.<sup>239</sup>

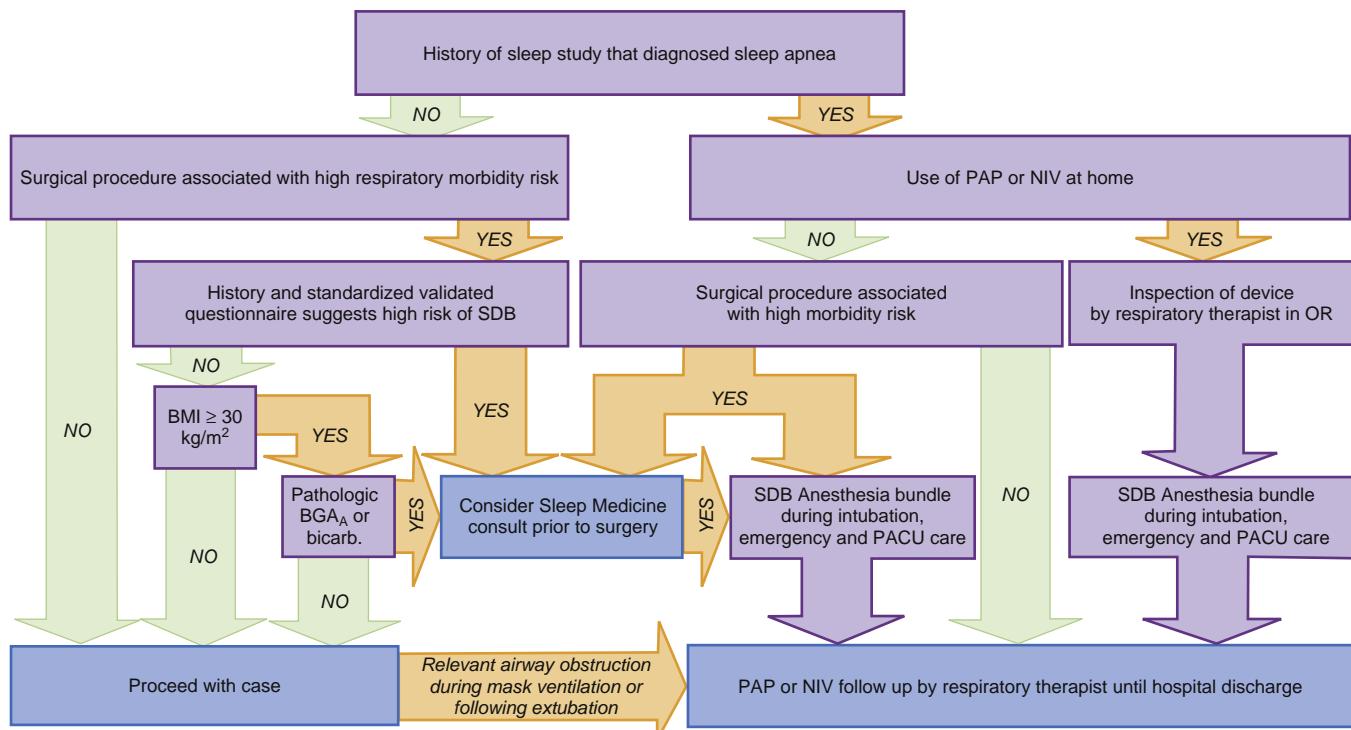
In summary, the specific mechanisms of anesthetics effects on circadian rhythm are unclear. The ability to distinguish between effects occurring directly on the circadian pacemaker and those occurring downstream from the pacemaker on other physiologic control systems requires additional research under rigorous experimental conditions.

Surgical treatment itself impairs sleep, expressed as reduced REM sleep duration even in the absence of general anesthesia.<sup>229,230</sup> Pain, inflammation, stress immobility, and anxiety seem to be contributing factors.<sup>240</sup> After surgery, patients show a significant impairment of sleep quality and duration. Eventually, it will be known whether specific anesthetics are preferable to avoid the adverse effects of sleep deprivation.

## SLEEP-DISORDERED BREATHING AND AIRWAY PATENCY DURING ANESTHESIA

Perioperative complications occur more often in patients with OSA than in healthy controls,<sup>241,242</sup> but the reasons for this observation are unclear. It is challenging to isolate the effect of OSA from the known adverse effects on perioperative outcome of typical OSA comorbidities, such as hypertension, diabetes, coronary artery disease, neurovascular vulnerability, and obesity. Fortunately, severe postoperative complications are uncommon. As a consequence, large trials are needed to isolate the causal relationship between SDB and perioperative complications, such as severe respiratory failure, thromboembolic complications, increased hospital length of stay, and mortality.

Independent of obesity, OSA is not associated with difficult tracheal intubation or mask ventilation.<sup>243-245</sup> However, recent metaanalyses reported a significantly higher risk of postoperative major cardiac and cerebrovascular events, newly detected postoperative atrial fibrillation and acute postoperative respiratory failure, compared with control subjects.<sup>246-248</sup> These findings need to be confirmed in future prospective studies with a larger sample size and a more homogenous population such that confounding factors can be controlled. OSA is associated with postoperative delirium,<sup>241,249</sup> which is an important perioperative complication associated with increased costs, morbidity, and mortality. However, it is currently unclear if this is due to repetitive hypoxia or sleep fragmentation. In contrast, a



**Fig 10.13** Clinical pathway for perioperative management of patients with sleep-disordered breathing. *BGA<sub>A</sub>*, Arterial blood gas analysis; *bicarb*, venous bicarbonate level; *BMI*, body mass index; *NIV*, noninvasive ventilation; *SDB*, sleep-disordered breathing; *PACU*, postanesthesia care unit; *PAP*, positive airway pressure.

recent study using the Nationwide Inpatient Sample database analyzed data from 1,058,710 patients undergoing elective surgery. These authors showed that patients previously diagnosed with SDB had significantly higher rates of emergent mechanical ventilation, use of NIV, and CPAP, as well as increased rates of respiratory failure. Nevertheless, the study also showed that patients with SDB had better outcomes after emergent intubation and had lower care-associated costs compared with their non-SDB counterparts.<sup>250</sup> Similar findings were reported by the same group for data from 91,028 patients undergoing bariatric surgery.<sup>251</sup> In this study, patients with a previous diagnosis of SDB had a shorter hospital length of stay and lower total costs compared with non-SDB patients. The reasons for the differences are unclear. Patients with a known history of sleep apnea may receive more sophisticated perioperative monitoring and more aggressive treatment of their respiratory disease, which might also explain the higher rate of postoperative reintubation in SDB patients reported in the same group.<sup>250</sup> Another possible explanation relates to the consequences of chronic nocturnal desaturation, which can have preventive effects in terms of the consequences of perioperative acute hypoxia. Most importantly, these findings indicate that the association of SDB and perioperative outcome is likely to be more than a unidirectional relationship. More likely is that SDB could have a dual effect, leading to increased rates of perioperative respiratory complications in patients with SDB, but additionally protecting the same population from the fatal consequences of these complications. The mechanism of the potential link between OSA and postoperative respiratory failure, as well as postoperative delirium, is probably multifactorial. Frequent episodes

of airway collapse in OSA lead to hypoxia, disrupted sleep, daytime sleepiness, and increased arousal threshold from sleep, all of which can be considered as potential precipitating or augmenting factors of postoperative complications. It is intriguing to note that patients with OSA appear to be most vulnerable to hypoxia on postoperative night two or three, the time interval during which postoperative delirium most typically manifests.

One population that might deserve additional attention in perioperative care is patients with OHS who, compared with obese patients, are more likely to be admitted to a hospital and require more healthcare resources.<sup>250,252</sup> In addition, higher rates of ICU admission, lengthier long-term care requirements at discharge, and higher mechanical ventilation rates have been reported in patients with OHS compared with severe obese patients without OHS.<sup>251-254</sup>

In summary, patients with SDB are more vulnerable to developing severe perioperative complications. Nevertheless, it is currently unclear whether these complications translate to a poorer overall postoperative outcome for these patients.

## PERIOPERATIVE MANAGEMENT IN PATIENTS WITH SLEEP-DISORDERED BREATHING

The standard of care for perioperative management of patients with SDB depends on the severity of the disease, comorbidities, and the threat associated with the planned surgical procedure. It is probably neither feasible nor necessary to conduct a sleep study in all obese patients at risk for sleep apnea who are scheduled for surgery; however, high-risk patients need to be identified and treated perioperatively. **Fig. 10.13** shows an algorithm that is being

developed by an interdisciplinary international group of clinicians. The algorithm is driven by the idea that patients who have been prescribed CPAP preoperatively should continue to use CPAP perioperatively. Patients who carry several risk factors (procedural and comorbidity-based) may need a preoperative sleep medicine consultation and/or a CPAP prescription.

### Preoperative Screening

Several strategies need to be considered to identify patients with SDB adequately.<sup>94,253,254</sup> Although clinical examination is the easiest and most cost-effective method of assessment using predisposing physical characteristics, it has a poor sensitivity and specificity of only 50% to 60% to diagnose OSA accurately.<sup>255,256</sup> However, the clinical value of using questionnaires relates to the fact that they help to identify a high-risk perioperative population, independently of the question of whether an individual patient has OSA. For example, the STOP-Bang questionnaire basically screens for comorbidities of OSA that we know increase the risk of perioperative complications (hypertension, obesity, male sex, older age) rather than direct breathing disorder-associated characteristics. The Score for Prediction of Obstructive Sleep Apnea might also be a helpful tool to predict patients with OSA and its perioperative outcome based on comorbidities and easily available clinical data.<sup>257</sup>

PSG is required to identify SDB specifically, but it cannot be used for preoperative screening of surgical patients. PSG is expensive, may delay surgery, and is inconvenient for the patient. A multistep approach of preoperative screening is required. Preoperative assessment should include a screening for SDB and for the current use of NIV. OSA might not represent real risk in patients scheduled for low-risk procedures from a surgery and anesthesia point of view. The authors believe that patients with no previously diagnosed SDB undergoing a low-risk surgical procedure should receive standard perioperative monitoring and treatment.

Patients undergoing high-risk surgical procedures should receive further workup using a clinical examination combined with standardized and validated questionnaires (e.g., Berlin).<sup>254,258</sup> Although this diagnostic algorithm might be a sufficient screening for OSA, it might be insufficient to detect OHS.<sup>251,253</sup> A blood gas analysis should be considered as a method to detect hypercapnia as a major symptom of OHS (criterion: awake daytime hypercapnia  $\text{PaCO}_2 \geq 45$  mm Hg). Alternatively, a venous bicarbonate concentration  $\geq 27$  mmol/L is highly sensitive (92%) for an increased  $\text{PaCO}_2$ , which combined with hypoxemia ( $\text{SpO}_2 \leq 94\%$ ) indicates a high risk of OHS in these patients.<sup>251,253,256,259</sup> Of note, OHS is a diagnosis by exclusion. Severe obstructive airway diseases, severe interstitial lung disease, severe chest wall disorders (e.g., kyphoscoliosis), severe hypothyroidism, neuromuscular disease, and congenital central hypoventilation syndrome need to be excluded, and further evaluation of sleep by a sleep medicine specialist before anesthesia should be considered. In these cases, the sleep specialist should determine the optimal diagnostic instruments in cooperation with the perioperative team, prescribe the perioperative auto-titrating CPAP device, and offer in collaboration with respiratory therapy specialists to improve tolerability of perioperative CPAP therapy.

### Perioperative Management of Patients with Possible Sleep-Disordered Breathing

Although the data on optimal intraoperative and perioperative management are still limited, and mainly based on studies with low sample size, the techniques and procedures summarized in **Box 10.2** might be considered during the perioperative management of patients with SDB.<sup>258</sup> Patients with a history of SDB who are undergoing surgery and anesthesia with high risk of morbidity should receive an “OSA anesthesia bundle” (see **Box 10.2**) that includes special procedures and preparations during tracheal intubation, extubation, pain therapy, and perioperative CPAP therapy.

**Tracheal Intubation.** Patients with OSA are frequently obese, and obesity is a risk factor for difficult intubation.<sup>244,259-261</sup> Patients should be preoxygenated efficiently before injection of the anesthetic drug. Sniffing and reverse Trendelenburg position are preferred before intubation, which improves maintenance of the passive (i.e., paralyzed) pharyngeal airway in patients with OSA<sup>260,262</sup> and increases functional residual capacity. To reduce the duration of paralysis, nondepolarizing neuromuscular blocking drugs should be used with caution supported by quantitative neuromuscular transmission monitoring. Immediately after successful intubation, a lung recruitment maneuver and the application of positive end-expiratory pressure for maintaining lung volume during surgery should be considered.<sup>261,263</sup>

**Intraoperative Treatment.** Impaired upper airway patency is of special concern whenever anesthetics are administered without a device that bypasses the collapsible upper airway—for example, during sedation for endoscopy.<sup>264,265</sup> While the overall rate of overt sedation-related complications for such procedures (e.g., endoscopy) appears low,<sup>266</sup> patients who are vulnerable to respiratory complications may suffer from sequelae of increased upper airway collapsibility beyond the immediately observable after intervention.

Opioids and GABAergic sedatives/hypnotics impair upper airway patency without any meaningful difference between compounds given at an equipotent dose of analgesics.<sup>267-270</sup> Of note, the impairing effects of GABAergic drugs on airway patency can be reversed by the respiratory stimulants (Fig. 10.14).<sup>266</sup> Thus it is recommended not to extubate patients at risk of postoperative airway collapse during hypocapnia but rather at mildly hypercarbic conditions.

Ketamine abolishes the impairment of upper airway patency during loss of consciousness and sleep,<sup>271</sup> and may be a viable adjunct to achieve postoperative pain therapy in patients at high risk of airway collapse.

Nondepolarizing neuromuscular blocking drugs should be titrated optimally by quantitative neuromuscular transmission monitoring to avoid residual neuromuscular blockade, which increases the risk of postoperative respiratory complications.<sup>272-275</sup> The effects of neuromuscular blockade should be reversed only when present, because inappropriate reversal can impair upper airway function in animals and humans.<sup>274-276</sup>

## BOX 10.2 Special Sleep-Disordered Breathing Anesthesia Bundle: Special Procedures Performed During Anesthesia in Patients With Diagnosed Sleep-Disordered Breathing and Positive Airway Pressure or Noninvasive Ventilation Treatment

### Preanesthesia Period

- Consider regional anesthetic techniques that minimize the chance of postoperative sedation.

### Induction Strategy

- Monitoring: capnogram, tidal volume measurement
- Sniffing position
- Reverse Trendelenburg position
- Consider intubation without nondepolarizing NMBA; consider succinylcholine.
- Triple airway maneuver with two hands
- Utilize lung recruitment maneuvers immediately after intubation and apply PEEP for maintaining lung volume during surgery.
- PCV with PEEP
- Short-acting anesthetics and narcotics preferred
- Avoid high-dose steroid NMBA.
- Use neuromuscular transmission monitoring.

### Intraoperative Management

- Whenever possible, use of sedatives and narcotics should be reduced.
- Agents with reduced impairing effect on upper airway patency might be considered (e.g., ketamine, pentobarbital).

- Neuromuscular blockade should be monitored.
- Residual neuromuscular blockade should be reversed.

### Extubation and Postanesthetic Care Unit

- Patient should be able to cooperate before extubation. Consider positioning of patients in PACU bed: upper body should be elevated by 45 degrees; lateral position preferred to minimize gravitational effects on the upper airway.
- In case of impaired respiratory function, a plan needs to be defined and documented for monitoring and treatment, including the consideration of noninvasive ventilation.
- Patients will be discharged to an unmonitored environment or home when they meet discharge criteria:
  - Vital signs within 20% from baseline
  - Adequate treatment of nausea
  - Pain score  $\leq 40\%$
  - Aldrete-score  $\geq 8$
  - Passed room air challenge test

### Pain Therapy

- Consider nonsteroidal antiinflammatory drugs to reduce opioid use whenever possible, if not contraindicated.
- Use caution when combining opioids with sedatives or hypnotics.

NMBA, Neuromuscular blocking agents; PACU, postanesthesia care unit; PCV, patient-controlled ventilation; PEEP, positive end-expiratory pressure.

**Postoperative Care.** OSA occurs during sleep and sedation;<sup>277,278</sup> therefore, tracheal extubation should be delayed until complete recovery of consciousness. Patients should be positioned with the upper body elevated by 45 degrees, which improves airway patency<sup>261,262</sup> and functional residual capacity. The lateral body position is an alternative for patients who do not tolerate an elevated upper body position. NIV is a viable treatment of postoperative respiratory failure and helps prevent deoxygenation and the development of postoperative negative pressure pulmonary edema; it can also prevent the respiratory depressant effects of opioids.<sup>276,279</sup>

Before discharge from the post anesthesia care unit, a room air-challenge test should be conducted. Several noninvasive monitoring devices have been developed for patients with and without risk for OSA. However, it is currently unclear if these devices can help prevent postoperative complications, and this requires further investigation.<sup>280,281</sup>

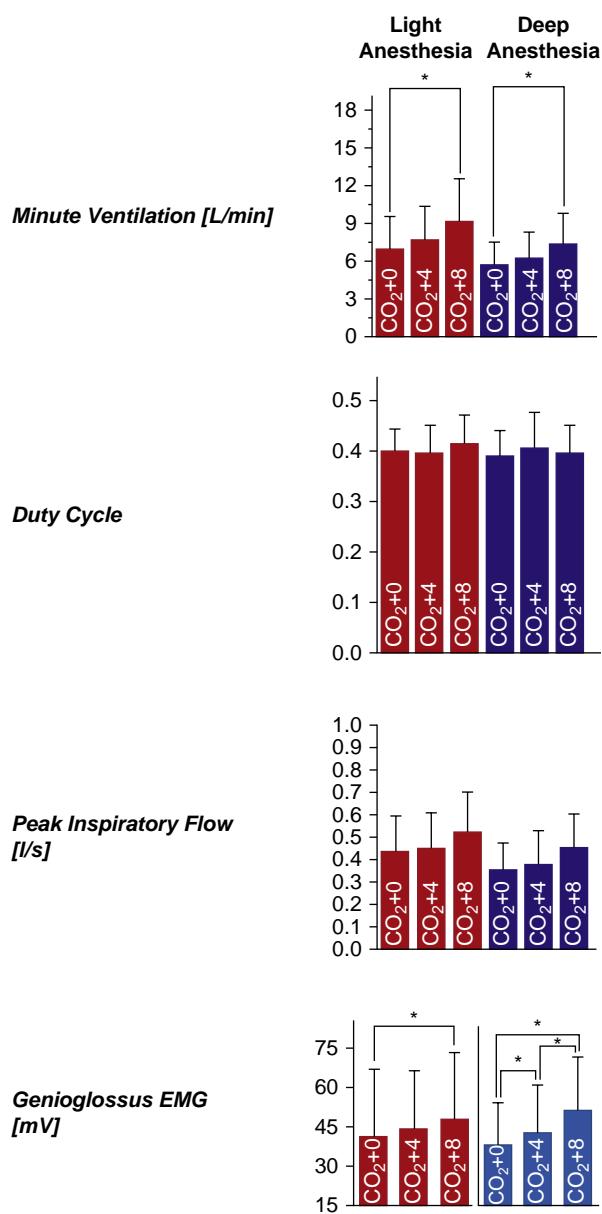
**Pain Therapy.** Pain treatment is of special concern during the postoperative period. Opioids dose-dependently reduce respiratory drive, and special caution is recommended when opioids are combined with sedatives or hypnotics. If not contraindicated, regional anesthesia and nonopioid analgesics should be considered to reduce opioid use whenever possible. If opioids are used, CPAP treatment throughout the early postoperative period may be beneficial in patients with high risk for OSA.<sup>282</sup> Pain intensity typically decreases over time following surgery. Decreasing opioid doses are typically required to maintain the balance of decreasing and increasing effects on respiratory drive.

Patients with SDB being treated with CPAP at home should proceed with these treatments throughout the perioperative period. Sufficient functioning of the treatment device needs to be checked preoperatively (see Box 10.2).

## KNOWLEDGE GAPS AND FUTURE RESEARCH

Although a bold body of evidence on the effect of sleep-disordered breathing throughout the perioperative period has been published during the last decades, there are still large gaps of knowledge.<sup>283,284</sup> Respiratory, cardiovascular, and neuropsychological complications, as well as unfavorable clinical outcomes, may be more or less common in patients with OSA. However, there are many comorbidities that are potential confounders, such as obesity, diabetes, dyslipidemia, coronary artery disease, and increasing age. OSA is a heterogeneous disease, and detailed physiologic phenotyping could identify pathophysiologic mechanisms that increase or decrease risk of perioperative complications of OSA. Multiple mechanistic pathways that can lead to OSA (e.g., compromised anatomy, dilator muscle dysfunction, low arousal threshold, elevated loop gain, inadequate lung volume tethering, and vascular leak) are potentially relevant in a perioperative setting.<sup>125</sup> In-depth physiological studies are required until phenotyping can be accomplished with less time-intensive studies or through PSG. Noninvasive and readily available physiological studies or clinical prediction models that can characterize patients who have high-risk phenotypes of OSA are an important area of future research.

In this context, adequate screening tools for OSA during the perioperative period need to be identified. As stated



**Fig. 10.14** Effect of carbon dioxide (CO<sub>2</sub>) level on genioglossus activity and respiratory function during anesthesia. Insufflation of CO<sub>2</sub> to an increased pCO<sub>2</sub> (+4 or +8 mm Hg) increases minute ventilation, peak inspiratory flow and upper airway dilating muscle activity (e.g. genioglossus muscle) in a dose-dependent fashion during deep (blue bars) and light (red bars) anesthesia. (Modified from Ruscic KJ, Bøgh Stokholm J, Patlak J, et al. Supplemental carbon dioxide stabilizes the upper airway in volunteers anesthetized with propofol. *Anesthesiology*. 2018;129(1):37–46.)

previously, PSG is often challenging to schedule before surgery, and ambulatory technologies may be more useful and should be studied. It might even be more important to identify patients at increased risk of postoperative complications due to specific type of surgery, required mode and depth of anesthesia and opioids, as well as other comorbidities, rather than the presence of SDB per se. It is currently unclear to which extent the risk for perioperative complications associated with SDB are due to or modulated by these coexisting factors. In addition, more severe OSA may be developed by some patients with no or mild OSA prior to anesthesia. Challenging factors are opioids, body position, or intravenous fluids.

Some studies found early postoperative monitoring to detect patients with high risk for such aggravation of OSA severity. Additional research is needed to determine if and how postoperative monitoring is able to help stratify the risk for postoperative OSA. During the last few years, different approaches were made to improve postoperative management of patients with OSA (as discussed previously). However, open questions remain: What is the role of supplemental oxygen postoperatively? What are the barriers to CPAP adherence in the perioperative setting? Can patient adherence and positive airway pressure effectiveness be increased with educational resources? Should other respiratory support interventions be examined either in isolation or bundled with positive airway pressure? Is there a role for targeted positive airway pressure therapy, even with CPAP naive patients in very high risk groups? What are the medicolegal liability and patient safety factors to consider when starting CPAP in the hospital?<sup>285</sup>

Future research should aim to answer these questions to further improve the perioperative management of patients with sleep disordered breathing.<sup>283</sup> Testing a bundled approach to care (e.g., an algorithm of care including monitoring, positive airway pressure, education, and other respiratory supports) rather than each component individually might be more useful in initial clinical trials, as this may be more likely to be effective in improving outcomes.

The incidence of perioperative complications is low, and collaborative research networks are needed to identify a sufficient number of patients with OSA and answer the important research questions on perioperative outcomes. Patients with OHS might be at high risk. A minimal set of data elements required in prospective cohort studies should be identified to facilitate multisite collaboration and metaanalysis of independent studies. Case-control studies might also be nested within larger cohort studies. This would facilitate the choice of an appropriate control group. These studies may improve risk stratification and lead to novel targeted therapies. In addition, the identification of interventions that can optimize safety in this population is also important. Initial intervention trials should focus on patients at highest risk for sleep disordered breathing.<sup>283</sup>

## Sleep and Sedation in the Intensive Care Unit

Impaired sleep is common in patients in the ICU,<sup>286</sup> with multiple contributing factors including noise, light, interruptions for medical procedures, and administration of fluids and nutrition, as well as endogenous factors such as pain, anxiety, and inflammation. Sleep duration in the ICU is variable depending on environmental conditions and the severity of the patient's disease.<sup>287</sup> Sleep fragmentation occurs consistently during sedation and mechanical ventilation.<sup>288,289</sup> The duration of deep NREM and REM sleep as well as circadian rhythms are severely reduced or abolished in ICU patients.<sup>290–292</sup> About 50% of sleep in these patients occurs during daytime hours.<sup>286,287</sup> Altered EEG activity, not fitting into the standard criteria for sleep and wakefulness, was reported to occur in up to 70% of ICU patients who were receiving sedatives or being mechanically ventilated.<sup>293</sup> As a result, alternative classifications for sleep in the ICU have been developed,<sup>294</sup> however, these scoring classifications have not yet been validated.

**TABLE 10.7** List of Studies Investigating Alteration of Circadian Rhythm and Sleep in Intensive Care Unit Patients

Measurement Method	Interactions	Reference
PSG studies	<ul style="list-style-type: none"> <li>■ Increased arousal during nighttime and disrupted sleep, due to:           <ul style="list-style-type: none"> <li>■ noise</li> <li>■ dim light</li> <li>■ medical intervention</li> </ul> </li> <li>■ Decrease N3- and REM-sleep</li> <li>■ Increase arousals and awakenings</li> <li>■ Multiple discrete sleep episodes per 24 h</li> <li>■ Atypical EEG signal:           <ul style="list-style-type: none"> <li>■ disrupted sleep</li> <li>■ nonphysiologic sleep</li> <li>■ architecture, or evidence of coma</li> </ul> </li> </ul>	292,296
Melatonin blood levels and urinary 6-sulfatoxymelatonin urine levels	<ul style="list-style-type: none"> <li>■ Increasing chronodisruption with disease severity (rehabilitation patients, ICU patients, ICU patients with severe sepsis)</li> <li>■ Delayed melatonin peak at night</li> <li>■ Reduced physiologic melatonin secretion at night, due to:           <ul style="list-style-type: none"> <li>■ sedation</li> <li>■ mechanical ventilation</li> <li>■ increased arousal</li> </ul> </li> <li>■ Increased melatonin levels during the day, due to:           <ul style="list-style-type: none"> <li>■ dim light</li> <li>■ severe sepsis</li> </ul> </li> </ul>	302-304 287,290,292,294 292,304-312 305,308,309 306,311
Blood pressure variation	<ul style="list-style-type: none"> <li>■ Reduced nocturnal blood pressure dip</li> </ul>	305
Body temperature variation	<ul style="list-style-type: none"> <li>■ Reduced temperature variation</li> <li>■ Altered circadian rhythm with nadir dispersed widely across 24 h</li> </ul>	23,305,313
Plasma cortisol level	<ul style="list-style-type: none"> <li>■ Abolished circadian rhythm</li> <li>■ Delayed peak of cortisol levels</li> </ul>	305,310

EEG, Electroencephalography; ICU, intensive care unit; N3, sleep stage 3; PSG, polysomnography; REM, rapid eye movement.

## NOISE AND LIGHT EXPOSURE

ICUs are among the most noisy areas in hospitals, with sound levels often exceeding those recommended by the World Health Organization (<45 dB).<sup>289,295</sup> Elbaz and associates<sup>296</sup> reported an increased incidence of arousals at sound levels above >77 dB in stable, mechanically ventilated ICU patients during the weaning phase. In the ICU setting, alarms from medical and monitoring devices were the most significant source of noise.

In addition to noise, changes in light exposure can alter sleep patterns and circadian rhythms. ICU patients are often exposed to dim light throughout the 24-hour cycle, resulting in increased light levels during the night and insufficient light exposure during the daytime.<sup>297,298</sup> This hinders the alignment (photoentrainment) of the internal circadian clock to the external 24-hour rhythm, potentially resulting in the disrupted sleep-wake pattern seen in many ICU patients.<sup>299</sup>

Impaired rhythmicity in melatonin secretion pattern in critically ill patients was reported in several studies (Table 10.7 for overview), and multiple factors influence melatonin rhythm in the ICU. Melatonin levels decrease with increasing age,<sup>300</sup> making older ICU patients more sensitive to circadian rhythm disruptions. Opioids increase melatonin levels throughout the 24-hour period.<sup>301</sup>

Similarly,  $\beta$ -agonists, including vasopressors, positive inotropes, and aerosolized albuterol, increase melatonin levels, whereas  $\beta$ -blockers decrease melatonin secretion. Also, endogenous production of catecholamines may induce periodic melatonin increases in patients with critical illness.<sup>305</sup> Benzodiazepines have inconsistent effects on melatonin.<sup>314,315</sup>

These interactive effects of critical illness and ICU treatment should be acknowledged while caring for ICU patients. Reduction of light and noise exposure during the night, and increased light levels during the day are recommended to improve sleep. In addition, earplugs and eye masks have been shown consistently to improve sleep quality in ICU patients and possibly reduce the risk of complications.<sup>316-319</sup>

## MEDICATION AND MEDICAL PROCEDURES

Interruptions of sleep due to medical or nursing procedures are environmental factors in the ICU. Studies in different ICU settings found high numbers of interventions to be performed during the nighttime, ranging up to 60 interventions per night.<sup>320-322</sup>

Both NIV and ventilation via breathing tube impair sleep architecture and quality.<sup>288,323</sup> It is unclear how the issue of ICU-associated circadian disruption can be prevented or treated. Data suggest that weaning procedures during the daytime combined with assist control ventilation during the nighttime improve sleep, expressed as reduced numbers of arousal in patients requiring long-term ventilation.<sup>291</sup>

## SLEEP AND SEDATION IN THE INTENSIVE CARE UNIT

Sedation is frequently required in the ICU to treat excessive agitation or to fulfill specific therapeutic needs; however, heavy sedation is associated with prolonged ICU and hospital stays.<sup>324</sup> GABA receptor agonists, such as propofol and benzodiazepines, may reduce REM sleep.<sup>325,326</sup>

Pain is a common experience for most patients in the ICU,<sup>327</sup> and failure to recognize pain can result in excessive administration of sedatives.<sup>324</sup> However, opioids have been shown to decrease REM-sleep and worsen sleep disorders, such as OSA in ICU patients.<sup>131,328</sup> Accordingly, an aggressive approach to managing pain while minimizing opioid utilization has been recommended.<sup>329</sup>

## PHARMACOLOGICAL TREATMENT OF SLEEP DISTURBANCES IN INTENSIVE CARE UNIT PATIENTS

Medications currently used for the treatment of insomnia in the ICU interact with the GABA system. GABAergic neurotransmission has multiple functions throughout the brain, leading to daytime sedation, confusion, anterograde amnesia, and delirium.<sup>330-332</sup>

Melatonin has been selected as alternative sleep-promoting medication for critically ill patients in some countries. However, studies on the use of melatonin for the treatment of sleep disturbances and potential complications (e.g., delirium) in ICU patients have produced conflicting results. Administration of melatonin improved subjective and objective sleep quality in a small number of studies.<sup>333-335</sup> Melatonin may have side-effects such as dizziness, nausea, drowsiness, hypotension, and headache, potentially critical in the ICU setting. Recently melatonin receptor agonists have been developed and marketed for patients with circadian rhythm disorders.<sup>336,337</sup> These drugs may have fewer off-target effects than melatonin, but studies on their application in the ICU are very limited. It is therefore difficult to recommend treatment with melatonin agonists of any kind for ICU patients.<sup>338</sup>

The orexin receptor antagonist suvorexant has been approved by the FDA for the treatment of primary insomnia and might be another promising new approach for the treatment of insomnia in ICU patients. In a 4-week study in 254 patients with primary insomnia, suvorexant significantly improved sleep efficiency from the first night until the end of the study compared with placebo in a dose-dependent manner. In addition, suvorexant significantly improved wake after sleep onset and reduced sleep latency,<sup>339</sup> without an apparent delirium-promoting effect.<sup>340</sup> Additional research in the efficacy and safety of orexin receptor antagonists with critically ill patients is needed.

## CONSEQUENCES OF SLEEP DISTURBANCE IN ICU PATIENTS

Compelling evidence links good sleep to proper metabolic, endocrine, immune, and neurobehavioral function.<sup>341-345</sup>

Regardless of controversies, the importance of a sufficient amount of good quality sleep for proper immunologic function, as well as the increased susceptibility for infection due to sleep loss, has gained increased acceptance.<sup>346</sup> Sleep deprivation during influenza vaccination delays the increase of antibody titers.<sup>347,348</sup> Sleep deprivation and insomnia is associated with decreased phagocytic activity of lymphocytes and natural killer T-cells, as well as lower levels of interleukin 2<sup>349</sup> and interleukin 7.<sup>350</sup> Interleukin 7 facilitates the transition of CD8 $\beta$

effector to memory T-cells and lengthens survival of the T-cell memory cells.<sup>351</sup> Prolonged sleep deprivation, as may occur in long term ICU patients, may induce a persistent production of proinflammatory cytokines, producing a chronic low-grade inflammation, as well as immunodeficiency.<sup>348</sup>

Even short sleep deprivation in otherwise healthy young subjects has been shown to be associated with impaired glucose tolerance and insulin resistance, similar to levels usually seen in patients in the early course of diabetes mellitus.<sup>352</sup> In addition, sleep deprivation can induce the onset of a catabolic state: increased oxygen consumption, carbon dioxide production, and catecholamine levels, likely as signs of a stress response.<sup>353</sup> Changes in the activity of the hypothalamo-pituitary-adrenal axis with altered plasma levels of cortisol and thyrotropin,<sup>354</sup> as well as increased levels of inflammatory cytokines, are seen during sleep deprivation.<sup>355</sup>

It is likely that postoperative sleep deprivation also affects respiratory function, characterized as increased vulnerability to respiratory muscle fatigue,<sup>356</sup> decrease in ventilatory response to hypercapnia,<sup>357</sup> and greater upper airway collapsibility.<sup>358</sup>

Cognitive impairment after even short-term sleep deprived conditions is intuitive. Sleep deprivation causes bidirectional changes in brain activity and connectivity, thereby mainly affecting attention and working memory, and an increased vulnerability to delirium in critically ill patients.<sup>359-361</sup>

In addition, recent studies found beneficial effects of realignment of the sleep-wake cycles by pharmacologic and chronotherapeutic methods on the risk for delirium in these patients.<sup>362-364</sup> However, sleep-promoting agents per se can increase the vulnerability to delirium, and the optimal sleep-promoting agent that also minimizes the risk of delirium needs to be identified.

## PERIOPERATIVE MANAGEMENT OF OTHER SLEEP DISORDERS

### Narcolepsy

Narcolepsy is a neurologic sleep disorder with a prevalence of 0.05% to 0.8% in most ethnic groups.<sup>365,366</sup> It is characterized by excessive daytime sleepiness, involuntary daytime sleep episodes, disturbed nocturnal sleep, and sleep-associated muscular hypotension. Narcolepsy is divided into narcolepsy with or without cataplexy (sudden loss of muscle tone without loss of consciousness).<sup>367</sup>

An autoimmune pathology against hypothalamic orexin neurons may be involved in the pathogenesis of narcolepsy.<sup>366</sup> A mutation of the HCRT receptor 2 or loss of HCRT neurons have been shown to cause a narcolepsy-like state in animals,<sup>368</sup> and the deficiency of HCRT has been shown to be associated with narcolepsy in humans.<sup>34</sup> HCRT is involved in control of several biological functions such as feeding, cardiovascular regulation, upper airway stability, pain, locomotion, stress, and addiction.<sup>369,370</sup> Environmental factors play a key role in the pathogenesis of the disorder, as the disease concordance rate between monozygotic twins is only 20% to 35%.

Treatment of narcolepsy consists of behavioral treatment, as well as pharmacologic treatment for (1) daytime

sleepiness and (2) cataplexies. Periodic and regular sleep times and scheduled daytime naps are recommended. Pharmaceutical treatments of daytime sleepiness include amphetamines, methylphenidate, modafinil, or selegiline (also effective for treatment of cataplexy), and cataplexies can be treated using tricyclic antidepressants, selective serotonin reuptake inhibitors, or  $\gamma$ -hydroxybutyrate/sodium oxybate. Medical treatment should always be accompanied by behavioral therapy.

Delayed emergence from anesthesia, postsurgical hypersomnia, and apneic episodes are in part related to an increased sensitivity to anesthetic drugs in narcolepsy patients.<sup>371-373</sup> Monitoring of anesthetic depth might be recommended in this patient population. Medical treatment of narcolepsy should be maintained during the preoperative period.<sup>374,375</sup> The most commonly used treatment of daytime sleepiness is modafinil, which acts via dopaminergic pathways and accelerates emergence from anesthesia.<sup>376,377</sup> Avoidance of sedative premedication and consideration of regional anesthesia may be indicated.<sup>378</sup> Of note, cataplectic events can also occur during regional anesthesia.<sup>379</sup>

### Restless Legs Syndrome and Periodic Limb Movement Disorder

Restless legs syndrome, or Ekbom syndrome, is a neurologic disorder with a prevalence of 2% to 5% as defined by four cardinal features, including (1) the urge to move the limbs, usually associated with paresthesias or dysesthesias, (2) aggravating effects of rest, (3) ameliorating effects of physical activity, and (4) symptoms that worsen during the course of day, with a peak during the evening or at night. Patients with restless legs syndrome usually also complain about sensory symptoms in the legs.

Isolated periodic limb movement during sleep is a rare symptom, commonly referred to as *periodic limb movement disorder*. The characteristic periodic episodes of repetitive limb movements during sleep occur most often in the lower extremities, but occasionally in the upper extremities. These movements can be associated with frequent arousals leading to sleep disruption, causing excessive daytime sleepiness, which often is the only symptom reported by the patients themselves in most cases.<sup>380</sup>

Symptomatic restless legs syndrome can occur in patients with iron deficiency and uremia, during pregnancy,<sup>381</sup> or during the use of neurotropic medications (dopamine antagonists, neuroleptics, selective serotonin reuptake inhibitors, tricyclic antidepressants, antihistamines, caffeine, alcohol, nicotine). Although daytime symptoms of restless legs syndrome can be sufficiently diagnosed clinically (clinical examination in combination with standardized questionnaires), a PSG is recommended to rule out SDB, especially in patients complaining of daytime sleepiness or sleep fragmentation.

According to the most recent guidelines of the AASM, the first-line treatment of restless legs syndrome should consist of dopamine agonists (i.e., ropinirole and pramipexole) in the evening. Furthermore, gabapentin enacarbil, levodopa with dopa decarboxylase inhibitor, or opioids can be used. Medication impairing the dopaminergic system (dopamine antagonists, neuroleptics, selective serotonin reuptake

inhibitors, and tricyclic antidepressants, antihistamines, caffeine, alcohol, and nicotine) should be avoided, if possible.

Exacerbation of restless legs syndrome may occur after general anesthesia,<sup>382</sup> and the urge to move the limbs may be misinterpreted as agitation or delirium.<sup>383</sup> The first manifestation of restless legs syndrome may occur after spinal anesthesia<sup>384</sup> or general anesthesia,<sup>384</sup> and the prevalence of restless legs syndrome after surgery seems to be higher than expected in this population.<sup>382</sup> To prevent perioperative exacerbation of symptoms, patients with restless legs syndrome should be scheduled for surgery early in the day. Restless legs syndrome medication should be continued until the day of surgery, whenever appropriate. Drugs that block the central dopamine transmission, such as neuroleptics, should be avoided. In contrast, ketamine might be the superior anesthetic drug for patients with restless legs syndrome.<sup>385</sup> In addition, intravenous or subcutaneous opioids and benzodiazepines during and after the surgery procedure might be beneficial in patients with restless legs syndrome. The best way to provide symptom relief in patients with restless legs syndrome might be early mobilization after surgery. In patients who are not eligible for mobilization, compression treatment<sup>386</sup> or intravenous administration of magnesium<sup>387</sup> and physostigmine<sup>388</sup> have been shown to lead to relief of restless legs syndrome symptoms. Iron and ferritin blood levels should be monitored closely before, during, and after surgery, especially in surgical cases with iron loss (i.e., bleeding), to prevent symptomatic restless legs syndrome symptoms.

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## KEY POINTS

- The brain has a high metabolic rate and receives approximately 12% to 15% of cardiac output. Under normal circumstances, cerebral blood flow (CBF) is approximately 50 mL/100 g/min. Gray matter receives 80% and white matter receives 20% of this blood flow.
- Approximately 60% of the brain's energy consumption supports electrophysiologic function. The remainder of the energy consumed by the brain is involved in cellular homeostatic activities.
- CBF is tightly coupled to local cerebral metabolism, a process called *neurovascular coupling*. When cerebral activity in a particular region of the brain increases, a corresponding increase in blood flow to that region takes place. Conversely, suppression of cerebral metabolism leads to a reduction in blood flow.
- CBF is autoregulated and remains constant over a mean arterial pressure (MAP) range estimated at 65 to 150 mm Hg, given normal venous pressure. CBF becomes pressure passive when MAP is either less than the lower limit or more than the upper limit of autoregulation. The lower and upper limits, as well as the range and slope of the plateau, manifest significant variability between individuals.
- CBF is also under chemical regulation. CBF varies directly with arterial carbon dioxide tension (Paco<sub>2</sub>) in the range of 25 to 70 mm Hg. When arterial partial pressure of oxygen (Pao<sub>2</sub>) decreases to less than 60 mm Hg, CBF increases dramatically. Reductions in body temperature influence CBF primarily by the suppression of cerebral metabolism.
- Systemic vasodilators (e.g., nitroglycerin, nitroprusside, hydralazine, and calcium channel blockers) vasodilate the cerebral circulation and can, depending on the MAP, increase CBF. Vasopressors such as phenylephrine, norepinephrine, ephedrine, and dopamine do not have appreciable direct effects on the cerebral circulation. Their effect on CBF is via their effect on arterial blood pressure. When the MAP is less than the lower limit of autoregulation, vasopressors increase the MAP and thereby increase CBF. If the MAP is within the limits of autoregulation, then vasopressor-induced increases in systemic pressure have little effect on CBF.
- All volatile anesthetics suppress cerebral metabolic rate (CMR) and, with the exception of halothane, can produce burst suppression of the electroencephalogram. At that level, the CMR is reduced by approximately 60%. Volatile anesthetics have dose-dependent effects on CBF. In doses less than the minimum alveolar concentration (MAC), CBF is modestly decreased. In doses larger than 1 MAC, direct cerebral vasodilation results in an increase in CBF and cerebral blood volume (CBV).
- Barbiturates, etomidate, and propofol decrease the CMR and can produce burst suppression of the electroencephalogram. At that level, the CMR is reduced by approximately 60%. Because neurovascular coupling is preserved, CBF is decreased. Opiates and benzodiazepines effect minor decreases in CBF and CMR. In contrast, ketamine can increase CBF significantly, in association with a modest increase in CMR.
- Brain stores of oxygen and substrates are limited, and the brain is extremely sensitive to decreases in CBF. Severe decreases in CBF (<6-10 mL/100 g/min) lead to rapid neuronal death. Ischemic injury is characterized by early excitotoxicity and delayed apoptosis.
- Barbiturates, propofol, ketamine, volatile anesthetics, and xenon have neuroprotective efficacy and can reduce ischemic cerebral injury in experimental models. This anesthetic neuroprotection is sustained only when the severity of the ischemic insult is mild; with moderate-to-severe injury, long-term neuroprotection is not achieved. The neuroprotective efficacy of anesthetics in humans is limited. Administration of etomidate can decrease regional blood flow, which can exacerbate ischemic brain injury.

This chapter reviews the effects of anesthetic drugs and techniques on cerebral physiology—in particular, their effects on cerebral blood flow (CBF) and metabolism. The final section presents a brief discussion of pathophysiologic states, including cerebral ischemia and cerebral protection. Attention is directed to the rationale for selection and appropriate use of the anesthetic agents for neuroanesthetic management. Chapter 57 presents the clinical management of these patients in detail. Neurologic monitoring, including the effects of anesthetics on the electroencephalogram (EEG) and evoked responses, is reviewed in Chapter 39.

## The Anatomy of the Cerebral Circulation

The arterial blood supply to the brain is composed of paired right and left internal carotid arteries, which give rise to the anterior circulation, and paired right and left vertebral arteries, which give rise to the posterior circulation. The connection of the two vertebral arteries forms the basilar artery. The internal carotid arteries and the basilar artery connect to form a vascular loop called the circle of Willis at the base of the brain that permits collateral circulation between both the right and left and the anterior and posterior perfusing arteries. Three paired arteries that originate from the circle of Willis perfuse the brain: anterior, middle, and posterior cerebral arteries. The posterior communicating arteries and the anterior communicating artery complete the loop. The anterior and the posterior circulations contribute equally to the circle of Willis.

Under normal circumstances, blood from the anterior and posterior circulations does not admix because the pressures in the two systems are equal. Similarly, side-to-side admixing of blood across the circle is limited. The vessels that originate from the circle provide blood flow to well-delineated regions of the brain. However, in pathologic circumstances during which occlusion of one of the arterial branches occurs, the circle of Willis can provide anterior-posterior or side-to-side collateralization to deliver flow to the region of the brain with reduced perfusion.

A complete circle of Willis is shown in Fig. 11.1A. However, substantial variability exists in the anatomy of the circle of Willis, and a significant proportion of individuals may have an incomplete circular loop.<sup>1</sup> The variations in the circle and their prevalence are shown in Fig. 11.1B.

Three sets of veins drain blood from the brain. The superficial cortical veins are within the pia mater on the brain's surface. Deep cortical veins drain the deeper structures of the brain. These veins drain into dural sinuses, of which the superior and inferior sagittal sinuses and the straight, transverse and sigmoid sinuses are the major dural sinuses. These ultimately drain into the right and left internal jugular veins. A schematic representation of the cerebral venous circulation is shown in Fig. 11.1C.

There is considerable asymmetry in the blood flow between the right and left internal jugular veins. In approximately 65% of patients, flow in the right IJV is greater than in the left; in the remainder, the left IJV is dominant.<sup>2</sup> The pattern of venous drainage may have implications for insertion of jugular venous catheters for the measurement of

jugular venous oxygen saturation (SjVO<sub>2</sub>). To ensure accurate measurement of SjVO<sub>2</sub>, it has been advocated that the catheter be inserted into the dominant jugular vein. In most patients, the right IJV will be the dominant vein.

## CEREBROSPINAL FLUID FORMATION AND CIRCULATION

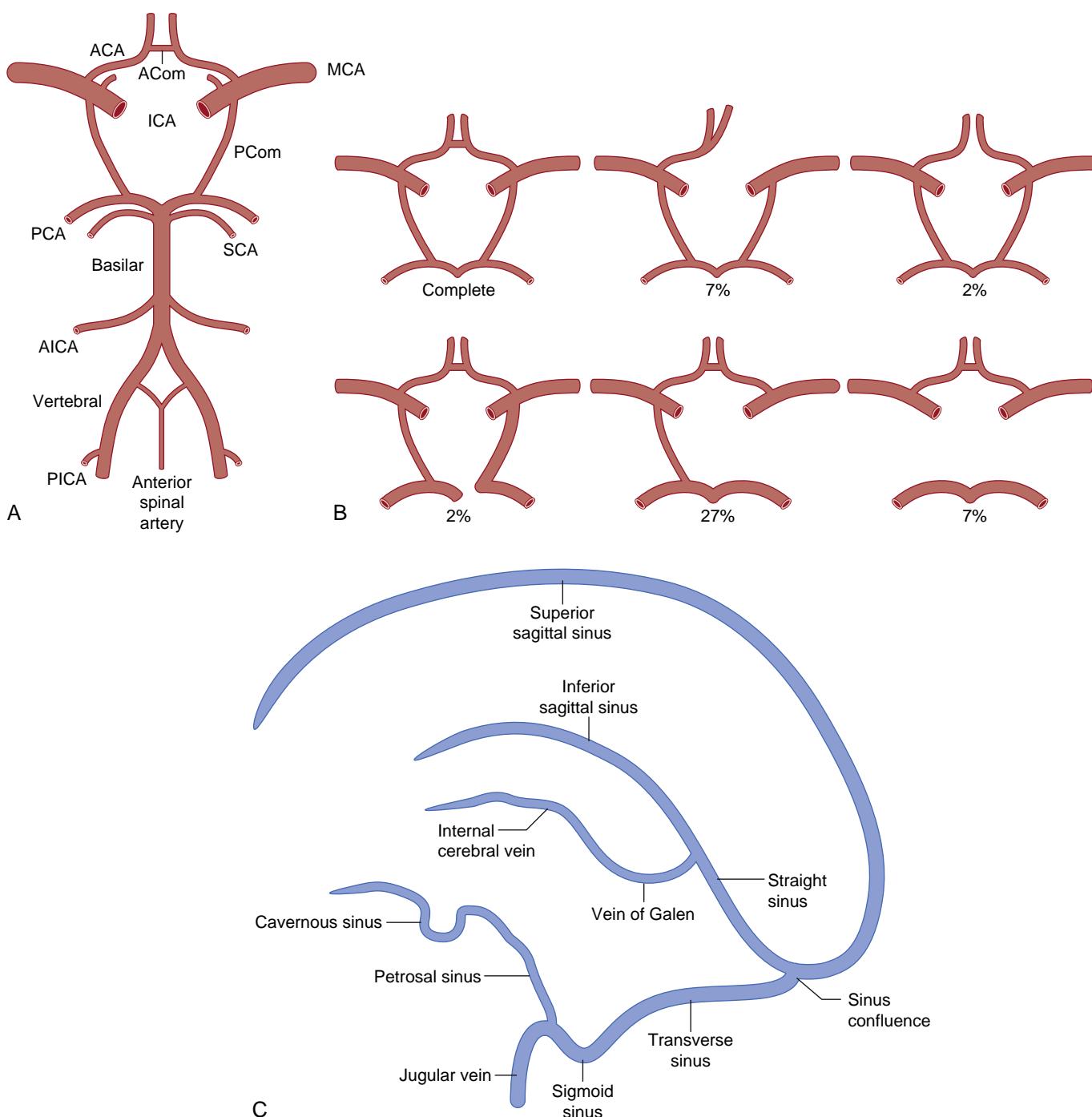
Cerebrospinal fluid (CSF) is produced primarily by the choroid plexus in the lateral, third, and fourth ventricles; there are small contributions from the endothelial cells and from fluid that is produced as a consequence of metabolic activity. CSF production is the result of hydrostatic efflux from capillaries into the perivascular space, and then active transport into the ventricles. CSF reabsorption occurs primarily via the arachnoid granulations present in the dural sinuses. A smaller proportion of CSF, which tracks along cranial and peripheral nerves, perivascular routes, and along white matter tracts, gains access to the cerebral venous system by transependymal flow. The total CSF space is approximately 150 mL and total daily CSF production averages 450 mL. Therefore, there is a substantial daily turnover of CSF. CSF production is also under the influence of the circadian rhythm, with the peak production of CSF occurring during sleep.<sup>3</sup>

Recently, the concept of the glymphatic pathway as a means by which waste products are removed from the brain has been advanced. Conceptually, the glymphatic pathway can be visualized as a system akin to the lymphatic system in the systemic circulation (note, however, that the brain does not contain lymphatics other than those present in the meninges). Functionally, CSF enters the periarterial space, a space that is bounded by the vessels and the end-feet of astrocytes. Aquaporin channels on the end-feet facilitate this water exchange. From the periarterial space, CSF is transported to the brain parenchyma, and from there to the perivenous space and on to the ventricles. As such, the glymphatic system serves as a waste disposal system.<sup>3</sup> Of considerable interest is the observation that the periarterial space increases significantly during sleep and during general anesthesia; hence, glymphatic transport and waste clearance is increased during these states. Among anesthetic agents, glymphatic transport is reduced by volatile agents but is less affected by dexmedetomidine.<sup>4</sup>

## REGULATION OF CEREBRAL BLOOD FLOW

Anesthetic drugs cause dose-related and reversible alterations in many aspects of cerebral physiology, including CBF, cerebral metabolic rate (CMR), and electrophysiologic function (EEG, evoked responses). The effects of anesthetic drugs and techniques have the potential to adversely affect the diseased brain and are thus of clinical importance in patients with neurosurgical disease. Conversely, the effects of general anesthesia on CBF and CMR can be altered to improve both the surgical course and the clinical outcome of patients with neurologic disorders.

The adult human brain weighs approximately 1350 g and therefore represents approximately 2% of total body weight. However, it receives 12% to 15% of cardiac output. This high flow rate is a reflection of the brain's high metabolic rate. At rest, the brain consumes oxygen at an average



**Fig. 11.1** Vascular anatomy of the blood supply to and drainage from the brain. (A) Arterial input into a complete circle of Willis. ACA, Anterior cerebral artery; ACom, anterior communicating artery; AICA, anterior inferior cerebellar artery; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; PCom, posterior communicating artery; PICA, posterior inferior cerebellar artery; SCA, superior cerebellar artery. (B) Variations in the anatomy of the circle of Willis. The prevalence of each of the variations, expressed as percentage of adult patients, is provided for each variant. (C) Venous drainage of the brain.

rate of approximately 3.5 mL of oxygen per 100 g of brain tissue per minute. Whole-brain oxygen consumption (50 mL/min) represents approximately 20% of total body oxygen utilization. Normal values for CBF, CMR, and other physiologic variables are provided in **Box 11.1**.

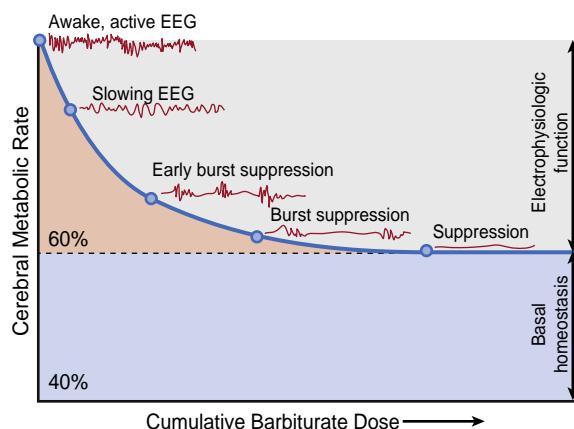
Approximately 60% of the brain's energy consumption supports electrophysiologic function. The depolarization-repolarization activity that occurs, reflected in the EEG, requires expenditure of energy for the maintenance

and restoration of ionic gradients and for the synthesis, transport, release, and reuptake of neurotransmitters. The remainder of the energy consumed by the brain is involved in cellular homeostatic activities (Fig. 11.2). Local CBF and CMR within the brain are very heterogeneous, and both are approximately four times greater in gray matter than in white matter. The cell population of the brain is also heterogeneous in its oxygen requirements. Glial cells make up approximately one half of the

### BOX 11.1 Normal Cerebral Physiologic Values (Values Updated)

CBF	
Global	45-55 mL/100 g/min
Cortical (mostly gray matter)	75-80 mL/100 g/min
Subcortical (mostly white matter)	8-20 mL/100 g/min
CMRO <sub>2</sub>	3-3.5 mL/100 g/min
CVR	1.5-2.1 mm Hg/100 g/min/mL
Cerebral venous PO <sub>2</sub>	32-44 mm Hg
Cerebral venous SO <sub>2</sub>	55%-70%
rSO <sub>2</sub>	55%-80%
SjVO <sub>2</sub>	60%-70%
ICP (supine)	8-12 mm Hg

CBF, Cerebral blood flow; CMRO<sub>2</sub>, cerebral metabolic rate of oxygen; CVR, cerebral vascular resistance; ICP, intracranial pressure; PO<sub>2</sub>, partial pressure of oxygen; rSO<sub>2</sub>, regional oxygen saturation measured by near-infrared spectroscopy; SO<sub>2</sub>, oxygen saturation; SjVO<sub>2</sub>, jugular venous oxygen saturation.



**Fig. 11.2** Interdependency of cerebral electrophysiologic function and cerebral metabolic rate (CMR). Administration of various anesthetics, including barbiturates, results in a dose-related reduction in the CMR of oxygen (CMRO<sub>2</sub>) and cerebral blood flow (CBF). The maximum reduction occurs with the dose that results in electrophysiologic silence. At this point, the energy utilization associated with electrophysiologic activity has been reduced to zero, but the energy utilization for cellular homeostasis persists unchanged. Additional barbiturates cause no further decrease in CBF or CMRO<sub>2</sub>. EEG, Electroencephalogram.

brain's volume and require less energy than neurons. Besides providing a physically supportive latticework for the brain, glial cells are important in the reuptake of neurotransmitters, in the delivery and removal of metabolic substrates and wastes, and in blood-brain barrier (BBB) function.

Given the limited local storage of energy substrate, the brain's substantial demand for substrate must be met by adequate delivery of oxygen and glucose. However, the space constraints imposed by the noncompliant cranium and meninges require that blood flow not be excessive. Not surprisingly, elaborate mechanisms regulate CBF. These mechanisms, which include myogenic, chemical, and autonomic neural factors, are listed in **Table 11.1**.

**TABLE 11.1** Factors Influencing Cerebral Blood Flow

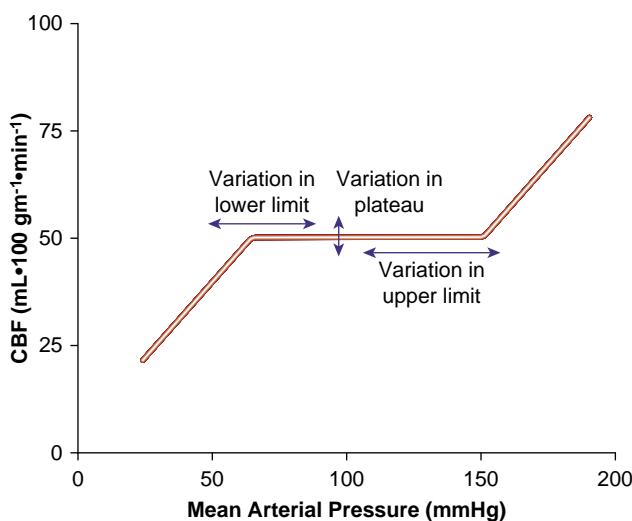
Factor	Comment
<b>CHEMICAL, METABOLIC, HUMORAL</b>	
CMR	CMR influence assumes intact flow-metabolism coupling, the mechanism of which is not fully understood.
Anesthetics	
Temperature	
Arousal; seizures	
Paco <sub>2</sub>	
Pao <sub>2</sub>	
Cardiac output	
Vasoactive drugs	
Anesthetics	
Vasodilators	
Vasopressors	
<b>MYOGENIC</b>	
Autoregulation; MAP	The autoregulation mechanism is fragile; in many pathologic states, CBF is regionally pressure passive.
<b>RHEOLOGIC</b>	
Blood viscosity	
<b>NEUROGENIC</b>	
Extracranial sympathetic and parasympathetic pathways	Contribution and clinical significance are poorly defined.
Intraaxial pathways	

See text for discussion.

CBF, Cerebral blood flow; CMR, cerebral metabolic rate; MAP, mean arterial pressure; Paco<sub>2</sub>, arterial partial pressure of carbon dioxide; Pao<sub>2</sub>, arterial partial pressure of oxygen.

### MYOGENIC REGULATION (AUTOREGULATION) OF CEREBRAL BLOOD FLOW

The conventional view of autoregulation is that the cerebral circulation adjusts its resistance to maintain CBF relatively constant over a wide range of mean arterial pressure (MAP) values. In normal human subjects, CBF is autoregulated between 70 mm Hg (lower limit of autoregulation, LLA) and 150 mm Hg (upper limit of autoregulation, ULA) (Fig. 11.3).<sup>5</sup> There is, however, considerable variation between subjects in the autoregulation limits. Cerebral perfusion pressure is the difference between the MAP and the intracranial pressure (ICP). Because ICP is not usually measured in normal subjects, cerebral perfusion pressure (CPP = MAP – ICP) is rarely available. Assuming a normal ICP of 5 to 10 mm Hg in a supine subject, an LLA of 70 mm Hg expressed as MAP corresponds to a LLA of approximately 60 to 65 mm Hg expressed as CPP. Above and below the autoregulatory plateau, CBF is pressure-dependent (pressure-passive) and linearly varies with CPP. Autoregulation is influenced by the time course over which the changes in CPP occur. Even within the range over which autoregulation normally occurs, a rapid change in arterial pressure will result in a transient (i.e., 3-4 minute) alteration in CBF.



**Fig. 11.3** The conventional view of cerebral autoregulation. Cerebral blood flow (CBF) is maintained within the normal range in the face of widely varying blood pressures. Below the lower limit of autoregulation, approximately 65 to 70 mm Hg in humans, and above the upper limit, approximately 150 mm Hg, the cerebral circulation is pressure passive and CBF decreases or increases, respectively, with corresponding changes in mean arterial pressure. Note that there is considerable intersubject variation in the limits of the autoregulatory plateau; the extent of this variation is depicted by the arrows. The autoregulatory curve should not be considered fixed and static but as a dynamically changing response to the cerebral circulation to changes in blood pressure.

The limits of autoregulation and the autoregulatory plateau are conceptual frameworks for the purpose of analysis. They do not represent physiologic “all-or-none” responses. There is considerable variability in the LLA and ULA as well as in the limits of the plateau (see the section on “An Integrated Contemporary View of Cerebral Autoregulation”).

The precise mechanisms by which autoregulation is accomplished and its overlap with neurovascular coupling are not known. According to the myogenic hypothesis, changes in CPP lead to direct changes in the tone of vascular smooth muscle; this process appears to be passive. Nitric oxide (NO) and calcium channels may participate in the vasodilation associated with hypotension.

## CHEMICAL REGULATION OF CEREBRAL BLOOD FLOW

Several factors, including changes in CMR, arterial partial pressure of carbon dioxide ( $\text{PaCO}_2$ ), and arterial partial pressure of oxygen ( $\text{PaO}_2$ ) cause alterations in the cerebral biochemical environment that result in adjustments in CBF.

### Cerebral Metabolic Rate

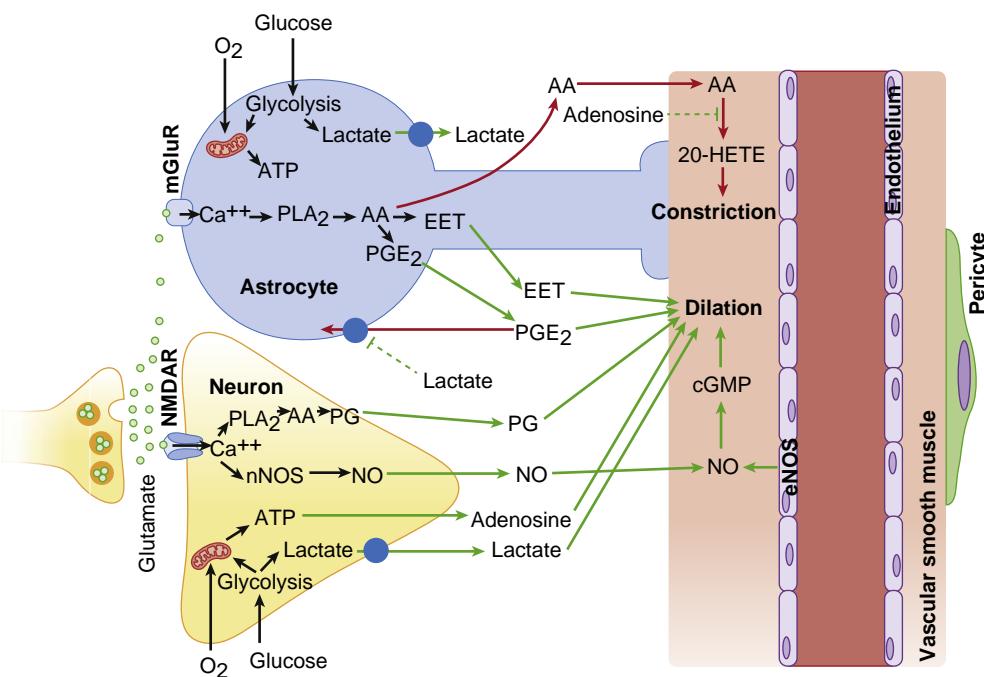
Regional CBF and metabolism are tightly coupled. They involve a complex physiologic process regulated, not by a single mechanism, but by a combination of metabolic, glial, neural, and vascular factors. Increased neuronal activity results in increased local brain metabolism, and this increase in the CMR is associated with a proportional change in CBF referred to as *neurovascular coupling*. The

traditional view of neurovascular coupling is that it is a positive feedback mechanism wherein increased neuronal activity results in a demand for energy; this demand is met by an increase in CBF. More recent data indicate that coupling is based on a feed-forward mechanism wherein neuronal activity directly increases CBF, thereby increasing energy supply.<sup>6</sup> Although the precise mechanisms that mediate neurovascular coupling have not been defined, the data available implicate local by-products of metabolism (e.g., potassium ion [ $\text{K}^+$ ], hydrogen ion [ $\text{H}^+$ ], lactate, adenosine, and adenosine triphosphate [ATP]). Increased synaptic activity with the attendant release of glutamate leads to the downstream generation of a variety of mediators that affect vascular tone (Fig. 11.4). Glutamate, released with increased neuronal activity, results in the synthesis and release of NO, a potent cerebral vasodilator that plays an important role in neurovascular coupling. Glia also play an important role in neurovascular coupling. Their processes make contact with neurons, and these processes may serve as conduits for the coupling of increased neuronal activity to increases in blood flow. Glutamate activation of metabotropic glutamate receptors (mGluR) in astrocytes leads to arachidonic acid (AA) metabolism and the subsequent generation of prostaglandins and epoxyeicosatrienoic acids. Oxygen modulates the relative contribution of these pathways, and in the setting of reduced oxygen tension at the tissue level, the release of adenosine can contribute to vascular dilation. The net result therefore on vascular tone is determined by the relative contribution of multiple signaling pathways. In addition, nerves that innervate cerebral vessels release peptide neurotransmitters such as vasoactive intestinal peptide (VIP), substance P, cholecystokinin, somatostatin, and calcitonin gene-related peptide. These neurotransmitters may also potentially be involved in neurovascular coupling.

CMR is influenced by several phenomena in the neurosurgical environment, including the functional state of the nervous system, anesthetic drugs, and temperature.

**Functional state.** CMR decreases during sleep and increases during sensory stimulation, mental tasks, or arousal of any cause. During epileptic activity, increases in the CMR may be extreme, whereas regionally, after brain injury and globally with coma, the CMR may be substantially reduced.

**Anesthetic drugs.** The effect of individual anesthetic drugs on the CMR is presented in greater detail in the second section of this chapter. In general, anesthetic drugs suppress the CMR, with the exception of ketamine and nitrous oxide ( $\text{N}_2\text{O}$ ). The component of the CMR on which they act is electrophysiologic function. With several anesthetics, including barbiturates, isoflurane, sevoflurane, desflurane, propofol, and etomidate, increasing plasma concentrations cause progressive suppression of EEG activity and a concomitant reduction in the CMR. However, increasing the plasma level beyond what is required to first achieve suppression of the EEG results in no further depression of the CMR. The component of the CMR required for the maintenance of cellular integrity, the “housekeeping” component, is unaltered by anesthetic drugs (see Fig. 11.2).



**Fig. 11.4** Cerebral neurovascular coupling. Synaptic activity leads to glutamate release, activation of glutamatergic receptors, and calcium entry in neurons. This results in a release of arachidonic acid (AA), prostaglandins (PGs), and nitric oxide (NO). Adenosine and lactate are generated from metabolic activity. These factors all lead to vascular dilation. Glutamate also activates metabotropic glutamate receptors (*mGluR*) in astrocytes, causing intracellular calcium entry, phospholipase A<sub>2</sub> (*PLA*<sub>2</sub>) activation, release of AA and epoxyeicosatrienoic (EET) acid and prostaglandin E<sub>2</sub> (*PGE*<sub>2</sub>). The latter two AA metabolites contribute to dilation. By contrast, AA can also be metabolized to 20-hydroxy-eicosatetraenoic acid (20-HETE) in vascular smooth muscle. 20-HETE is a potent vascular constrictor. *cGMP*, Cyclic guanosine monophosphate; *eNOS*, endothelial nitric oxide synthase; *NMDAR*, N-methyl D-aspartate (NMDA) glutamate receptor; *nNOS*, neuronal nitric oxide synthase. (Modified from Attwell D, Buchan AM, Charpak S, et al. Glial and neuronal control of brain blood flow. *Nature*. 2010;468(7321):232–243.)

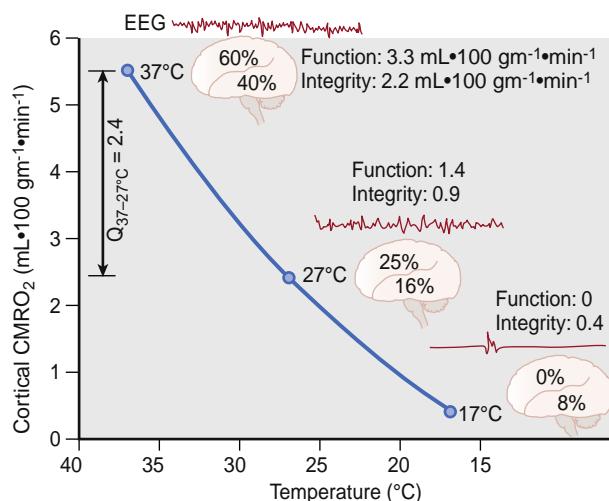
When the complete suppression of EEG is achieved, the cerebral metabolic rate of oxygen (CMRO<sub>2</sub>) is similar irrespective of the anesthetic agent used to achieve EEG suppression. Yet anesthetic-induced EEG suppression is not a single physiologic state and is influenced by the drug used to produce suppression. When barbiturates are administered to the point of EEG suppression, a uniform depression in the CBF and CMR occurs throughout the brain. When suppression occurs during the administration of isoflurane and sevoflurane, the relative reductions in the CMR and CBF are more intense in the neocortex than in other portions of the cerebrum. Electrophysiologic responsiveness also varies. Cortical somatosensory evoked responses to median nerve stimulation can be readily recorded at doses of thiopental far in excess of those required to cause complete suppression of the EEG but are difficult to elicit at concentrations of isoflurane associated with a burst-suppression pattern (~1.5 minimum alveolar concentration [MAC]). In addition, the EEG characteristics of the burst-suppression states that occur just before complete suppression differ among anesthetic drugs. These differences may be of some relevance to discussions of differences in the neuroprotective potential of drugs that can produce EEG suppression.

**Temperature.** The effects of hypothermia on the brain have been reviewed in detail.<sup>7</sup> The CMR decreases by 6% to 7% per degree Celsius of temperature reduction. In addition to anesthetic drugs, hypothermia can also cause complete suppression of the EEG (at approximately

18°C–20°C). However, in contrast to anesthetic drugs, temperature reduction beyond that at which EEG suppression first occurs does produce a further decrease in the CMR (Fig. 11.5). This decrease occurs because anesthetic drugs reduce only the component of the CMR associated with neuronal function, whereas hypothermia decreases the rate of energy utilization associated with both electrophysiologic function and the basal component related to the maintenance of cellular integrity. Mild hypothermia preferentially suppresses the basal component of the CMR. The CMRO<sub>2</sub> at 18°C is less than 10% of normothermic control values, which may explain the brain's tolerance for moderate periods of circulatory arrest at these and colder temperatures.

Hyperthermia has an opposite influence on cerebral physiologic function. Between 37°C and 42°C, CBF and CMR increase. However, above 42°C, a dramatic reduction in cerebral oxygen consumption occurs, an indication of a threshold for a toxic effect of hyperthermia that may occur as a result of protein (enzyme) denaturation.

**PaCO<sub>2</sub>.** CBF varies directly with PaCO<sub>2</sub> (Fig. 11.6A), especially within the range of physiologic variation of PaCO<sub>2</sub>. CBF changes 1 to 2 mL/100 g/min for each 1 mm Hg change in PaCO<sub>2</sub> around normal PaCO<sub>2</sub> values. This response is attenuated at a PaCO<sub>2</sub> less than 25 mm Hg. Under normal circumstances, the sensitivity of CBF to changes in PaCO<sub>2</sub> ( $\Delta$ CBF/ $\Delta$ PaCO<sub>2</sub>) is positively correlated with resting levels of CBF. Accordingly, anesthetic drugs that alter resting CBF cause changes in the response of the cerebral circulation

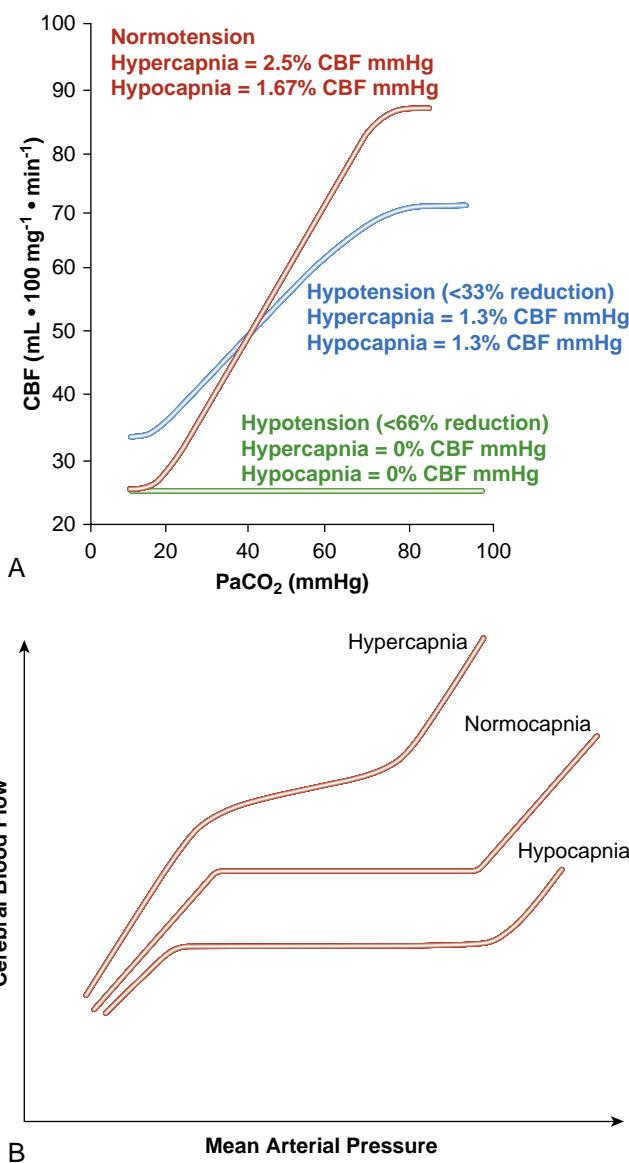


**Fig. 11.5** Effect of temperature reduction on the cerebral metabolic rate of oxygen ( $\text{CMRO}_2$ ) in the cortex. Hypothermia reduces both of the components of cerebral metabolic activity identified in Fig. 11.2—that associated with neuronal electrophysiologic activity (Function) and that associated with the maintenance of cellular homeostasis (Integrity). This is in contrast to anesthetics that alter only the functional component. The ratio of cerebral metabolic rate (CMR) at  $37^\circ\text{C}$  to that at  $27^\circ\text{C}$ , the Q<sub>10</sub> ratio, is shown in the graph. Note that the  $\text{CMRO}_2$  in the cortex (gray matter) is greater than global  $\text{CMRO}_2$ , considering the lower metabolic rate in white matter. *EEG*, Electroencephalogram. (Modified from Michenfelder JD. *Anesthesia and the brain: clinical, functional, metabolic, and vascular correlates*. New York: Churchill Livingstone; 1988.)

to  $\text{CO}_2$ . The magnitude of the reduction in CBF caused by hypocapnia is more intense when resting CBF is increased (as might occur during anesthesia with volatile agents). Conversely, when resting CBF is reduced, the magnitude of the hypocapnia-induced reduction in CBF is decreased slightly. It should be noted that  $\text{CO}_2$  responsiveness has been observed in normal brain during anesthesia with all the anesthetic drugs that have been studied.

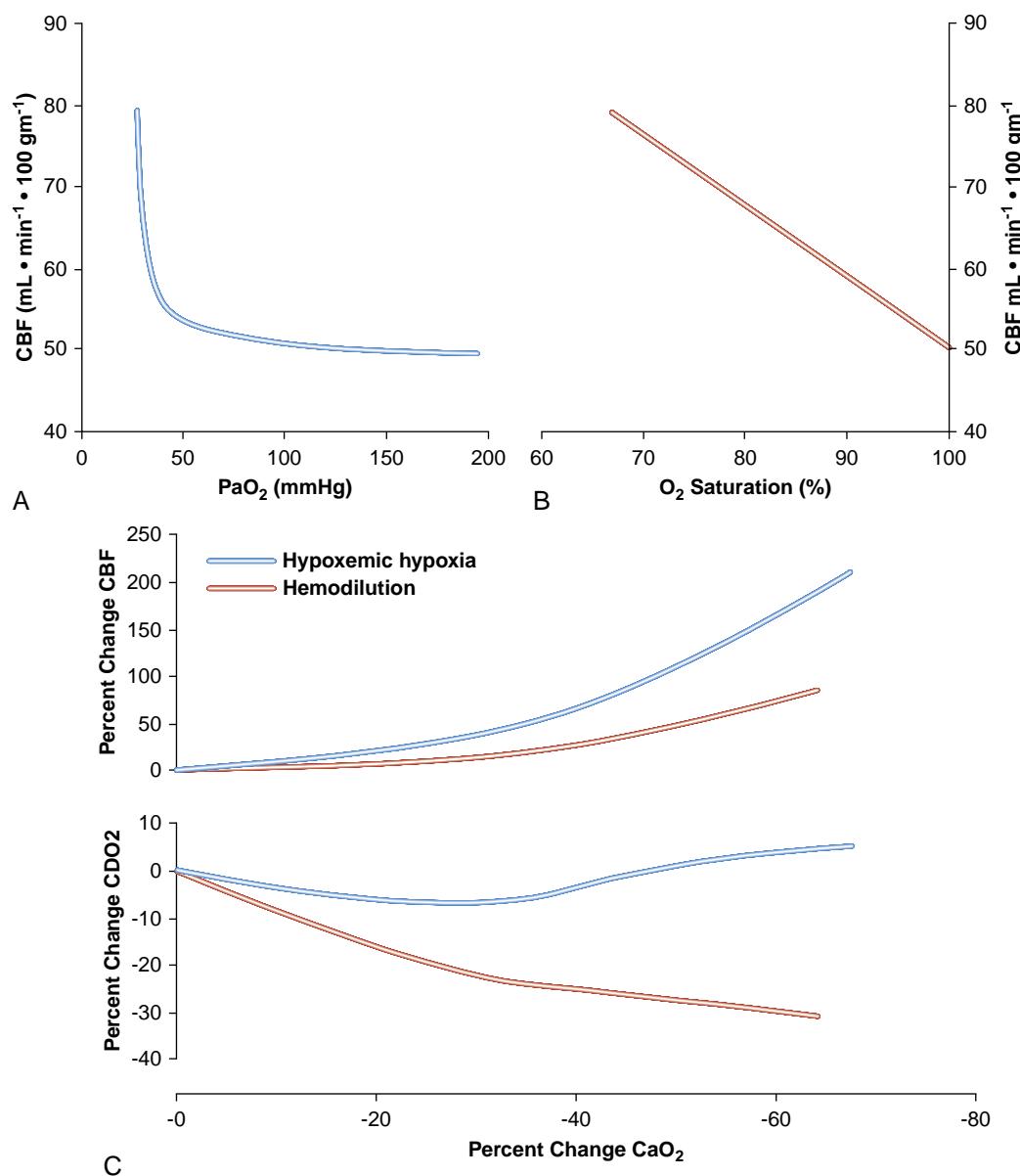
The role of MAP in the  $\text{CO}_2$  responsiveness of the cerebral circulation is further highlighted by the impact of modest and severe hypotension.<sup>8</sup> With the former, the increase in CBF attendant upon hypercarbia is significantly reduced, whereas hypocapnia-induced vasoconstriction is only modestly affected. When hypotension is severe, a cerebrovascular response to changes in  $\text{Paco}_2$  is not observed (Fig. 11.6A). The level of  $\text{Paco}_2$  also modulates cerebral autoregulation. With hypercarbia, cerebral autoregulatory response to hypertension is attenuated. By contrast, with the induction of hypocapnia, CBF is autoregulated over a wider MAP range (Fig 11.6B).

The changes in CBF caused by  $\text{Paco}_2$  are dependent on pH alterations in the extracellular fluid of the brain. NO, in particular NO of neuronal origin, is an important although not exclusive mediator of  $\text{CO}_2$ -induced vasodilation.<sup>10</sup> The vasodilatory response to hypercarbia is also mediated in part by prostaglandins. The changes in extracellular pH and CBF rapidly occur after  $\text{Paco}_2$  adjustments because  $\text{CO}_2$  freely diffuses across the cerebrovascular endothelium and the BBB. In contrast with *respiratory* acidosis, acute systemic *metabolic* acidosis has little immediate effect on CBF because the BBB excludes  $\text{H}^+$  from the perivascular space. The CBF changes in response to alterations in  $\text{Paco}_2$



**Fig. 11.6** *A*, Relationship between cerebral blood flow (CBF) and partial pressure of carbon dioxide ( $\text{Paco}_2$ ). CBF increases linearly with increases in arterial  $\text{Paco}_2$ . Below a  $\text{Paco}_2$  of 25 mm Hg, further reduction in CBF is limited. Similarly, the increase in CBF above a  $\text{Paco}_2$  of approximately 75 to 80 mm Hg is also attenuated. The cerebrovascular responsiveness to  $\text{Paco}_2$  is influenced significantly by blood pressure. With moderate hypotension (mean arterial pressure [MAP] reduction of <33%), the cerebrovascular responsiveness to changes in  $\text{Paco}_2$  is attenuated significantly. With severe hypotension (MAP reduction of approximately 66%),  $\text{CO}_2$  responsiveness is abolished. *B*, The effect of  $\text{Paco}_2$  variation on cerebral autoregulation. Hypercarbia induces cerebral vasodilation and, consequently, the autoregulatory response to hypertension is less effective. By contrast, hypocapnia results in greater CBF autoregulation over a wider MAP variation. (Modified from Willie<sup>8</sup> and Richards<sup>9</sup>.)

rapidly occur, but they are not sustained. Despite the maintenance of an increased arterial pH, CBF returns toward normal over a period of 6 to 8 hours because the pH of CSF gradually returns to normal levels as a result of extrusion of bicarbonate (see Fig. 57.6). Consequently, a patient who has had a sustained period of hyperventilation or hypoventilation deserves special consideration. Acute restoration of a normal  $\text{Paco}_2$  value will result in a significant CSF acidosis (after hypocapnia) or alkalosis (after hypercapnia). The



**Fig. 11.7** (A) Relationship between cerebral blood flow (CBF) and partial pressure of oxygen ( $\text{PaO}_2$ ). Between the range of 60 and 200 mm Hg,  $\text{PaO}_2$  has little impact on CBF. A reduction in  $\text{PaO}_2$  to less than 60 mm Hg results in hemoglobin desaturation. There is significant cerebral vasodilation and a marked increase in CBF. (B) The relationship between hemoglobin saturation and CBF is inversely linear, with a gradual increase in CBF as saturation is decreased. (C) The impact of a reduction in cerebral oxygen delivery ( $\text{CDO}_2$ ), either by hypoxic hypoxia or by hemodilution, is depicted. CBF increases significantly either with hypoxia or hemodilution; however, the CBF response is much greater with hypoxia (upper panel). The total cerebral oxygen delivery is better maintained with hypoxia than hemodilution at a comparable level of arterial oxygen content ( $\text{CaO}_2$ ) because of the greater CBF increase that occurs with the former. (Modified from Hoiland et al.<sup>11</sup> and Todd et al.<sup>354,355</sup>.)

former results in increased CBF with a concomitant increase in ICP that depends on the prevailing intracranial compliance. The latter conveys a theoretic risk for ischemia.

**PaO<sub>2</sub>.** Changes in  $\text{PaO}_2$  from 60 to more than 300 mm Hg have little influence on CBF. A reduction in  $\text{PaO}_2$  below 60 mm Hg rapidly increases CBF (Fig. 11.7A). Below a  $\text{PaO}_2$  of 60 mm Hg, there is a rapid reduction in oxyhemoglobin saturation. The relationship between oxyhemoglobin saturation, as evaluated by pulse oximetry, and CBF is inversely linear (see Fig. 11.7B). The mechanisms mediating cerebral vasodilation during hypoxia may include neurogenic effects initiated by peripheral and neuraxial

chemoreceptors, as well as local humoral influences. A reduction in arterial oxygen content, and therefore cerebral oxygen delivery, can be achieved either by a reduction in  $\text{PaO}_2$  (hypoxic hypoxia) or by a reduction in hemoglobin concentration (anemia, hemodilution). Both hemodilution and hypoxic hypoxia lead to cerebral vasodilation and an increase in CBF. Of the two variables, however, hypoxic hypoxia is a far more potent variable in CBF augmentation than hemodilution. Cerebral oxygen delivery is better maintained during hypoxia when arterial content is equivalently reduced by hypoxia or hemodilution (see Fig. 11.7C). Deoxyhemoglobin plays a central role in hypoxia-induced increases in CBF by causing the release of NO and

its metabolites, as well as ATP.<sup>11</sup> Hypoxia-induced opening of ATP-dependent K<sup>+</sup> channels in vascular smooth muscle leads to hyperpolarization and vasodilation. The rostral ventrolateral medulla (RVLM) serves as an oxygen sensor within the brain. Stimulation of the RVM by hypoxia results in an increase in CBF (but not CMR), and lesions of the RVLM suppress the magnitude of the CBF response to hypoxia. The response to hypoxia is synergistic with the hyperemia produced by hypercapnia and acidosis. At high Pao<sub>2</sub> values, CBF modestly decreases. At 1 atmosphere of oxygen, CBF is reduced by approximately 12%.

## NEUROGENIC REGULATION OF CEREBRAL BLOOD FLOW

The cerebral vasculature is extensively innervated.<sup>12</sup> The density of innervation declines with vessel size, and the greatest neurogenic influence appears to be exerted on larger cerebral arteries. This innervation includes cholinergic (parasympathetic and nonparasympathetic), adrenergic (sympathetic and nonsympathetic), serotonergic, and VIPergic systems of extraaxial and intraaxial origin. An extracranial sympathetic influence via the superior cervical ganglion, as well as parasympathetic innervation via the sphenopalatine ganglion, certainly exists in animals. The intraaxial pathways likely result from innervation arising from several nuclei, including the locus coeruleus, the fastigial nucleus, the dorsal raphe nucleus, and the basal magnocellular nucleus of Meynert. Evidence of the functional significance of neurogenic influences has been derived from studies of CBF autoregulation and ischemic injury. Hemorrhagic shock, a state of high sympathetic tone, results in less CBF at a given MAP than occurs when hypotension is produced with sympatholytic drugs. During shock, a sympathetically mediated vasoconstrictive effect shifts the lower end of the autoregulatory curve to the right. It is not clear what the relative contributions of humoral and neural mechanisms are to this phenomenon; however, a neurogenic component certainly exists because sympathetic denervation increases CBF during hemorrhagic shock. Moreover, sympathetic denervation produced by a blockade of the stellate ganglion can increase CBF in humans.<sup>13</sup> Activation of cerebral sympathetic innervation also shifts the ULA to the right and offers some protection against hypertension-induced increases in CBF (which can in certain circumstances lead to a breakdown of the BBB).<sup>8</sup> Experimental interventions that alter these neurogenic control pathways influence outcome after standardized ischemic insults, presumably by influences on vascular tone and therefore CBF. The nature and influence of such pathways in humans are not known, and their manipulation for the purposes of clinical management remains to be systematically investigated.

## EFFECTS OF BLOOD VISCOSITY ON CEREBRAL BLOOD FLOW

Blood viscosity can influence CBF. Hematocrit is the single most important determinant of blood viscosity.<sup>14</sup> In healthy humans, variation of the hematocrit within the normal range (33%–45%) probably results in only modest alterations in CBF. Beyond this range, changes are more

substantial. In anemia, cerebral vascular resistance is reduced and CBF increases. However, this may result not only from a reduction in viscosity but also as a compensatory response to reduced oxygen delivery.<sup>15</sup> Although arterial oxygen content can be reduced by both hypoxia and by hemodilution, the increase in CBF that accompanies hypoxia is of a greater magnitude than that by hemodilution induced reduction in oxygen delivery.<sup>11</sup> The effect of a reduction in viscosity on CBF is more important with focal cerebral ischemia, a condition in which vasodilation in response to impaired oxygen delivery is probably already maximal. In this situation, reducing viscosity by hemodilution increases CBF in the ischemic territory. In patients with focal cerebral ischemia, a hematocrit of 30% to 34% will result in optimal delivery of oxygen. However, manipulation of viscosity in patients with acute ischemic stroke is not of benefit in reducing the extent of cerebral injury. Therefore, viscosity is not a target of manipulation in patients at risk as a result of cerebral ischemia, with the possible exception of those with hematocrit values higher than 55%.

## CARDIAC OUTPUT

The conventional view of cerebral hemodynamics is that perfusion pressure (MAP or CPP) is the primary determinant of CBF and that the influence of cardiac output is limited. More recent data suggest that cardiac output impacts cerebral perfusion. In several investigations in which central blood volume was modulated, either reduced by application of lower body negative pressure, or increased by the infusion of fluid, a linear relationship between cardiac output and CBF, as measured as middle cerebral artery flow velocity (MCAfv) by transcranial Doppler, was clearly demonstrated.<sup>8,16–20</sup> An analysis of the pooled data from these investigations indicates that a reduction in cardiac output of approximately 30% leads to a decrease in CBF by about 10%.<sup>21</sup> In patients undergoing hip arthroplasty under hypotensive epidural anesthesia, the administration of epinephrine led to a maintenance of CBF even though the MAP was below the LLA.<sup>22</sup> Presumably, this maintenance of CBF was due to an epinephrine-induced increase in cardiac output. An association between CO and CBF has also been observed in acute stroke, subarachnoid hemorrhage-induced vasospasm, and sepsis. However, the CO–CBF relationship has not been demonstrated uniformly; in fact, augmentation of CO does not increase CBF in several disease states, including traumatic head injury, neurologic surgery, and cardiac surgery.<sup>21</sup> Collectively, the available data suggest that CO does influence CBF and that this effect may be of particular relevance in situations in which circulating volume is reduced and in shock states.

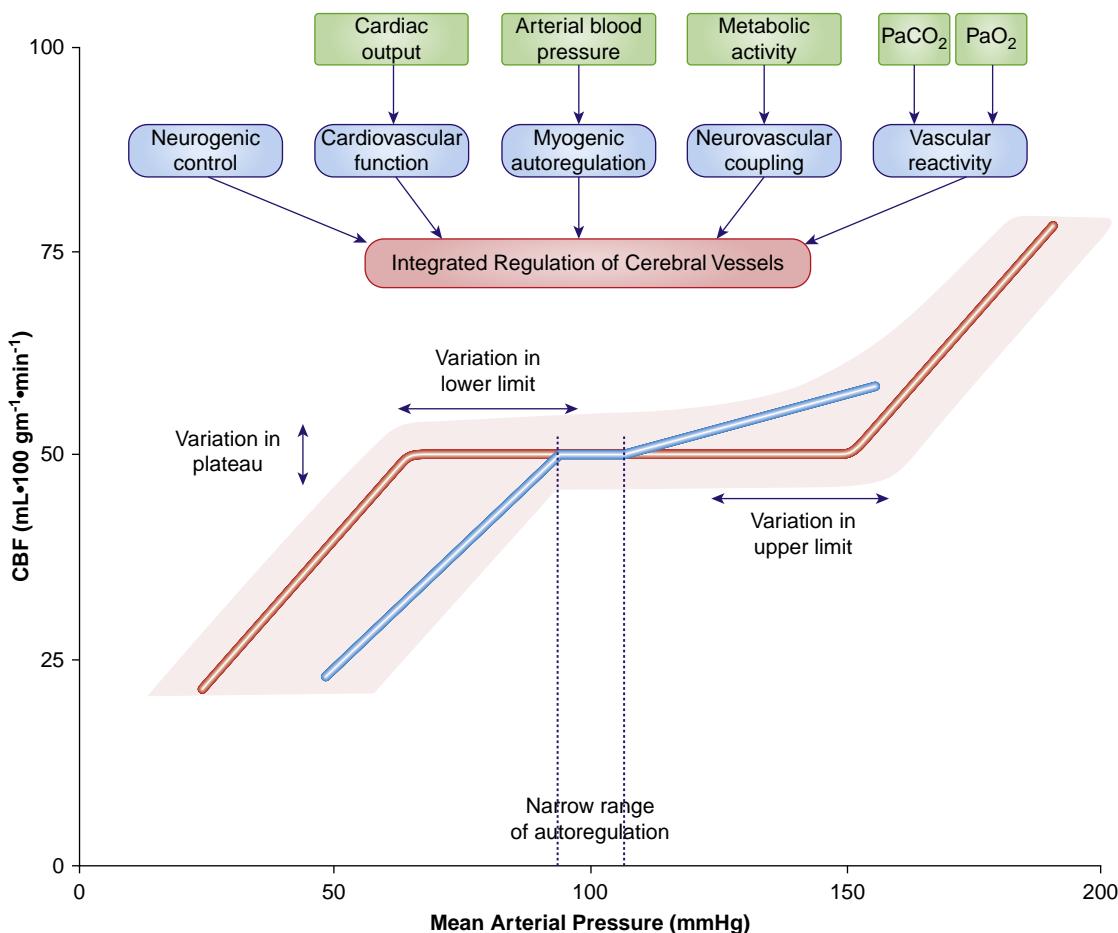
## AN INTEGRATED CONTEMPORARY VIEW OF CEREBRAL AUTOREGULATION

The conventional view of cerebral autoregulation is that CBF is held constant as MAP increases between the lower limit and ULA. The currently available data, however, indicate that this view is now outmoded and is in need of revision. As discussed previously, CBF and the cerebral vasculature are influenced by a variety of variables. Clearly, MAP (perfusion pressure) is a major determinant of CBF. Cardiac output is

increasingly being recognized as an important determinant of CBF. Cardiac output in turn is dependent on adequate circulatory volume, cardiac preload, contractility, afterload, and heart rate and rhythm. The presence of cardiovascular disease, in particular congestive heart failure, will limit the capacity of autoregulatory mechanisms to maintain CBF in response to hypotension. Arterial blood gas tensions affect vasomotor tone, and both hypercarbia and hypoxia attenuate autoregulation. The contribution of the sympathetic nervous system is of importance in the cerebrovascular response to hypertension. At the same time, sympathetic nerves reduce the vasodilatory capacity of the cerebral vessels during hypotension. A variety of medications can impact autoregulation, either through modulation of sympathetic nervous system activity ( $\beta$ -antagonists,  $\alpha_2$ -agonists) or by direct reduction of vasomotor tone (calcium channel antagonists, nitrates, angiotensin receptor blockers, angiotensin converting enzyme [ACE] inhibitors). Anesthetics modulate autoregulation by a number of means, including suppression of metabolism, alteration of

neurovascular coupling to a higher flow–metabolism ratio, suppression of autonomic neural activity, and by direct effect on cerebral vasomotor tone, and alteration of cardiac function and systemic circulatory tone.

Cerebrovascular tone and CBF are therefore under the control of a complex regulatory system (Fig. 11.8). Given the multitude of factors that determine the capacity of the cerebral circulation to respond to changes in perfusion pressure, the premise that cerebral autoregulation is static is now untenable. Rather, cerebral autoregulation should be viewed as a dynamic process and that the morphologic form of the autoregulatory curve is the result of the integration of all the variables that affect cerebrovascular tone in an interdependent manner.<sup>8,23</sup> Therefore, a continuum of vascular responsiveness in both the lower and upper limits and in the plateau probably exists as the ability of the cerebrovascular bed to dilate or constrict is exhausted. In a review of the available data from investigations in humans, the range of pressures that defined the LLA spanned from 33 mm Hg to as high as 108 mm Hg.<sup>5</sup>



**Fig. 11.8** Integrative regulation of cerebral blood flow (CBF). The conventional view of cerebral autoregulation is that CBF is maintained constant with a variation in mean arterial pressure (MAP) of 65 to 150 mm Hg. A more contemporary view is that cerebral autoregulation is a dynamic process that is under the influence of a number of variables including myogenic autoregulation, neurovascular coupling, arterial  $\text{CO}_2$  and  $\text{O}_2$  tensions, autonomic (neurogenic) activity, and cardiovascular function. Anesthetic agents in particular affect autoregulation at multiple levels: suppression of metabolism, alteration in arterial blood gas tensions, direct cerebral vasodilation, suppression of autonomic activity, and modulation of cardiovascular function. Therefore, CBF at any given moment is a product of the composite of these variables. There is considerable variation in lower and upper limits as well as the plateau of the autoregulatory curve. The conventional autoregulatory curve is depicted in red. The red shaded area represents the range of variation in CBF. The autoregulatory curve depicted in blue was derived from 48 healthy human subjects. In that group, the lower limit of autoregulation was approximately 90 mm Hg and the range over which CBF remained relatively constant was only 10 mm Hg.  $\text{PaCO}_2$ , Arterial partial pressure of carbon dioxide;  $\text{PaO}_2$ , arterial partial pressure of oxygen. (Modified from Tan et al.,<sup>24</sup> Willie et al.,<sup>8</sup> and Meng and Gelb.<sup>23</sup>)

In healthy humans subjected to lower body negative pressure to reduce central blood volume and to reduce blood pressure, the autoregulatory plateau spanned a range of only 10 mm Hg ( $\pm 5$  mm Hg from baseline)<sup>24</sup> as opposed to a range of 100 mm Hg in the once conventional representations of autoregulation. Above and below this narrow plateau, CBF was pressure passive. Even within this narrow plateau, a modest increase in CBF with increases in blood pressure is observable—that is, the plateau is not flat. The slope of the percentage change in MAP to percentage change in CBF relationship has been demonstrated to be  $0.81 \pm 0.77$  with induction of hypotension and  $0.21 \pm 0.47$  with the induction of hypertension. These data are consistent with the premise that the capacity of the cerebral circulation to adapt to increases in blood pressure is considerably greater than adaptation to hypotension.<sup>8</sup> Based on these more recent observations, the conventional view of autoregulation is probably not applicable to most subjects, and a revision of the framework of cerebral circulatory control along the lines of recent data is needed.<sup>8,23</sup> In this respect, it is the view of the authors that cerebral autoregulation should be accurately represented by a family of autoregulatory curves rather than a single static curve (see Fig. 11.8). In these dynamic autoregulatory curves, there is considerable heterogeneity in the LLA and ULA, as well as in the limits and slope of the plateau.

**Clinical implications:** Maintenance of cerebral perfusion is essential, and identification of a target range of MAP in individual patients is a key part of anesthetic management. Given the substantial variability in cerebral autoregulatory capacity, it may be difficult to identify the target range based on an LLA in most patients. Selection of the target range based on the baseline pressure, after due consideration of comorbid conditions that may impact cerebrovascular and cardiovascular performance, may be preferable. In attempts to maintain adequate perfusion pressure, the traditional approach of systemic vasoconstriction, for example with  $\alpha_1$ -agonists, is reasonable. However, the adequate maintenance of circulatory volume and of cardiac output should also be considered; administration of agents that can also increase cardiac output may be of value. This may be of particular relevance in patients with compromised cardiac function.

## VASOACTIVE DRUGS

Many drugs with intrinsic vascular effects are used in contemporary anesthetic practice, including both anesthetic drugs and numerous vasoactive drugs specifically used for hemodynamic manipulation. This section deals with the latter. The actions of anesthetics are discussed in the “Effects of Anesthetics on Cerebral Blood Flow and Cerebral Metabolic Rate” section.

### Systemic Vasodilators

Most drugs used to induce hypotension, including sodium nitroprusside, nitroglycerin, hydralazine, adenosine, and calcium channel blockers (CCBs), also cause cerebral vasodilation. As a result, CBF either increases or is maintained at pre-hypotensive levels. In addition, when hypotension

is induced with a cerebral vasodilator, CBF is maintained at lower MAP values than when induced by either hemorrhage or a noncerebral vasodilator. In contrast to direct vasodilators, the ACE inhibitor enalapril does not have any significant effect on CBF. Anesthetics that simultaneously vasodilate the cerebral circulation cause increases in cerebral blood volume (CBV) with the potential to increase ICP. The effects of these anesthetics on ICP are less dramatic when hypotension is slowly induced, which probably reflects the more effective interplay of compensatory mechanisms (i.e., shifts in CSF and venous blood) when changes occur more slowly.

### Catecholamine Agonists and Antagonists

Numerous drugs with agonist and antagonist activity at catecholamine receptors ( $\alpha_1$ ,  $\alpha_2$ ,  $\beta_1$ ,  $\beta_2$ , and dopamine) are in common use. The effects of these vasoactive drugs on cerebral physiology are dependent on basal arterial blood pressure, the magnitude of the drug-induced arterial blood pressure changes, the status of the autoregulation mechanism, and the status of the BBB. A drug may have direct effects on cerebral vascular smooth muscle or indirect effects mediated by the cerebral autoregulatory response to changes in systemic blood pressure (or both types of effects). When autoregulation is preserved, increases in systemic pressure should increase CBF if basal blood pressure is outside the limits of autoregulation. When basal pressure is within the normal autoregulatory range, an increase in systemic arterial pressure does not significantly affect CBF because the normal autoregulatory response to a rising MAP entails cerebral vasoconstriction (i.e., an increase in cerebral vascular resistance) to maintain a constant CBF. When autoregulation is defective, CBF will vary in direct relation to arterial pressure. The information in the following paragraphs and in Table 11.2 emphasizes data obtained from investigations of vasopressors in intact preparations, and gives priority to the results obtained in humans and higher primates.

**$\alpha_1$ -Agonists.** Will the administration of  $\alpha_1$ -agonists (phenylephrine, norepinephrine) reduce CBF?

Studies in humans and nonhuman primates do not confirm this concern. Intracarotid infusions of norepinephrine in doses that significantly increase the MAP result in no change in CBF. Norepinephrine can increase CBF, but such increases might occur if autoregulation were defective or its limit exceeded.  $\beta$ -Mimetic drugs (norepinephrine has  $\beta_1$  activity) may cause activation of cerebral metabolism<sup>25</sup> with a coupled increase in CBF. This effect is more apparent when these drugs can gain greater access to the brain parenchyma via a defective BBB (see Table 11.2). Administration of phenylephrine to patients undergoing cardiopulmonary bypass does not decrease CBF. In spinal cord-injured patients with relative hypotension, the administration of the  $\alpha_1$ -agonist midodrine increased perfusion pressure and increased flow velocity in the middle cerebral artery (MCA) and the posterior cerebral artery.<sup>26</sup> In healthy patients,<sup>27</sup> and in those undergoing surgery in the beach chair position,<sup>28</sup> the administration of phenylephrine maintains or augments MCAf. Collectively, these data suggest that norepinephrine and phenylephrine maintain cerebral perfusion.

**TABLE 11.2** Best Estimates of the Influence of Pure Catecholamine Receptor Agonists and Specific Pressor Substances on Cerebral Blood Flow and Cerebral Metabolic Rate

Agonist	Cerebral Blood Flow	Cerebral Metabolic Rate
<b>PURE</b>		
$\alpha_1$	0/–	0
$\alpha_2$	–	–
$\beta$	+	+
$\beta$ (BBB open)	+++	+++
Dopamine	++	0
Dopamine (high dose)	–	?0
Fenoldopam	–	?0
<b>MIXED</b>		
Norepinephrine	0/–	0/+
Norepinephrine (BBB open)	+	+
Epinephrine	+	+
Epinephrine (BBB open)	+++	+++

The number of symbols indicates the magnitude of the effect.

Where species differences occurred, data from primates were given preference. See text for complete discussion.

BBB, Blood-brain barrier; +, increase; –, decrease; 0, no effect.

The traditional view that CBF can be maintained by the administration of  $\alpha_1$ -agonists without any adverse effect on cerebral oxygenation has been challenged. In anesthetized patients,<sup>29–31</sup> phenylephrine administration by bolus modestly reduced regional cerebral oxygen saturation (rSO<sub>2</sub>), measured by near-infrared oximetry. Ephedrine, although increasing arterial blood pressure to a similar extent as phenylephrine, did not reduce rSO<sub>2</sub>, presumably because of its ability to maintain cardiac output. In human volunteers, a norepinephrine-induced increase in arterial blood pressure slightly reduced MCAf<sub>v</sub> and cerebral oxygen saturation (ScO<sub>2</sub>) and SjVO<sub>2</sub>.<sup>32</sup> By contrast, although phenylephrine decreased rSO<sub>2</sub>, MCAf<sub>v</sub> was increased and SjVO<sub>2</sub> was unchanged.<sup>33</sup> These data have led to the question of whether phenylephrine and norepinephrine administration negatively impact cerebral oxygenation. Several factors argue against this possibility.<sup>34</sup> The first concern is methodology. Near-infrared spectroscopy (NIRS) measures oxygenated and deoxygenated blood in a defined region of brain and is a composite of arterial, capillary, and venous blood. Vasopressors affect both arterial and venous tone. Even a minor change in the volume of arterial and venous volumes within the region of the brain can affect the rSO<sub>2</sub> measurement. Moreover, extracranial contamination is a significant component of the rSO<sub>2</sub> values reported by the currently available NIRS monitors.<sup>35</sup> This contamination is more important than the slight reduction in ScO<sub>2</sub> observed in these investigations. In the absence of direct measurement of brain tissue oxygenation, a modest reduction in ScO<sub>2</sub> in the face of increasing arterial blood pressure cannot be taken as evidence of impairment of cerebral oxygenation. In addition, phenylephrine did not decrease SjVO<sub>2</sub>, a more global measurement of cerebral oxygenation. Although norepinephrine decreased SjVO<sub>2</sub> by approximately 3% (a mild reduction at best), its administration has been previously shown to

increase the CMRO<sub>2</sub>. Finally, the minor reduction in rSO<sub>2</sub> effected by phenylephrine is no longer apparent when an increase in the CMRO<sub>2</sub> is concurrent. Phenylephrine apparently does not prevent an increase in CBF when such an increase is warranted by increased brain metabolism.

These studies were conducted in patients with a normal central nervous system (CNS). Although unlikely, the concern is that  $\alpha_1$ -agonists might reduce cerebral perfusion in the injured brain. In patients with a head injury, the administration of phenylephrine increased CPP and did not reduce regional CBF.<sup>36</sup> Transient changes may occur in CBF and rSO<sub>2</sub> (on the order of 2–5 minutes) in response to bolus doses of phenylephrine; however, with a continuous infusion,  $\alpha_1$ -agonists have little direct influence on CBF and cerebral oxygenation in humans.<sup>34</sup> Thus maintenance of CPP with these vasopressors does not have an adverse effect on the brain.

**$\alpha_2$ -Agonists.**  $\alpha_2$ -Agonists have both analgesic and sedative effects. This class of drugs includes dexmedetomidine and clonidine, with the latter being a significantly less specific and less potent  $\alpha_2$ -agonist. Two investigations in human volunteers have confirmed the ability of dexmedetomidine to decrease CBF. Dexmedetomidine dose-dependently decreased MCAf<sub>v</sub>, with the maximum reduction being approximately 25%.<sup>37</sup> Dexmedetomidine (1  $\mu$ g/kg loading dose and infusion at either 0.2 or 0.6  $\mu$ g/kg/hr) decreased CBF by approximately 30%<sup>38</sup> in healthy human volunteers. In both these investigations, the CMR was not measured; whether the reduction in CBF was due to a direct vasoconstrictor activity of dexmedetomidine or to suppression of the CMR with a corresponding reduction in CBF is not clear. In a more recent study of dexmedetomidine during which both MCAf<sub>v</sub> and the CMR were measured in healthy humans, dexmedetomidine decreased MCAf<sub>v</sub> in parallel with a reduction in the CMR.<sup>39</sup> Similarly, in healthy patients<sup>40</sup> and those with

traumatic brain injury<sup>41</sup> undergoing sedation with dexmedetomidine, the reduction in CBF was matched by a parallel reduction in CMR. Thus the effects of dexmedetomidine on CBF were primarily mediated by its ability to suppress the CMR; the reduction in CBF is commensurate with the reduction in CMR, and there is no evidence that dexmedetomidine causes cerebral ischemia. However, the well-known effect of dexmedetomidine in decreasing arterial blood pressure merits careful consideration if used in patients who are critically dependent on collateral perfusion pressure, especially in the recovery phase of anesthetic.

**β-Agonists.** β-receptor agonists, in small doses, have little direct effect on the cerebral vasculature. In larger doses and in association with physiologic stress, they can cause an increase in the CMR with an accompanying increase in CBF. The β<sub>1</sub>-receptor is probably the mediator of these effects. In doses that do not result in substantial changes in the MAP, intracarotid epinephrine does not change CBF in nonanesthetized humans. However, with larger doses that lead to an increase in the MAP, both CBF and CMRO<sub>2</sub> can increase by approximately 20%. A recent investigation has demonstrated that the administration of epinephrine in patients undergoing surgery under hypotensive epidural anesthesia can increase MCAfV, presumably by augmenting cardiac output (as discussed previously).<sup>22</sup>

Dobutamine can increase CBF and CMR by 20% and 30%, respectively. Dobutamine can increase CBF independent of its effect on blood pressure; the increase in CBF has been attributed to the augmentation of cardiac output by dobutamine.<sup>36</sup>

Evidence suggests that a defect in the BBB enhances the effect of β-agonists.<sup>42</sup> Intracarotid norepinephrine, which does not normally affect CBF and CMR, increases CBF and CMR when BBB permeability is increased with hypertonic drugs. Epinephrine caused an elevation in the CMRO<sub>2</sub>, but only when the BBB was made permeable.<sup>42</sup> These observations beg the interpretation that β-agonists will increase CBF and CMR *only* when the BBB is injured. However, when epinephrine was given in doses that did not significantly increase the MAP, increases in CBF and CMR occurred. Accordingly, BBB injury may exaggerate but is not a necessary condition in humans for the occurrence of β-mediated increases in CBF and CMR.

**β-Blockers.** β-Adrenergic blockers either reduce or have no effect on CBF and CMR. In two investigations in humans, propranolol, 5 mg intravenously,<sup>43</sup> and labetalol, 0.75 mg/kg intravenously,<sup>44</sup> had no effect on CBF and cerebral blood flow velocity (CBFV), respectively. Modest reductions in CBF occur after the administration of labetalol to patients undergoing craniotomy who become hypertensive during emergence from anesthesia. Esmolol shortens seizures induced by electroconvulsive therapy (ECT), which suggests that esmolol does cross the normal BBB. Catecholamine levels at the time of β-blocker administration or the status of the BBB (or both) may influence the effect of these drugs. β-Adrenergic blockers are unlikely to have adverse effects on patients with intracranial pathology, other than effects secondary to changes in perfusion pressure.

**Dopaminergic agents.** Dopamine can be used for the treatment of hemodynamic dysfunction. It also augments the function of the normal cardiovascular system when an increase in the MAP is desired as an adjunct to the treatment of focal cerebral ischemia, especially in the setting of vasospasm. Nonetheless, its effects on CBF and CMR have not been defined with certainty. The likely predominant effect of dopamine in the normal cerebral vasculature, when administered in small doses, is probably slight vasodilation with a minimal change in the CMR.<sup>45</sup> Increased CMR in discrete regions of the brain, such as the choroid plexus and basal ganglia, can occur. However, overall cortical blood flow is not influenced. Vasoconstriction of the cerebral circulation is not observed even when dopamine is administered in doses of up to 100 µg/kg/min.<sup>45</sup> Fenoldopam is a dopamine agonist with activity at the DA<sub>1</sub>-receptor and α<sub>2</sub>-receptor. The administration of fenoldopam leads to systemic vasodilation and a decrease in arterial blood pressure. In humans, fenoldopam decreased systemic blood pressure to a level that was above the LLA; however, a modest (≈15%) reduction was observed in CBF that did not increase to normal levels when systemic blood pressure was supported.<sup>46</sup> The reason for the reduction of CBF is not clear.

**Calcium channel blockers.** CCBs are frequently used to treat acute hypertension in the neurologically injured patient population. Cerebral vessels are richly endowed with calcium channels, in particular the L-type calcium channel. CCBs therefore induce vasodilation of the pial and cerebral arteries. In healthy humans, intravenous administration of nimodipine does not change CBF; however, when the slight decrease in MAP and changes in PacO<sub>2</sub> are taken into consideration, CBF increased by approximately 5% to 10%.<sup>47</sup> CMR and CO<sub>2</sub> reactivity are maintained. Nimodipine in human subjects does, however, blunt autoregulation moderately.<sup>48</sup> Intraarterial nimodipine for the treatment of cerebral vasospasm after subarachnoid hemorrhage increased regional CBF significantly provided MAP was maintained, indicating that nimodipine is a cerebral vasodilator.<sup>49</sup>

Nicardipine is perhaps the most commonly used CCB for perioperative blood pressure control because of its short half-life and easy titratability. Nicardipine is a modest cerebral vasodilator and has repeatedly been shown to increase CBF or CBFV while reducing systemic MAP. Cerebral CO<sub>2</sub> reactivity appears to be well preserved in the presence of nicardipine.<sup>50,51</sup>

Clevidipine is a third generation dihydropyridine CCB that has an ultrashort half-life because it undergoes rapid esterase-mediated metabolism. Its use in both the cardiac and neurologic patient populations has increased significantly given its rapid titratability. In healthy volunteers, clevidipine did not increase MCAfV. However, a substantial reduction in MAP of approximately 25% occurred.<sup>52</sup> The lack of increase in MCAfV in the face of hypotension suggests that clevidipine is a cerebral vasodilator and, like nicardipine, probably attenuates autoregulation to a moderate extent. CO<sub>2</sub> reactivity is preserved.

The available data indicate that CCBs are moderate cerebral vasodilators. Their net impact on CBF is therefore

dependent on the extent of systemic vasodilation and MAP. When MAP is maintained, increases in CBF should be expected.

### Angiotensin II, Angiotensin-Converting Enzyme Inhibitors, and Angiotensin Receptor Antagonists

There has been a renaissance of the use of angiotensin II (AII) for the treatment of vasodilatory shock that is refractory to conventional vasopressor agents. In these shock states, AII increased MAP and reduced the need for other vasopressors including norepinephrine and vasopressin. The acute effect of AII on the cerebral circulation has received only modest attention. Acute administration of AII increases cerebral microvascular constriction without affecting CBF; this effect precedes its impact on blood pressure. However, AII attenuates regional hyperemia that occurs with an increase in regional metabolism, thereby adversely impacting neurovascular coupling.<sup>53</sup> Given that CBF is maintained in the face of increased blood pressure, autoregulation and CO<sub>2</sub> responsiveness appear to be maintained.<sup>54</sup>

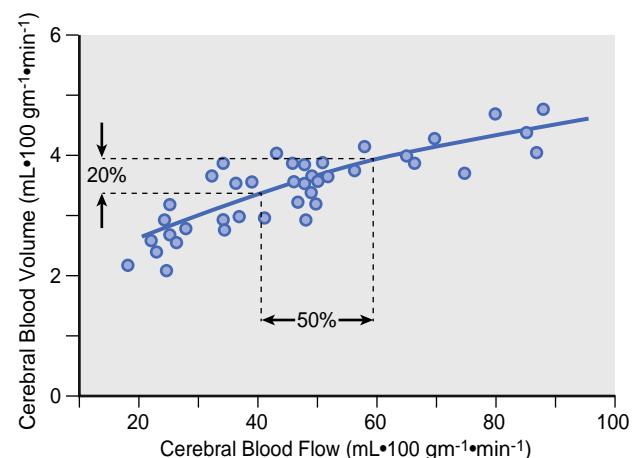
Both ACE inhibitors and angiotensin-receptor blockers (ARBs) are commonly used to treat hypertension. In the surgical setting and in the neurocritical care unit, these drugs are administered to control arterial blood pressure acutely. ACE inhibitors and ARBs reduce arterial blood pressure when hypertension is present. However, they do not affect resting CBF, and autoregulation is maintained.<sup>55</sup> However, acute administration of ACE inhibitors and ARBs decreases the LLA (left shift of the autoregulatory curve in experimental animals);<sup>56</sup> the significance of this finding in humans is not clear. In patients with acute stroke, ACE inhibitors and ARBs reduce arterial blood pressure but do not acutely affect CBF.<sup>57,58</sup> Apparently, these drugs do not reduce CBF when arterial blood pressure is modestly decreased.

### AGE

The loss of neurons is progressive in the normally aging brain from young adulthood to advanced age. There is approximately 10% neuronal loss in healthy aged brain.<sup>59</sup> The loss of myelinated fibers results in reduced white matter volume.<sup>60</sup> By contrast, the loss of synapses in the aged brain is considerably greater. The majority of excitatory synapses in the brain are on dendritic spines. Dendrite branching and volume decrease progressively, and the number of dendritic spines is reduced by approximately 25% to 35%.<sup>60</sup> Comitant with the loss of neuropil, both CBF and CMRO<sub>2</sub> decrease by 15% to 20% at the age of 80 years.<sup>61</sup> Cerebral circulatory responsiveness to changes in Paco<sub>2</sub> and to hypoxia are slightly reduced in the healthy aged brain.<sup>4,62</sup>

## Effects of Anesthetics on Cerebral Blood Flow and Cerebral Metabolic Rate

This section discusses the effects of anesthetic drugs on CBF and CMR. It includes limited mention of the influences on autoregulation, CO<sub>2</sub> responsiveness, and CBV. Effects on

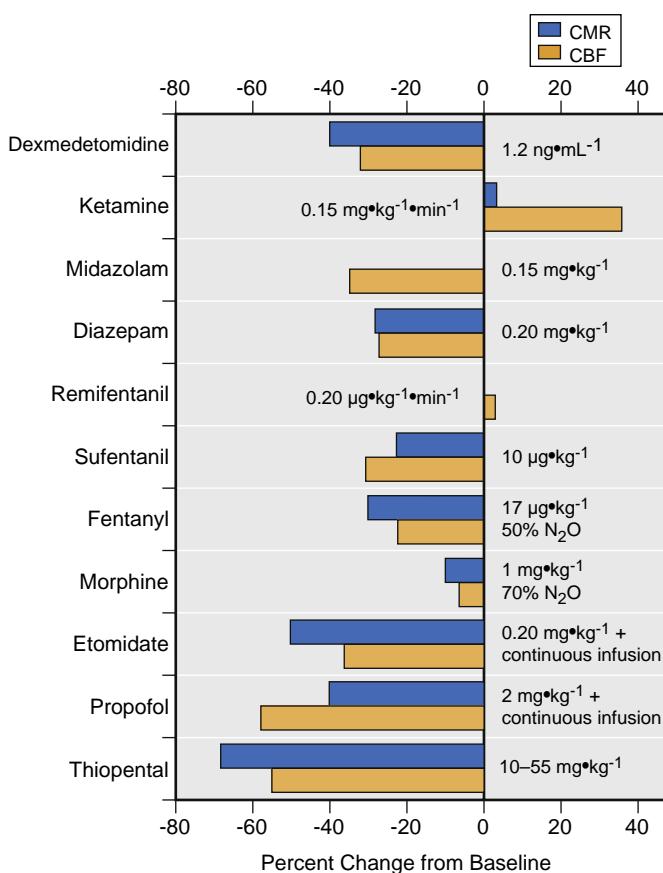


**Fig. 11.9** Relationship between cerebral blood flow (CBF) and cerebral blood volume (CBV). Although a linear relationship exists between CBF and CBV, the magnitude of the change in CBV for a given change in CBF is considerably less. An increase in CBF of 50% results in a change in CBV of only 20%.

CSF dynamics, the BBB, and epileptogenesis are discussed later in the chapter.

In the practice of neuroanesthesia, the manner in which anesthetic drugs and techniques influence CBF receives prime attention. The rationale is twofold. First, the delivery of energy substrates is dependent on CBF, and modest alterations in CBF can influence neuronal outcome substantially in the setting of ischemia. Second, control and manipulation of CBF are central to the management of ICP because as CBF varies in response to vasoconstrictor-vasodilator influences, CBV varies with it.<sup>63</sup> With respect to ICP, CBV is the more critical variable. In the normal brain, CBV is approximately 5 mL/100 g of brain, and over a Paco<sub>2</sub> range of approximately 25 to 70 mm Hg, CBV changes by approximately 0.049 mL/100 g for each 1 mm Hg change in Paco<sub>2</sub>. In an adult brain weighing approximately 1400 g, this change can amount to 20 mL in total CBV for a Paco<sub>2</sub> range of 25 to 55 mm Hg. Because CBV is more difficult to measure than CBF few data exist, especially in humans.

Although CBV and CBF usually vary in parallel, the magnitude of change in CBV is less than the magnitude of change in CBF (Fig. 11.9). In addition, CBV and CBF vary independently under some circumstances. During cerebral ischemia, for example, CBV increases, whereas CBF is reduced significantly. Autoregulation normally serves to prevent MAP-related increases in CBV. In fact, as the cerebral circulation constricts to maintain a constant CBF in the face of an increasing MAP, CBV actually decreases. When autoregulation is impaired or its upper limit ( $\approx$ 150 mm Hg) is exceeded, CBF and CBV then increase in parallel as arterial blood pressure increases (see Fig. 11.8). A decreasing MAP results in a progressive increase in CBV as the cerebral circulation dilates to maintain constant flow, and exaggerated increases in CBV occur as the MAP decreases to less than the LLA. In normal subjects, the initial increases in CBV do not increase ICP because there is latitude for compensatory adjustments by other intracranial compartments (e.g., translocation of venous blood and CSF to extracerebral vessels and the spinal CSF space, respectively). When



**Fig. 11.10** Changes in cerebral blood flow (CBF) and the cerebral metabolic rate of oxygen ( $\text{CMRO}_2$ ) caused by intravenous anesthetic drugs. The data are derived from human investigations and are presented as percent change from nonanesthetized control values. Dexmedetomidine CMR values were determined on a background of 0.5% isoflurane anesthesia (see the text for details). No data for the  $\text{CMRO}_2$  effects of midazolam in humans are available. CMR, Cerebral metabolic rate. (Data from references 25, 47–59.)

intracranial compliance\* is reduced, an increase in CBV can cause herniation or sufficiently reduce CPP to cause ischemia.

## INTRAVENOUS ANESTHETIC DRUGS

The action of most intravenous anesthetics leads to parallel reductions in CMR and CBF. Ketamine, which causes an increase in the CMR and CBF, is the exception. The effects of selected intravenous anesthetic drugs on human CBF are compared in Fig. 11.10.<sup>38,65–77</sup>

Intravenous anesthetics maintain neurovascular coupling, and consequently changes in CBF induced by intravenous anesthetics are largely the result of the effects on the CMR with parallel (coupled) changes in CBF. Intravenous anesthetics have direct effects on vascular tone. Barbiturates, for example, cause relaxation of isolated cerebral

\*Note a well-entrenched misuse of terminology.<sup>64</sup> The “compliance” curve that is commonly drawn to describe the ICP-volume relationship (see Fig. 57-3) actually depicts the relationship  $\Delta\text{P}/\Delta\text{V}$  (elastance) and not  $\Delta\text{V}/\Delta\text{P}$  (compliance). References to “reduced compliance” in this text would more correctly be rendered as “increased elastance.” However, because the existing literature most commonly uses the “compliance” terminology, the authors have left the misuse uncorrected herein.

vessels in vitro. However, *in vivo*, barbiturates suppress CMR, and the net effect at the point of EEG suppression is vasoconstriction and a substantial decrease in CBF.<sup>78</sup> In general, autoregulation and  $\text{CO}_2$  responsiveness are preserved during the administration of intravenous anesthetic drugs.

## Barbiturates

A dose-dependent reduction in CBF and CMR occurs with barbiturates. With the onset of anesthesia, both CBF and  $\text{CMRO}_2$  are reduced by approximately 30%. When large doses of thiopental cause complete EEG suppression, CBF and CMR are reduced by approximately 50% to 60%.<sup>78,79</sup> Further increases in the barbiturate dose have no additional effect on the CMR.<sup>78</sup> These observations suggest that the major effect of nontoxic doses of depressant anesthetics is a reduction in the component of cerebral metabolism that is linked to electrical brain function (e.g., neurophysiologic activity) with only minimal effects on the second component, which is related to cellular homeostasis (see Fig. 11.2).

Tolerance to the CBF and CMR effects of barbiturates may quickly develop.<sup>80</sup> In patients with severe head injury in whom *barbiturate coma* was maintained for 72 hours, the blood concentration of thiopental required to maintain EEG burst suppression was observed to be increased by the end of the first 24 hours and continued to increase over the next 48 hours.<sup>81</sup> During deep pentobarbital anesthesia, autoregulation and  $\text{CO}_2$  responsiveness are maintained.

## Propofol

The effects of propofol (2,6-diisopropylphenol) on CBF and CMR are similar to those of barbiturates. Both CBF and CMR decrease after the administration of propofol in humans.<sup>82</sup> In healthy volunteers, surgical levels of propofol reduced regional CBF by 53% to 79% in comparison with the awake state.<sup>83,84</sup> Cerebral glucose metabolism in volunteers was evaluated by positron-emission tomography (PET) before and during infusion of propofol to the point of unresponsiveness, and resulted in a decrease of the whole-brain metabolic rate of 48% to 58%, with limited regional heterogeneity.<sup>85</sup> When compared with isoflurane-fentanyl or sevoflurane-fentanyl anesthesia, a combination of propofol and fentanyl decreased subdural pressure in patients with intracranial tumors and decreased the arteriovenous oxygen content difference ( $\text{AVDO}_2$ ).<sup>86</sup> Collectively, these investigations in human subjects indicate that propofol effects reductions in the CMR and secondarily decreases CBF, CBV, and ICP.

Both  $\text{CO}_2$  responsiveness and autoregulation are preserved in humans during the administration of propofol,<sup>87,88</sup> even when administered in doses that produce burst suppression of the EEG.<sup>89</sup> The magnitude of the reduction in CBF during hypoxia is decreased during propofol administration. This effect is probably due to the cerebral vasoconstriction induced by suppression of CMR, which limits further hypoxia-mediated vasoconstriction.

## Etomidate

The effects of etomidate on CBF and CMR are also similar to those of barbiturates. Roughly parallel reductions in CBF and CMR occur in humans,<sup>65,90</sup> and in general, they are accompanied by progressive suppression of the EEG.

Induction of anesthesia with either thiopental or etomidate resulted in a similar reduction in MCA<sub>av</sub> by approximately 27%.<sup>91</sup> The changes in CBF and CMR are substantial. Etomidate, 0.2 mg/kg, reduced CBF and CMR by 34% and 45%, respectively, in adults.<sup>65</sup> As is the case with barbiturates, no further reduction in the CMR occurs when additional drug is administered beyond a dose sufficient to produce EEG suppression. Although this latter phenomenon has not been demonstrated in humans, etomidate has been demonstrated to reduce ICP only when EEG activity is well preserved; etomidate is ineffective in reducing ICP when EEG activity is suppressed in head injured patients.<sup>92</sup> The global CMR suppression attainable with etomidate is slightly less profound than that achieved with isoflurane and barbiturates. This finding is consistent with the observation that unlike barbiturates, which cause CMR suppression throughout the brain, the CMR suppression caused by etomidate is regionally variable and occurs predominantly in forebrain structures.

Etomidate is effective in reducing ICP without causing a reduction in CPP in patients with intracranial tumors<sup>93</sup> and patients with head injuries.<sup>94</sup> However, the administration of etomidate resulted in an exacerbation of brain tissue hypoxia and acidosis in patients in whom the MCA was temporarily occluded during surgery.<sup>95</sup> Additional concerns regarding the occurrence of adrenocortical suppression caused by enzyme inhibition and renal injury caused by the propylene glycol vehicle<sup>96</sup> will probably preclude more than episodic use.

Reactivity to CO<sub>2</sub> is preserved in humans during the administration of etomidate.<sup>65,90</sup> Autoregulation has not been evaluated. Myoclonus and epileptogenesis are discussed in the section, "Epileptogenesis."

## Narcotics

Inconsistencies can be found in the available information, but narcotics likely have relatively little effect on CBF and CMR in the normal, unstimulated nervous system. When changes do occur, the general pattern is one of modest reductions in both CBF and CMR. The inconsistencies in the literature may largely arise because the control states entailed paralysis and nominal sedation in many studies, often with N<sub>2</sub>O alone. In these studies, in which substantial reductions in CBF and CMR were frequently observed, the effect of the narcotic was probably a combination of the inherent effect of the drug plus a substantial component attributable to reduction of arousal. Comparable effects related to reduction of arousal may occur and can be clinically important. However, they should be viewed as non-specific effects of sedation or pain control, or both, rather than specific properties of narcotics. The following discussion emphasizes investigations in which control measurements were unlikely to have been significantly influenced by arousal phenomena.

**Morphine.** When morphine (~1 mg/kg) was administered as the sole drug to humans, no effect on global CBF and a 41% decrease in the CMRO<sub>2</sub> were observed. The latter is a substantial reduction, and the absence of a simultaneous adjustment in CBF is surprising. No other investigations of morphine have been conducted in

humans alone. Administration of morphine (1 mg/kg and 3 mg/kg) with 70% N<sub>2</sub>O to patients did not significantly change CBF or CMR.<sup>48</sup> The N<sub>2</sub>O that was used might be expected to have caused a tendency toward increases in CBF. The relative absence of *net* changes in these variables from awake control measurements suggests a small-to-moderate depressive effect of morphine on CBF and CMR at this large dose. However, morphine can cause a substantial release of histamine in individual patients. Histamine is a cerebral vasodilator that will cause an increase in CBV and a CBF effect that will vary, depending on the systemic blood pressure response.

Autoregulation was observed to be intact between MAP values of 60 and 120 mm Hg in human volunteers anesthetized with a combination of morphine, 2 mg/kg, and 70% N<sub>2</sub>O.<sup>97</sup>

**Fentanyl.** Fentanyl, in a dose range of 12 to 30 (mean, 16) µg/kg, in combination with 50% N<sub>2</sub>O, reduced CBF and CMR modestly, by 21% and 26%, respectively, in comparison to the awake control state. The data for fentanyl-N<sub>2</sub>O presented in Fig. 11.10 are derived from these patients. In combination with 0.4 mg/kg of diazepam, high dose fentanyl (100 µg/kg) led to a reduction of CBF by 25%, although part of this effect may well have been a result of benzodiazepine (see later discussion in the section, "Benzodiazepine") rather than fentanyl *per se*. In sedative doses of 1.5 µg/kg, fentanyl increased CBF in the frontal, temporal, and cerebellar areas simultaneous with decreases in discrete areas associated with pain-related processing. CO<sub>2</sub> responsiveness and autoregulation are unaffected, and the hyperemic CBF response to hypoxia remains intact.

In conclusion, fentanyl will cause a moderate global reduction in CBF and CMR in the normal quiescent brain and will, similar to morphine, cause larger reductions when administered during arousal.

**Alfentanil.** Administration of alfentanil, 320 µg/kg, to pentobarbital-anesthetized dogs<sup>98</sup> did not affect CBF, CMR, CO<sub>2</sub> responsiveness, autoregulation, or CBF response to hypoxia. No studies of the effects of alfentanil on the CMR in humans have been conducted. In patients in whom anesthesia was induced with thiopental, administration of 25 to 50 µg/kg of alfentanil transiently decreased MCA<sub>av</sub>, indicating a slight reduction in CBF.<sup>99</sup> By contrast,<sup>100</sup> no change in MCA<sub>av</sub> was observed in response to 25 to 50 µg/kg of alfentanil given to patients during the maintenance of anesthesia with isoflurane-N<sub>2</sub>O. An evaluation of the surgical field in patients undergoing craniotomy to whom alfentanil was administered did not reveal any adverse events.<sup>101,102</sup>

In general, alfentanil does not significantly impact the cerebral circulation, provided that alfentanil induced reduction in MAP is prevented.

**Sufentanil.** Studies in humans indicate that sufentanil causes, depending on the dose, either no change or a modest reduction in CBF and CMR. Induction of anesthesia with 10 µg/kg of sufentanil<sup>68</sup> resulted in a 29% reduction in CBF and a 22% reduction in CMRO<sub>2</sub>. In healthy human volunteers, 0.5 µg/kg of sufentanil<sup>103</sup> does not affect CBF.

Sufentanil, at doses of 1.0 and 2.0  $\mu\text{g}/\text{kg}$ , decreases MCAfV in head injured patients with increased ICP.

A logical conclusion is that no change and no reduction in ICP occur as a result of the administration of either sufentanil or alfentanil. However, in some investigations in humans, sufentanil was associated with modest increases in ICP. The increases in ICP associated with sufentanil are likely the consequence, in part, of a normal autoregulatory response to the sudden reduction in MAP that can occur as a consequence of sufentanil administration.<sup>104</sup> Therefore sufentanil and fentanyl should be administered in a manner that does not produce a sudden reduction of MAP. Such a decrease will reduce CPP and may increase ICP, each of which, in sufficient extreme, may be deleterious. However, ICP increases attributed to sufentanil are small. Furthermore, conditions in the surgical field, including pressure under brain retractors<sup>101</sup> and the state of brain relaxation, revealed no adverse influences attributable to sufentanil. Accordingly, sufentanil need not be viewed as contraindicated in any way, although its effect on MAP should be followed closely.

**Remifentanil.** Investigations of moderate doses of remifentanil in patients have revealed effects similar to those of other synthetic narcotics (with the exception of its substantially shorter duration of action). In patients undergoing craniotomy for supratentorial space-occupying lesions, 1  $\mu\text{g}/\text{kg}$  of remifentanil caused no change in ICP.<sup>105</sup> In a second investigation in patients undergoing craniotomies, approximately 0.35  $\mu\text{g}/\text{kg}/\text{min}$  of remifentanil resulted in CBF values comparable to those observed with moderately deep anesthesia with either isoflurane- $\text{N}_2\text{O}$  or fentanyl- $\text{N}_2\text{O}$ ,<sup>106</sup> and  $\text{CO}_2$  responsiveness was preserved. Greater doses of remifentanil may have more substantial effects. MCAfV decreased by 30% in response to 5  $\mu\text{g}/\text{kg}$ , followed by 3  $\mu\text{g}/\text{kg}/\text{min}$  of remifentanil at a constant MAP in patients being anesthetized for bypass surgery.<sup>69</sup> However, a lower dose of 2  $\mu\text{g}/\text{kg}$ , followed by an infusion of 3  $\mu\text{g}/\text{kg}/\text{min}$ , did not affect MCAfV. Quantitatively, the effects of remifentanil appear to be similar to those of sufentanil.

Remifentanil was administered with other drugs that might influence cerebral hemodynamics. More recent studies in human volunteers have demonstrated that the infusion of small (sedative) doses of remifentanil can increase CBF. A PET study in human subjects to whom remifentanil, 0.05 and 0.15  $\mu\text{g}/\text{kg}/\text{min}$ , was administered revealed increases in CBF in the prefrontal, inferior parietal, and supplementary motor cortices; reductions in CBF were observed in the cerebellum, superior temporal lobe, and midbrain gray matter.<sup>105</sup> The relative increase in CBF was greater with the administration of the larger dose of remifentanil. Similar data were obtained by Lorenz and colleagues,<sup>107</sup> who used magnetic resonance imaging (MRI) to determine CBF.<sup>107</sup> In a PET investigation in human volunteers,<sup>108</sup> remifentanil-induced increases in regional CBF within the limbic system were observed. Although the underlying mechanisms of the increases in CBF are not clear, disinhibition produced by the small-dose remifentanil infusion, or perhaps the sensation of side effects (e.g., warmth, comfort, pruritus),<sup>107</sup> may have contributed. When combined with  $\text{N}_2\text{O}$ , CBF and  $\text{CO}_2$  reactivity is similar in patients given

remifentanil or fentanyl.<sup>106</sup> In conclusion, sedative doses of remifentanil alone can cause minor increases in CBF. With larger doses or with the concomitant administration of anesthetic adjuvants, CBF is either unaltered or modestly reduced.

### Benzodiazepines

Benzodiazepines cause parallel reductions in CBF and CMR in humans. CBF and CMRO<sub>2</sub> decreased by 25% when 15 mg of diazepam was given to patients with head injuries. The effects of midazolam on CBF (but not on CMR) have also been studied in humans. Administration of 0.15 mg/kg of midazolam to awake healthy human volunteers resulted in a 30% to 34% reduction in CBF.<sup>71,109</sup> In an investigation using PET scanning, a similar dose of midazolam led to a global 12% reduction in CBF; the decreases occurred preferentially in the brain regions associated with arousal, attention, and memory.<sup>110</sup>  $\text{CO}_2$  responsiveness was preserved.<sup>111</sup>

The available data indicate that benzodiazepines cause a moderate reduction in CBF in humans, which is coupled to metabolism. The extent of the maximal reductions of CBF and CMR produced by benzodiazepines is probably intermediate between the decreases caused by narcotics (modest) and barbiturates (substantial). It appears that benzodiazepines should be safe to administer to patients with intracranial hypertension, provided that respiratory depression (and an associated increase in  $\text{Paco}_2$ ) or hypotension do not occur.

Flumazenil is a highly specific, competitive benzodiazepine receptor antagonist. It had no effect on CBF when administered to nonanesthetized human volunteers.<sup>109,112</sup> However, flumazenil reverses the CBF-, CMR-, and ICP-lowering effects of midazolam. When patients were aroused from midazolam anesthesia with flumazenil at the conclusion of craniotomy for brain tumor resection,<sup>113</sup> no change in either CBF or CMR was observed. By contrast, severe increases in ICP occurred when flumazenil was given to patients with severe head injury in whom ICP was not well controlled.<sup>114</sup> These latter observations are consistent with animal investigations during which flumazenil not only reversed the CBF and CMR effects of midazolam, but it also caused a substantial, although short-lived, overshoot above premidazolam levels in both CBF and ICP by 44% to 56% and 180% to 217%, respectively. The CMR did not rise above control levels, thus indicating that the increase in CBF was not metabolically coupled. The CBF overshoot effect is unexplained, but it may be a neurogenically mediated arousal phenomenon. Flumazenil should be used cautiously to reverse benzodiazepine sedation in patients with impaired intracranial compliance.

### Droperidol

No human investigations of the CBF and CMR effects of droperidol have been conducted in isolation. However, the information available from animal investigations and combination drug administration in humans,<sup>115</sup> taken together, suggests that droperidol is not a cerebral vasodilator and probably has little effect on CBF and CMR in humans. The occasional increases in ICP that have been observed<sup>115</sup> probably reflect normal autoregulation-mediated vasodilation in response to an abrupt decrease in MAP.

## Ketamine

Among the intravenous anesthetics, ketamine is unique in its ability to cause increases in both CBF and CMR.<sup>116</sup> Animal studies indicate that the changes in the CMR are regionally variable; substantial increases occur in limbic system structures with modest changes or small decreases in cortical structures.<sup>117</sup> PET studies in humans have demonstrated that subanesthetic doses of ketamine (0.2–0.3 mg/kg) can increase global CMR by approximately 25%.<sup>118</sup> The greatest increase in the CMR occurred in the frontal and anterior cingulate cortex. A relative reduction in the CMR in the cerebellum was also observed. Commercially available formulations of ketamine contain both the (S)- and (R)-ketamine enantiomers. The (S)-ketamine enantiomer substantially increases CMR, whereas the (R) enantiomer tends to decrease the CMR, particularly in the temporomedial cortex and in the cerebellum.<sup>119</sup> These changes in the CMR are accompanied by corresponding changes in CBF.<sup>120</sup> Global, as well as regional, increases in CBF in humans that were not accompanied by similar increases in the CMRO<sub>2</sub> after the administration of (S)-ketamine enantiomer have been observed. Both subanesthetic and anesthetic doses of ketamine increased global CBF by approximately 14% and 36%, respectively, without altering global CMRO<sub>2</sub>. As expected, in the face of an unchanged CMR and increased CBF, the oxygen extraction ratio was reduced.<sup>77</sup> The majority of investigations indicate that autoregulation is maintained during ketamine anesthesia,<sup>121</sup> and CO<sub>2</sub> responsiveness is preserved. A recent metaanalysis concluded that, in humans, ketamine administration increases CBF, particularly in the anterior cingulate gyrus, medial prefrontal cortex, and occipital lobes. In aggregate, the available data indicate that ketamine does increase CBF, and the accompanying increase in CMR is at best modest. Ketamine does not increase CBV.<sup>122</sup>

The anticipated increase in ICP with an increase in CBF has not been confirmed to occur in humans. When examined in their entirety, the available data indicate that ketamine does not increase ICP in patients with nontraumatic neurologic illness<sup>122</sup> nor in patients with traumatic brain injury.<sup>122</sup> In fact, decreases in ICP occur when relatively large anesthetic doses of ketamine (1.5–5 mg/kg) are administered to patients with head injuries who are sedated with propofol.<sup>123</sup> However, it should be noted that, in most of the studies in which the ICP effects of ketamine have been evaluated, patients received sedative agents in addition to ketamine. It has been established that anesthetic drugs (diazepam, midazolam, isoflurane-N<sub>2</sub>O, propofol, opioids, methohexitol) blunt or eliminate the increases in ICP or CBF associated with ketamine.<sup>116,124,125</sup> Accordingly, although ketamine is probably best avoided as the sole anesthetic drug in patients with impaired intracranial compliance, it may be cautiously given to patients who are simultaneously receiving adjunctive sedative drugs.

## Lidocaine

In nonanesthetized human volunteers, reductions in CBF and CMR of 24% and 20%, respectively, were observed after the administration of 5 mg/kg of lidocaine over a 30-minute period, followed by an infusion of 45 µg/kg/min.<sup>126</sup> When very large doses (160 mg/kg) were given to dogs

maintained on cardiopulmonary bypass, the reduction in the CMRO<sub>2</sub> was apparently more than that observed with large-dose barbiturates.<sup>127</sup> The membrane-stabilizing effect of lidocaine probably reduces the energy required for the maintenance of membrane integrity.

The effectiveness of bolus doses of thiopental, 3 mg/kg, and lidocaine, 1.5 mg/kg, in controlling the acute increase in ICP that occurred after the application of a pin head holder or skin incision in patients undergoing craniotomies has been assessed.<sup>128</sup> The two regimens were equally effective in causing a reduction in ICP. However, the decrease in the MAP was greater with thiopental. Accordingly, a bolus dose of lidocaine is a reasonable adjunct to the prevention or treatment of acute increases in ICP and can prevent increases in ICP associated with endotracheal suctioning. Although large doses of lidocaine can produce seizures in humans, lidocaine-induced seizures have not been reported in anesthetized humans. Nonetheless, lidocaine doses should be adjusted to achieve serum levels less than the seizure threshold (>5–10 µg/mL) in awake humans. After a 2-mg/kg bolus, peak serum concentrations of 6.6 to 8.5 µg/mL are below the seizure threshold. Bolus doses of 1.5 to 2.0 mg/kg therefore seem appropriate.

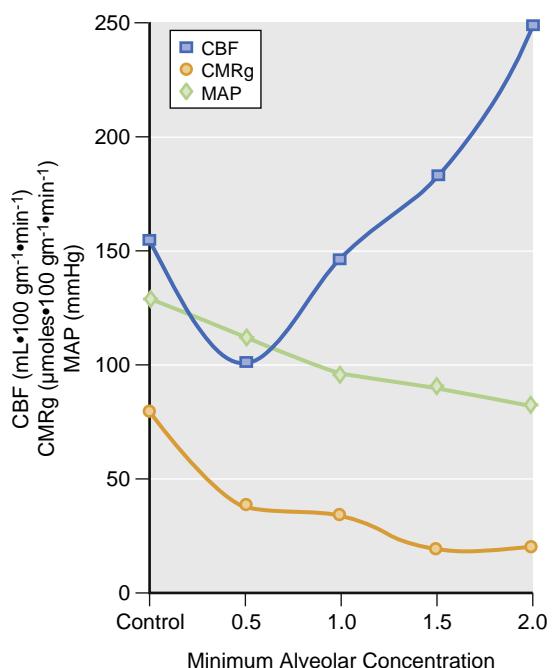
## INHALED ANESTHETICS

### Volatile Anesthetics

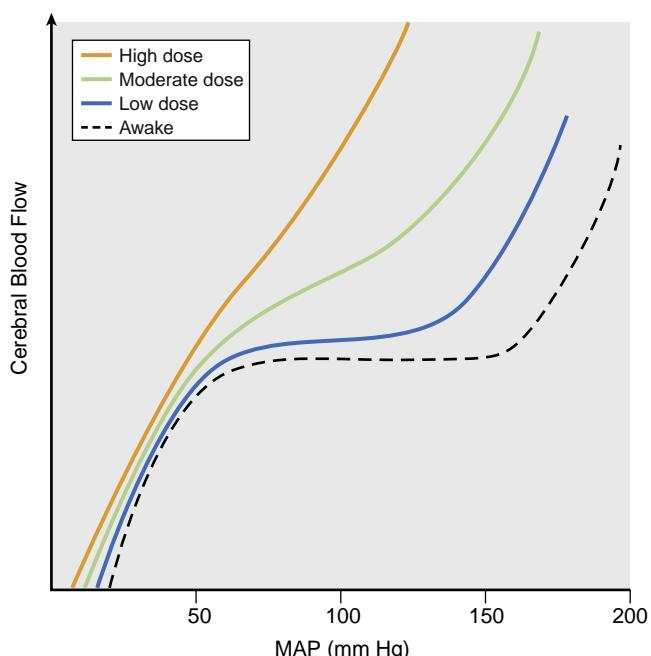
The pattern of volatile anesthetic effects on cerebral physiology is quite different than that of intravenous anesthetics, which generally cause parallel reductions in CMR and CBF. All volatile anesthetics, in a manner similar to intravenous sedative-hypnotic drugs, suppress cerebral metabolism in a dose-related fashion.<sup>129–132</sup> Volatile anesthetics also possess intrinsic cerebral vasodilatory activity as a result of direct effects on vascular smooth muscle. The net effect of volatile anesthetics on CBF is therefore a balance between a reduction in CBF caused by CMR suppression and an augmentation of CBF caused by the direct cerebral vasodilation. When administered at a dose of 0.5 MAC, CMR suppression-induced reduction in CBF predominates, and net CBF decreases in comparison with the awake state. At 1 MAC, concentrations of isoflurane, sevoflurane, or desflurane, CBF remains unchanged; at this concentration, CMR suppression and vasodilatory effects are in balance. Beyond 1 MAC, the vasodilatory activity predominates, and CBF significantly increases, even though the CMR is substantially reduced (Fig. 11.11).<sup>133</sup> Vasodilation with increasing doses of volatile agents lead to an attenuation of cerebral autoregulation. With large doses, autoregulation is abolished and cerebral perfusion becomes pressure passive (Fig. 11.12).

The increase in CBF produced by volatile anesthetics at doses larger than 1 MAC has been referred to as reflecting a loss of neurovascular coupling. However, coupling (CBF adjustments paralleling changes in the CMR) persists during anesthesia with volatile anesthetics.<sup>134–138</sup> Accordingly, the conclusion should be that the CBF/CMR ratio is altered (increased) by volatile anesthetics. This alteration is dose related, and under steady-state conditions, increasing doses of volatile agents lead to greater CBF/CMRO<sub>2</sub> ratios<sup>130,139</sup>—that is, higher MAC levels cause greater luxury perfusion.

The important clinical consequences of the administration of volatile anesthetics are derived from the increases in



**Fig. 11.11** Relationship between changes in the cerebral metabolic rate of glucose (CMRg) and cerebral blood flow (CBF) in the motor-sensory cortex in rats during isoflurane anesthesia. The majority of the suppression in the CMR caused by isoflurane has occurred by 1 minimum alveolar concentration; CBF is not increased in this concentration range. Thereafter, additional isoflurane causes little further reduction in the CMR, and cerebral vasodilation occurs. These data ( $\pm$  standard deviation) from Maekawa and colleagues<sup>133</sup> suggest the importance of metabolic coupling in determining the effects of isoflurane on CBF. MAP, Mean arterial pressure.



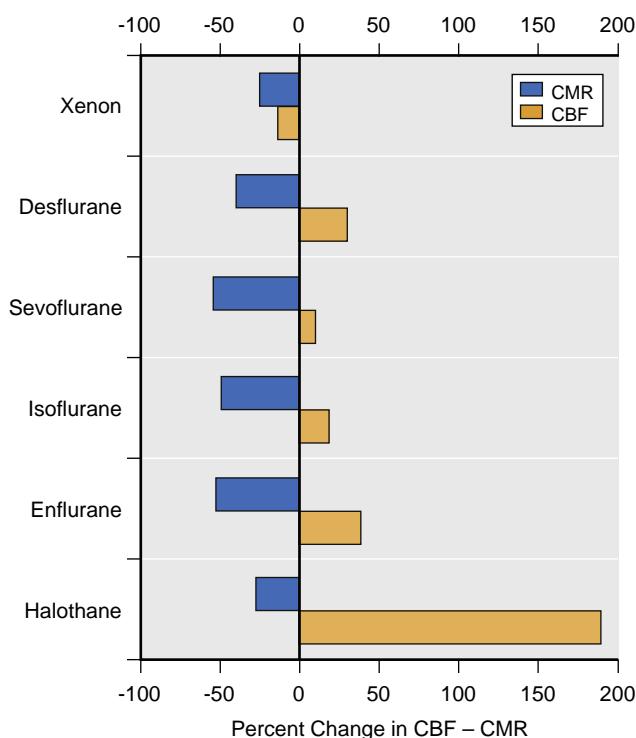
**Fig. 11.12** Schematic representation of the effect of increasing concentrations of a typical volatile anesthetic drug on autoregulation of cerebral blood flow. Dose-dependent cerebral vasodilation results in attenuation of autoregulatory response to increasing mean arterial pressure (MAP). Both the upper and lower thresholds are shifted to the left.

CBF and CBV—and consequently ICP—that can occur. Of the commonly used volatile anesthetics, the order of vaso-dilating potency is approximately halothane  $\gg$  enflurane  $>$  desflurane  $\approx$  isoflurane  $>$  sevoflurane.

**Effects on cerebral blood flow.** Volatile anesthetics possess intrinsic vasodilatory activity, and they not only modify cerebral autoregulation, but they also produce a dose-dependent decrease in arterial blood pressure. Hence, their effects on CBF and CMR are best evaluated when arterial blood pressure is maintained at a constant level. In addition, the cerebrovascular effects of volatile anesthetics are modulated by the simultaneous administration of other CNS-active drugs. The control state—awake, sedated, or anesthetized—against which the CBF and CMR effects of volatile anesthetics are compared, is important to recognize. The best information concerning the cerebrovascular effects of volatile anesthetics is obtained in studies during which a nonanesthetized (awake) control state is used.

Data on the cerebrovascular effects of halothane and enflurane are limited. Initial studies in humans demonstrated that the administration of 1 MAC halothane significantly increases CBF, even when systemic blood pressure is substantially reduced, in comparison with preanesthetic CBF. When the MAP is maintained at 80 mm Hg, 1.1 MAC levels of halothane increase CBF by as much as 191% and decrease the CMR by approximately 10% (Fig. 11.13).<sup>140,141</sup> When compared with awake values, 1.2 MAC enflurane also increased CBF and decreased CMR by 45% and 15%, respectively.<sup>142</sup> The dramatic increases in CBF with a simultaneous modest reduction in the CMR attest to the cerebral vasodilatory properties of halothane and enflurane. Isoflurane, by contrast, does not increase CBF as much as halothane or enflurane. At concentrations of 1.1 MAC, isoflurane increases CBF by approximately 19% when arterial blood pressure is maintained within the normal range. The CMR is reduced by approximately 45%.<sup>137</sup>

Both sevoflurane and desflurane can reduce CBF significantly in humans when compared with CBF in awake, nonanesthetized patients. At 1 MAC concentrations, sevoflurane<sup>143</sup> and desflurane<sup>142</sup> decreased CBF by 38% and 22% and CMR by 39% and 35%, respectively. These results, which suggest that the cerebral vasodilation produced by isoflurane is greater than that produced by sevoflurane and desflurane, were obtained with CBF measured by the Kety-Schmidt technique. This technique primarily measures CBF within the cortex and therefore may have substantially underestimated global CBF. PET studies in healthy humans have shown that sevoflurane dose-dependently suppresses the CMRO<sub>2</sub> and CBF; at 1 MAC levels, the reduction in CBF and CMRO<sub>2</sub> is approximately 50% and 50% to 60%, respectively.<sup>83,84</sup> Even with a significant reduction in CBF, the administration of sevoflurane does not cause a decrease in CBV. Other investigations in humans, most using the measurement of MCAv by transcranial Doppler, indicate that differences in the effects of isoflurane, desflurane (Fig. 11.14A), and sevoflurane are modest.<sup>144-147</sup> Unfortunately, a strictly quantitative comparison among these volatile anesthetics is not possible because of the variations in arterial blood pressure among study group patients. In addition, some discrepancy exists among studies in the

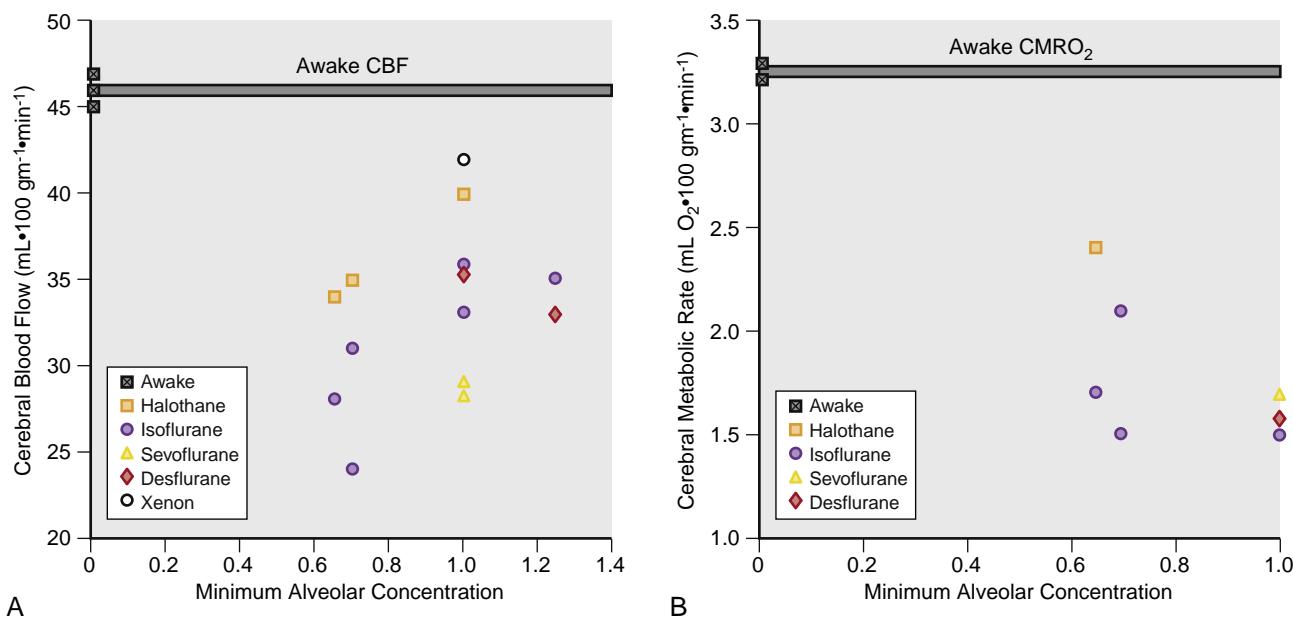


**Fig. 11.13** Estimated changes in cerebral blood flow (CBF) and the cerebral metabolic rate of oxygen (CMRO<sub>2</sub>) caused by volatile anesthetics. The CBF data for halothane, enflurane, and isoflurane were obtained during anesthesia (with blood pressure support) at 1.1 minimum alveolar concentration (MAC) in humans<sup>356</sup> and are expressed as percent change from awake control values. The CMRO<sub>2</sub> data for halothane, enflurane, and isoflurane were obtained in cats<sup>130,140</sup> and are expressed as percent change from N<sub>2</sub>O-sedated control values. The data for sevoflurane were obtained during 1.1 MAC anesthesia in rabbits and are expressed as percent change from a morphine-N<sub>2</sub>O-anesthetized control state.<sup>132</sup> CBF values were obtained in patients who received 1 MAC sevoflurane anesthesia.<sup>143</sup> Desflurane data were obtained in patients to whom 1 MAC desflurane was administered.<sup>141</sup> CMR, Cerebral metabolic rate.

literature regarding the magnitude of the effects of volatile anesthetics on CBF. Much of this inconsistency may occur as a result of the interaction of regionally selective CBF methods with the heterogeneity within the cerebrum of the CBF effects of volatile anesthetics. (See the later section, “Distribution of Changes in Cerebral Blood Flow/Cerebral Metabolic Rate.”)

The anesthetic properties of xenon were recognized several decades ago, but this anesthetic is only now being evaluated for possible use in patients. The MAC of xenon has been estimated to be 63% to 71%, with female patients having significantly lower MAC values (51%).<sup>147</sup> Xenon exerts its anesthetic effect via noncompetitive antagonism of the N-methyl-D-aspartate receptor (NMDAR),<sup>148</sup> although activation of the TREK two-pore K<sup>+</sup> channel may also play a role.<sup>149</sup> In healthy humans, the administration of 1 MAC xenon resulted in a reduction in CBF by approximately 15% in the cortex and by 35% in the cerebellum. Interestingly, CBF in white matter increased by 22%.<sup>150</sup> This reduction in CBF is accompanied by a parallel reduction of the cerebral metabolic rate of glucose (CMRG) by 26%.<sup>151</sup> Cerebral autoregulation and CO<sub>2</sub> reactivity are preserved during xenon anesthesia in animals.<sup>152</sup> Under background pentobarbital anesthesia in an experimental model of increased ICP, the administration of xenon did not increase ICP, and the response to both hypocapnia and hypercapnia was preserved.<sup>153</sup> Diffusion of xenon into air-containing spaces such as the bowel does occur, although the magnitude of air expansion is considerably less than that with N<sub>2</sub>O.<sup>154</sup> Nonetheless, caution will have to be exercised with the use of xenon in patients with intracranial air. These data indicate that xenon has a favorable profile for neuroanesthesia.

**Effects on cerebral metabolic rate.** All volatile anesthetics cause reductions in CMR. The degree of reduction in CMRO<sub>2</sub> that occurs at a given MAC is less with halothane

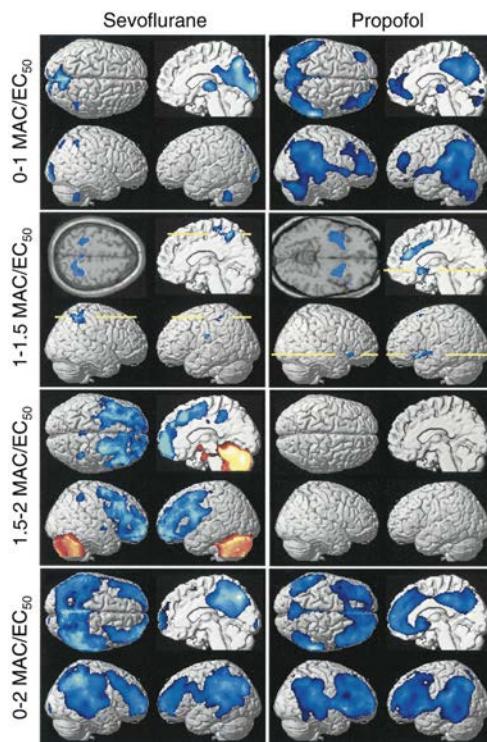


**Fig. 11.14** Effect of volatile anesthetics on cerebral blood flow (CBF) (A) and the cerebral metabolic rate of oxygen (CMRO<sub>2</sub>) (B) in awake humans. The results are a composite of CBF and CMRO<sub>2</sub> values obtained from a number of separate investigations.<sup>72,130,131,135-137,139-146,356-358</sup> In these studies, arterial partial pressure of carbon dioxide (Paco<sub>2</sub>) was maintained in the normocapnic range (~35–40 mm Hg), and mean arterial pressure was supported. In most of the investigations, CBF was measured by a radioactive xenon washout technique; this technique primarily measures cortical CBF and, as such, may underestimate global CBF. This, in addition to species differences, probably account for the disparities between the data on the CBF effects attributed to volatile agents in this figure and Fig. 11.13.

than with the other four anesthetics. Sevoflurane's effect on the  $\text{CMRO}_2$  is very similar to that of isoflurane. The available information, derived in separate investigations, suggests that desflurane causes slightly less suppression of the  $\text{CMRO}_2$  than isoflurane, especially at concentrations above 1 MAC.<sup>131</sup> Although a direct comparison of the  $\text{CMRO}_2$  effects of all of the volatile anesthetics has not been performed in humans, doses of 1 MAC isoflurane, sevoflurane, and desflurane clearly reduce the  $\text{CMRO}_2$  by 25%,<sup>155</sup> 38%,<sup>141</sup> and 22%,<sup>156</sup> respectively. In PET studies, halothane (0.9 MAC) and isoflurane (0.5 MAC) can decrease the  $\text{CMR}_g$  by 40% and 46%, respectively.<sup>85,157</sup> The decrease in the  $\text{CMRO}_2$  is dose-related. With isoflurane (and almost certainly desflurane and sevoflurane as well), the maximal reduction is simultaneously attained with the occurrence of EEG suppression,<sup>131</sup> which occurs at clinically relevant concentrations, in the range of 1.5 to 2 MAC in humans. With additional isoflurane, 6% end-tidal concentration results in no further reduction in the CMR and no indication of metabolic toxicity. Halothane presents a contrast to this pattern. Halothane concentrations more than 4 MAC are required to achieve EEG suppression in animals, and additional halothane causes a further reduction in the  $\text{CMRO}_2$  in concert with alterations in energy charge. The latter changes, which are reversible, suggest interference with oxidative phosphorylation by halothane.

Some nonlinearity exists in the CBF and CMR dose-response relationships for volatile anesthetics. The initial appearance of an EEG pattern associated with the onset of anesthesia with halothane, enflurane, and isoflurane is accompanied by a sharp decline in the  $\text{CMRO}_2$ .<sup>131</sup> Thereafter, the  $\text{CMRO}_2$  declines in a slower dose-dependent manner. Such an effect has also been demonstrated for sevoflurane. In a dose escalation study in humans, the greatest reduction in entropy (i.e., a measure of anesthetic depth) was observed with 1 MAC sevoflurane anesthesia, with lesser reductions occurring at increasing concentrations.<sup>158</sup>

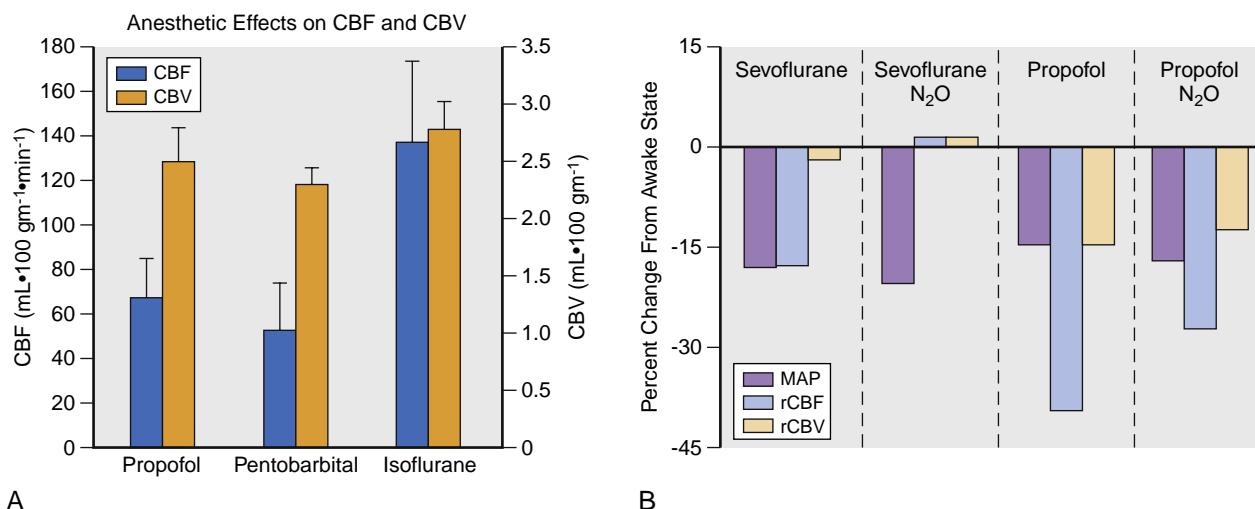
**Distribution of changes in cerebral blood flow and cerebral metabolic rate.** The regional distribution of anesthetic-induced changes in CBF and CMR differs significantly between halothane and isoflurane. Halothane produces relatively homogeneous changes throughout the brain. CBF is globally increased, and CMR is globally depressed. The changes caused by isoflurane are more heterogeneous. Increases in CBF are greater in subcortical areas and hindbrain structures than in the neocortex.<sup>136,159</sup> The converse is true for the CMR, with a larger reduction in the neocortex than in the subcortex.<sup>133</sup> In humans, 1 MAC sevoflurane (Fig. 11.15) results in a reduction in CBF within the cortex and the cerebellum. With an increase in sevoflurane dose, CBF within the cortex decreases further. By contrast, flow increases in the cerebellum with doses greater than 1.5 MAC.<sup>83</sup> These effects of sevoflurane are similar to those produced by isoflurane.<sup>83,159</sup> Desflurane has not been evaluated by local CBF studies. However, considering the similarity of its effects on the EEG (suggesting similar cortical CMR and CBF effects), an assumption of similar heterogeneity in CBF distribution seems reasonable, pending further



**Fig. 11.15** Dose-dependent redistribution of cerebral blood flow (CBF) in humans. Positron-emission tomography (PET) scans demonstrate a dose-dependent reduction in CBF in both sevoflurane-anesthetized (left) and propofol-anesthetized (right) subjects. During sevoflurane anesthesia, there is a concentration dependent reduction in CBF within the cerebrum (indicated by blue color). An increase in concentration from 1.5 to 2 minimum alveolar concentration (MAC) leads to an increase in CBF within the cerebellum (indicated by the yellow-red color). A gradual reduction in the mean arterial pressure (MAP) occurred with increasing concentrations of sevoflurane, and the MAP was not supported. The CBF values would be expected to be considerably greater had blood pressure been maintained within the normal range. Therefore the CBF values represented in this figure probably underestimate true CBF during sevoflurane anesthesia. Propofol was administered in  $\text{EC}_{50}$  equivalents, defined as the plasma concentration that prevented movement in response to a surgical stimulus in 50% of patients. The target plasma propofol concentrations were 0, 6, 9, and 12  $\mu\text{g}/\text{mL}$ . In propofol-anesthetized subjects, CBF was uniformly decreased and redistribution of CBF was not observed. (Modified from Kaisti K, Metsähönen L, Teräs M, et al. Effects of surgical levels of propofol and sevoflurane anesthesia on cerebral blood flow in healthy subjects studied with positron emission tomography. *Anesthesiology*. 2002;96:1358–1370.)

investigation. These distribution differences may explain certain apparent contradictions in reported CBF effects in the existing literature for isoflurane. Methods that assess global hemodynamic effects reveal greater changes than those that emphasize the cortical compartment. For instance, when a xenon surface washout technique is employed (measurement of local cortical flow only), no increase in CBF occurred when isoflurane was administered to patients undergoing craniotomy.<sup>160</sup>

**Time dependence of cerebral blood flow effects.** The effects of volatile anesthetics on CBF are time-dependent in animal investigations. After an initial increase, CBF decreases and reaches a steady state near pre-volatile agent levels between 2.5 and 5 hours after exposure.<sup>161–163</sup> The mechanism of this effect is not



**Fig. 11.16** Effect of anesthetic drugs on cerebral blood flow (CBF) and cerebral blood volume (CBV). (A) When compared with isoflurane, propofol and pentobarbital effected substantial reductions in CBF. However, reductions in CBV were more modest.<sup>151</sup> (B) Although sevoflurane effected a significant reduction in regional CBF (rCBF), regional CBV (rCBV) was unchanged. Had blood pressure been supported to normal levels, rCBV may have been greater than the awake state. By contrast, propofol effected a significant reduction in both rCBF and rCBV. These data indicate that the magnitude of the effect of anesthetics on rCBF is substantially greater than on rCBV. Hence, decreases in rCBF may not lead to equivalent reductions in rCBV. MAP, Mean arterial pressure;  $\text{N}_2\text{O}$ , nitrous oxide.

understood, and the phenomenon was not evident in humans studied during a 3- or 6-hour exposure to halothane, isoflurane, desflurane, or sevoflurane.<sup>146,164</sup>

**Cerebral blood volume.** The extensive investigation of the influence of volatile anesthetics on CBF has been primarily based on the concern that the cerebral vasodilation produced by volatile anesthetics might increase ICP. However, it is CBV and not CBF, *per se*, that influences ICP. Most of the intracranial blood is within the cerebral venous circulation; although a reasonable correlation exists between vasodilation-induced increases in CBF and CBV, the magnitude of changes in CBF is considerably greater than that in CBV (see Fig. 11.9). Hence, changes in CBF do not reliably predict changes in CBV and, by extension, in ICP. CBV is considerably greater during isoflurane anesthesia than during propofol or pentobarbital anesthesia.<sup>63</sup> In human volunteers, 1 MAC sevoflurane reduced regional CBF but not regional CBV; by contrast, propofol reduced both regional CBF and regional CBV (Fig. 11.16).<sup>84</sup> In addition, CBV responds to changes in  $\text{Paco}_2$  by a reduction in CBV with hypocapnia and an increase in CBV with hypercapnia. The magnitude of the change in CBV is, however, less than the change in CBF. In aggregate, although the effect of anesthetics and interventions on CBF may parallel the effect on CBV, substantial qualitative and quantitative differences may well be observed.

**Carbon dioxide responsiveness and autoregulation.**  $\text{CO}_2$  responsiveness is well maintained during anesthesia with all volatile anesthetics.<sup>145,165,166</sup> As with all vasodilators, CBF is preserved up to lower MAP values during the administration of volatile anesthetics with no evidence of differences among the various anesthetics. Direct comparisons of CBF with isoflurane, desflurane, and sevoflurane anesthesia during hypotension are not available. By contrast, autoregulation of CBF in response to increasing arterial blood pressure is impaired, which is most apparent with the

anesthetics that cause the most cerebral vasodilation and are dose related. Sevoflurane may cause less impairment of the autoregulatory response to increasing blood pressure than other volatile anesthetics. Recent studies surprisingly report no change in MCAv in response to phenylephrine-induced increases in the MAP during anesthesia with 1.2 to 1.5 MAC sevoflurane<sup>167,168</sup> or in CBF during hemorrhagic hypotension.<sup>169</sup> The autoregulatory response to increasing blood pressure may be pertinent during acute episodes of hypertension, such as during laryngoscopy or mismatch of surgical stimulation to anesthetic depth.

**Cerebral vasodilation by anesthetics—clinical implications.** Isoflurane, desflurane, and sevoflurane may have a modest cerebral vasodilating effect in the human cortex when administered at doses of 1 MAC or less. In fact, the administration of volatile anesthetics may produce a net decrease in CBF (see Fig. 11.14A). These data, however, should be interpreted with the knowledge that the critical variable of interest in the clinical setting is CBV. Although a direct correlation exists between CBF and CBV, as noted earlier, the relationship is not strictly 1:1. The magnitude of the changes in CBV is significantly less than the magnitude of the changes in CBF, and modest reductions in CBF may not necessarily be accompanied by reductions in CBV. This finding is exemplified by clinical investigations in which a significant increase in ICP (and by extension, CBV) was observed in patients to whom isoflurane was administered at doses that should reduce CBF.<sup>170,171</sup> Although induction of hypocapnia mitigated the increase in ICP, hyperventilation may not be effective in blunting isoflurane-induced increases in ICP in patients with intracranial tumors.<sup>172</sup> In experimental investigations of cerebral injury, volatile anesthetics significantly increased ICP, which was not ameliorated by hypocapnia.<sup>173</sup> Collectively, these data suggest that volatile anesthetics have modest effects on cerebral hemodynamics in patients with normal intracranial compliance. However,

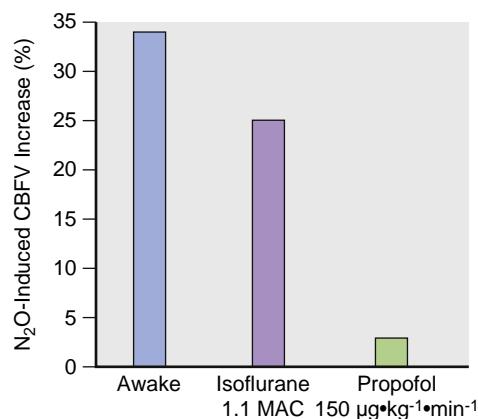
in patients with abnormal intracranial compliance, the potential for volatile anesthetic-induced increases in CBF and ICP exist. Accordingly, volatile anesthetics should be used with caution in the setting of large or rapidly expanding mass lesions, unstable ICP, or other significant cerebral physiologic derangements in which  $\text{CO}_2$  responsiveness and neurovascular coupling may be impaired. When they occur (e.g., a somnolent, vomiting patient with papilledema; a large mass; compressed basal cisterns), the clinician may well be advised to use a predominantly intravenous technique until such time as the cranium and dura are open and the effect of the anesthetic technique can be directly evaluated. Such circumstances will be relatively uncommon in elective neurosurgery.

Situations in which the CMR has been decreased by drug administration or disease processes should also justify caution in the use of volatile anesthetics. As previously noted, the vasodilation mediated increase in CBF induced by a volatile anesthetic is in part, and at low doses, offset by an opposing metabolically mediated vasoconstriction (see Fig. 11.11). In situations in which the CMR is already reduced, the vasodilatory activity will predominate and, therefore, the increase in CBF will be greater. For example, when CMR is only slightly reduced by morphine, isoflurane does not cause significant increase in CBF. However, under thiopental anesthesia, the introduction of isoflurane significantly increases CBF.<sup>135</sup> Similarly, prior propofol anesthesia produces near maximal suppression of CMR; in this situation, introduction of any of the volatile agents leads to significant increases in CBF.<sup>89</sup> In essence, antecedent CMR suppression unmasks the vasodilatory action of volatile anesthetics. These data also suggest that caution must be exercised in the administration of volatile anesthetics in pathologic conditions, such as traumatic brain injury, in which metabolism is already reduced.

The net vasodilating effects of equi-MAC concentrations of isoflurane, desflurane, and sevoflurane are less in humans than that of halothane, and the former are probably therefore preferable if a volatile anesthetic is to be used in the setting of impaired intracranial compliance. When hypocapnia is established before the introduction of halothane, the increases in ICP that might otherwise occur in a normocapnic patient with poor intracranial compliance can be prevented or greatly attenuated. Nonetheless, isoflurane, desflurane, or sevoflurane are preferred because the margin for error is probably wider than with halothane.

### Nitrous Oxide

$\text{N}_2\text{O}$  can cause increases in CBF, CMR, and ICP. At least a portion of the increases in CBF and CMR may be the result of a sympathoadrenal-stimulating effect of  $\text{N}_2\text{O}$ . The magnitude of the effect considerably varies according to the presence or absence of other anesthetic drugs (Fig. 11.17).<sup>174,175</sup> When  $\text{N}_2\text{O}$  is administered alone, substantial increases in CBF and ICP can occur. In sharp contrast, when  $\text{N}_2\text{O}$  is administered in combination with intravenous drugs, including barbiturates, benzodiazepines, narcotics, and propofol, its cerebral-vasodilating effect is attenuated or even completely inhibited. The addition of  $\text{N}_2\text{O}$  to anesthesia established with a volatile anesthetic will result in moderate increases in CBF.



**Fig. 11.17** Mean percent increases in cerebral blood flow velocity (CBFV) in the middle cerebral artery of normocapnic subjects exposed to 60% nitrous oxide ( $\text{N}_2\text{O}$ ) after control recording in three conditions: awake;<sup>174</sup> 1.1 minimum alveolar concentration (MAC) of isoflurane;<sup>179</sup> and propofol, 150  $\mu\text{g}/\text{kg}\cdot\text{min}^{-1}$ .<sup>175</sup>

The most dramatic increases in ICP or CBF in humans and experimental animals have occurred when  $\text{N}_2\text{O}$  was administered alone or with minimal background anesthesia. For instance, before and during spontaneous breathing of 66%  $\text{N}_2\text{O}$  by patients with intracranial tumors, mean ICP increased from 13 to 40 mm Hg.<sup>176</sup> The increases in CBF observed in humans are more modest than those observed in animals but are still substantial.<sup>174</sup> Whether these substantial increases represent the effects of  $\text{N}_2\text{O}$ , per se, or whether they reflect the nonspecific effects of a second-stage arousal phenomenon is not known.

When  $\text{N}_2\text{O}$  is administered in conjunction with certain intravenous anesthetics, its CBF effect may be considerably attenuated. In an investigation of patients with intracranial tumors and poor intracranial compliance (mean preinduction ICP, 27 mm Hg),<sup>177</sup> 50%  $\text{N}_2\text{O}$  introduced during barbiturate anesthesia and after the induction of hypocapnia had a negligible effect on ICP. Benzodiazepines administered alone have been shown to blunt the CBF response to  $\text{N}_2\text{O}$  in both animals and humans.<sup>107</sup> Narcotics appear to have a similar effect. Anesthesia with 1 mg/kg morphine and 70%  $\text{N}_2\text{O}$  resulted in no change in CBF from awake control values.<sup>66</sup> Because of the very minor effect of morphine on CBF, these data suggest that  $\text{N}_2\text{O}$  did not cause substantial cerebral vasodilation. Although the addition of  $\text{N}_2\text{O}$  to propofol anesthesia in children increased MCAv in one study,<sup>178</sup> similar increases were not demonstrated by other investigators.<sup>175</sup>

In most investigations, including several in humans, during which  $\text{N}_2\text{O}$  has been added to a volatile anesthetic of 1 MAC or greater, substantial increases in CBF have been recorded.<sup>179,180</sup> A comparison of an approximately equi-MAC substitution of  $\text{N}_2\text{O}$  for isoflurane revealed that CBF was greater by 43% with 0.75 MAC isoflurane and 65%  $\text{N}_2\text{O}$  in comparison to 1.5 MAC isoflurane.<sup>181</sup> Several investigations have confirmed that CBF will be less with 1 MAC isoflurane than with a 1 MAC combination achieved with 50% to 65%  $\text{N}_2\text{O}$  and isoflurane.<sup>179,181,182</sup> These observations are consistent with a substantial additive vasodilating effect of  $\text{N}_2\text{O}$  in the presence of a volatile agent.

This vasodilating effect of  $\text{N}_2\text{O}$  may be positively correlated with the concentration of inhaled drug<sup>180</sup> and

suggests that, in general, the increase in CBF caused by  $\text{N}_2\text{O}$  is exaggerated at higher concentrations of both halothane and isoflurane. Of importance, however, is the observation that the administration of 50%  $\text{N}_2\text{O}$  to healthy volunteers did not significantly alter CBV.<sup>183</sup> In support of this observation,  $\text{N}_2\text{O}$  did not have any effect on CBV when added to a background of 1 MAC sevoflurane anesthesia.<sup>84</sup> Although  $\text{N}_2\text{O}$  can increase CBF, these data indicate that its effect on CBV is modest.

### Effects of nitrous oxide on cerebral metabolic rate.

No uniform agreement has been reached concerning the effect of  $\text{N}_2\text{O}$  on the CMR. Parallel changes in CBF and CMR, increases in CBF without alteration of the CMR, and CMR alteration occurring without changes in CBF have all been reported. These findings are, doubtless, the product of differences in species, methods, depth of background anesthesia, and interactions with simultaneously administered anesthetics. In a recent investigation in humans, the administration of 70%  $\text{N}_2\text{O}$  on a background of either sevoflurane or propofol anesthesia resulted in modest increases in the CMRO<sub>2</sub>, thus indicating that  $\text{N}_2\text{O}$  does indeed increase cerebral metabolism.<sup>84</sup>

The CBF response to CO<sub>2</sub> is preserved during the administration of  $\text{N}_2\text{O}$ .<sup>184</sup>

**Clinical implications.** Despite the inconsistencies that are evident, the vasodilatory action of  $\text{N}_2\text{O}$  can be clinically significant in neurosurgical patients with reduced intracranial compliance. However,  $\text{N}_2\text{O}$ -induced cerebral vasodilation can be considerably blunted by the simultaneous administration of intravenous anesthetics. By contrast, the addition of  $\text{N}_2\text{O}$  to a volatile drug-based anesthetic can modestly increase cerebral metabolism and blood flow.  $\text{N}_2\text{O}$  has been widely used in neurosurgery, and banishing it is inconsistent with the accumulated experience. Nonetheless, in circumstances wherein ICP is persistently elevated or the surgical field is persistently *tight*,  $\text{N}_2\text{O}$  should be viewed as a potential contributing factor. Because  $\text{N}_2\text{O}$  rapidly enters a closed gas space, it should be avoided or omitted when a closed intracranial gas space may exist or intravascular air is a concern.

## MUSCLE RELAXANTS

### Nondepolarizing Relaxants

The only recognized effect of nondepolarizing muscle relaxants on the cerebral vasculature occurs via the release of histamine. Histamine can result in a reduction in CPP because of the simultaneous increase in ICP (caused by cerebral vasodilation) and a decrease in the MAP. It is not entirely clear whether histamine directly causes cerebral vasodilation or whether it is a secondary (autoregulatory) response to a reduction in the MAP. *d*-Tubocurarine is the most potent histamine releaser among available muscle relaxants. Metocurine, atracurium, and mivacurium also release histamine in lesser quantities. This effect is likely to be clinically inconsequential unless these muscle relaxants are administered in the large doses necessary to achieve endotracheal intubation conditions rapidly. Of this group of drugs, cisatracurium has the least histamine-releasing effect. No evidence of histamine release was observed after the administration of 0.15 mg/kg of cisatracurium to

neurosurgical patients in the intensive care unit.<sup>185</sup> Yet, cisatracurium's slow onset of action makes it less useful for a rapid sequence induction of anesthesia.

Vecuronium, in relatively large doses, does not have a significant effect on cerebral physiology in patients with brain tumors. The other aminosteroids, pipecuronium and rocuronium, should be similarly without direct effect, and no adverse events have been reported.

The indirect actions of relaxants may also have effects on cerebral physiology. Muscle relaxation may reduce ICP because coughing and straining are prevented, which decrease central venous pressure with a concomitant reduction in cerebral venous outflow impedance.

A metabolite of atracurium, laudanosine, may be epileptogenic. However, although large doses of atracurium caused an EEG arousal pattern in dogs, CBF, CMR, and ICP were unaltered.<sup>186</sup> In rabbits, the administration of laudanosine did not increase the severity of the epileptoid activity caused by the direct application of a cephalosporin to the cortical surface.<sup>187</sup> It appears highly unlikely that epileptogenesis will occur in humans with modest atracurium administration.<sup>188</sup>

In summary, vecuronium, pipecuronium, rocuronium, atracurium, mivacurium, cisatracurium, metocurine, and pancuronium (if acute MAP increases are prevented with the latter) are all reasonable muscle relaxants for use in patients with or at risk for intracranial hypertension. Doses of metocurine, atracurium, and mivacurium should be limited to ranges not associated with hypotension.

Rocuronium is increasingly being used for the induction of anesthesia, as well as for intraoperative relaxation. It has the most rapid onset time of any nondepolarizing muscle relaxant. With sugammadex, even a profound neuromuscular blockade can be rapidly reversed (see Chapters 27 and 28). The cerebrovascular effects of sugammadex have not yet been evaluated.

### Succinylcholine

Succinylcholine can produce modest increases (~5 mm Hg) in ICP in lightly anesthetized humans. This effect appears to be the result of cerebral activation (as evidenced by EEG changes and increases in CBF) caused by afferent activity from the muscle spindle apparatus.<sup>189</sup> As might be expected with what appears to be an arousal phenomenon, deep anesthesia prevents succinylcholine-induced increases in ICP. The increase in ICP is also blocked by paralysis with vecuronium and by defasciculation with metocurine, 0.03 mg/kg.<sup>190</sup> The efficacy of other defasciculating anesthetics has not been examined in humans.

Although succinylcholine can produce increases in ICP, it can still be used for a rapid sequence induction of anesthesia. No change in ICP was observed after the administration of succinylcholine, 1 mg/kg, to 10 nonparalyzed, ventilated neurosurgical patients in the intensive care unit, 6 of whom had sustained a head injury.<sup>191</sup> Their observations are relevant because it is in precisely this population of patients that the issue of the use of succinylcholine arises most frequently. Considering that the ICP effects of succinylcholine may be an arousal phenomenon caused by increased afferent traffic from muscle spindles,<sup>189</sup> it is reasonable to assume that disease processes that substantially blunt the level of consciousness might similarly blunt this response. As with many anesthetics, the concern should

**TABLE 11.3** Effects of Anesthetic Agents on the Rate of Cerebrospinal Fluid Secretion and Absorption

	Halothane	Enflurane	Isoflurane	Desflurane	Fentanyl	Etomidate
Secretion	↓	↑	—	↑	—	↓
Absorption	↓	↓	↑	—	↑	↑

Upward arrows indicate an increase in the rate of cerebrospinal fluid absorption or secretion, and downward arrows indicate a decrease. The information is presented nonquantitatively, and effects may vary with dose.

not be whether it is used but how it is used. When contraindications do not exist, with proper attention to the control of  $\text{CO}_2$  tension, arterial blood pressure, and depth of anesthesia and after defasciculation, little hazard should attend succinylcholine administration.

## Other Effects of Anesthetics on Cerebral Physiology

### CEREBROSPINAL FLUID DYNAMICS

Anesthetics have been shown to influence both the rate of formation and the rate of reabsorption of CSF. Table 11.3 provides nonquantitative information about the direction of the influences of common anesthetic drugs. All the information has been derived from animals,<sup>192-198</sup> and these processes have not been examined in humans. Of the volatile anesthetics, halothane decreases the secretion of CSF, isoflurane has no effect, and enflurane and desflurane increase secretion. Absorption of CSF is reduced by halothane and enflurane, unchanged by desflurane, and increased by isoflurane. A theoretic concern might be in the setting of a prolonged closed-cranium procedure in a patient with poor intracranial compliance. The most deleterious potential combination of effects in a patient with poor intracranial compliance is increased CSF production and decreased reabsorption. This pattern occurs with enflurane in the dog, which is perhaps another reason (in addition to the potential for epileptogenesis in the presence of cerebral injury and hypocapnia) for omission of enflurane in this circumstance.

### BLOOD-BRAIN BARRIER

In the majority of the body's capillary beds, fenestrations between endothelial cells are approximately 65 Å in diameter. In the brain, with the exception of the choroid plexus, in the pituitary, and in the area postrema, tight junctions reduce this pore size to approximately 8 Å. As a result, large molecules and most ions are prevented from entering the brain's interstitium (BBB). A limited number of studies of anesthetic effects on the BBB have been conducted. In experimental animals, 1% isoflurane leads to extravasation of albumin into the thalamus, indicating some compromise of the BBB integrity. At higher doses, isoflurane (3%) significantly increases protein extravasation, not only in the thalamus but also in the cortex.<sup>199</sup> This disruption of the BBB is quantitatively similar to that achieved by mannitol. In experimental models of brain injury, isoflurane has been reported to both exacerbate<sup>200</sup> and ameliorate<sup>201</sup> edema formation in the injured brain. Whether these effects are the result of isoflurane action at the BBB, *per se*, or to hemodynamic perturbations attendant upon anesthesia is not known. The clinical relevance of the potential BBB

modulation by anesthetics is not clear. To the authors' knowledge, no peer-reviewed investigation has attempted a comparison of anesthetic effects on BBB function during anesthesia in normotensive humans.

### EPILEPTOGENESIS

An extensive review of the pro- and anticonvulsant effects of anesthetics and adjuvants is available.<sup>202,203</sup> Several commonly used anesthetics have some epileptogenic potential, particularly in predisposed individuals. A concern is that seizure activity may go unrecognized in an anesthetized and paralyzed patient and may result in neuronal injury if substrate demand (CMR) exceeds supply for a prolonged period.<sup>204</sup> A second concern is that the epileptogenic effect will persist in the postanesthesia period when seizures may occur in less well-controlled circumstances than those that exist in the surgical unit. In practice, it appears that spontaneous seizures during or after anesthesia have been extremely rare events. Nonetheless, in patients with processes that might predispose them to seizures, the use of potentially epileptogenic drugs should be avoided in situations during which reasonable alternatives are available.

### Volatile Anesthetics

Enflurane is potentially epileptogenic in clinical setting. Of particular relevance to neuroanesthesia is the observation that hypocapnia potentiates seizure-type discharges during enflurane anesthesia. A 50% decrease in the  $\text{CMRO}_2$  was noted in human volunteers anesthetized with 3% enflurane; however, with the onset of seizure activity, the  $\text{CMRO}_2$  returned to normal,<sup>205</sup> thus indicating preservation of neurovascular coupling. No evidence suggests that this type of EEG activity is deleterious when oxygen delivery is maintained during the event. However, because seizure activity can elevate brain metabolism by as much as 400%, the use of enflurane, especially at high doses and with hypocapnia, should probably be avoided in patients predisposed to seizures.

The EEG-activating property of enflurane has been used intraoperatively to activate and identify seizure foci that are to be surgically resected, and in this situation, spike activity not preoperatively present has been observed to persist after surgery.<sup>206</sup> However, adverse outcomes related to enflurane-induced seizures have not been reported.

Isoflurane can cause EEG spiking and myoclonus, but it has not been associated, in the experimental setting, with the frank epileptoid activity induced by enflurane. The clinical experience with isoflurane is extremely large, and unexplained seizure-like activity has been reported in only two patients. One occurrence was intraoperative,<sup>207</sup> and the other was immediately postoperative.<sup>208</sup> Therefore epileptogenesis does not appear to be a clinical concern with isoflurane. In fact, isoflurane has been successfully used to control EEG seizure activity in refractory status epilepticus.<sup>209</sup>

Seizures occur during the induction of anesthesia with high concentrations of sevoflurane in children, including those without a recognized seizure diathesis.<sup>210</sup> In two healthy humans, EEG burst suppression with 2 MAC sevoflurane was accompanied by epileptiform discharges that were observed during EEG monitoring.<sup>211</sup> These discharges were associated with a significant increase in CBF, thus demonstrating that neurovascular coupling was preserved. In patients with temporal lobe epilepsy, the administration of 1.5 MAC sevoflurane elicited widespread paroxysmal EEG activity. Of note was the observation that the paroxysmal activity was not restricted to the ictal focus and that the administration of sevoflurane did not provide any assistance in localizing the epileptogenic region of the brain.<sup>212</sup> The development of tonic-clonic movements suggestive of seizure activity has also been reported in otherwise healthy patients on emergence from sevoflurane anesthesia.<sup>213,214</sup> In all of the reported cases of seizure activity attributable to sevoflurane anesthesia, untoward sequelae have not been documented. These reports highlight sevoflurane's ability, albeit small, to evoke epileptiform activity; accordingly, the use of sevoflurane in patients with epilepsy should be undertaken with appropriate caution.

### Methohexitol

Myoclonic activity is sometimes observed with methohexitol. Accordingly, this anesthetic has been used to activate seizure foci during cortical mapping.<sup>211</sup> In neurosurgical patients to whom larger doses of methohexitol were administered to produce burst suppression of the EEG, refractory seizures have occurred.<sup>215</sup> Consequently, it appears that patients with seizures of temporal lobe origin, typically of the psychomotor variety or those to whom large doses are administered, are at risk for seizure activation by methohexitol. However, prolonged seizure activity after single-dose methohexitol administration has not been reported in patients who undergo ECT.

### Ketamine

Ketamine can elicit seizures in patients with an epileptic diathesis.<sup>216</sup> Depth electrode recordings in epileptic patients have revealed the occurrence of isolated subcortical seizure activity originating in the limbic and thalamic areas during ketamine anesthesia and demonstrated that this subcortical activation may not be reflected in surface EEG recordings. On only two occasions, seizures have also been reported after ketamine anesthesia in subjects who were neurologically normal;<sup>217,218</sup> seizure thresholds may have been lowered by aminophylline in one of these instances. However, ketamine has also been employed for the purpose of controlling status epilepticus. Therefore, ketamine-induced seizure activity is not of significant concern.

### Etomidate

Etomidate frequently produces myoclonus that is not associated with epileptiform activity on the EEG.<sup>219</sup> A single instance of severe, sustained myoclonus immediately after anesthesia with etomidate by infusion has been reported.<sup>220</sup> Etomidate has also been shown to precipitate generalized epileptic EEG activity in epileptic patients,<sup>221</sup> and its use in this population should probably be avoided. However, it has been electively used in low doses to activate seizure foci for

the purposes of intraoperative EEG localization.<sup>222</sup> In the experience of the authors (unpublished), selective activation of a quiescent focus can be achieved with 0.1 mg/kg etomidate. Larger doses are more likely to lead to generalized activation.

Etomidate is also associated with longer seizures in response to ECT than seizures that occur after the administration of methohexitol or propofol. Remarkably, etomidate, in the dose range of 0.15 to 0.3 mg/kg, does not cause dose-related seizure inhibition during ECT, as is readily demonstrated with methohexitol or propofol.

The preceding information notwithstanding, no convincing reports indicate epileptogenesis in subjects who are neurologically normal, and the use of etomidate need not be restricted on this basis. In fact, etomidate has been used to control refractory status epilepticus.

### Propofol

Abnormal body movements and opisthotonus can occur after propofol anesthesia. However, systematic studies in humans,<sup>223</sup> although identifying the occurrence of occasional dystonic and choreiform movements, have failed to confirm propofol as a proconvulsant. Furthermore, ECT seizures were shorter after induction with propofol than after induction with methohexitol,<sup>224</sup> which is more consistent with an *anticonvulsant* effect. In addition, propofol sedation has been widely used during *awake* resection of seizure foci and other intracranial lesions. Although pronounced high-amplitude beta-frequency activity in the EEG has been observed,<sup>225</sup> unexpected incidences of seizures have not been reported.

### Narcotics

Seizures or limbic system hypermetabolism (or both) can be readily elicited in some animal species with narcotics. Although an increase in CBF in deep brain structures associated with pain processing has been observed in human volunteers,<sup>226</sup> humans do not have a clinically apparent correlate of the hypermetabolism effect observed in animals. Several anecdotal accounts, unaccompanied by EEG recordings, have reported the occurrence of grand mal convulsions in patients who received both high and low doses of fentanyl. However, systematic investigations of EEG changes during the administration of relatively large doses of fentanyl, sufentanil, and alfentanil in humans have *not* documented neuroexcitatory activity,<sup>227</sup> and the seizures may have been an exaggerated rigidity phenomenon. There are exceptions. Partial complex seizures on the induction of anesthesia with fentanyl in patients undergoing anterior temporal lobectomy have been reported.<sup>228</sup> Eight of the nine patients displayed electrical seizure activity at a range of clinically relevant fentanyl doses (mean, 26 µg/kg).<sup>228</sup> Another study found that alfentanil, 50 µg/kg, augmented temporal lobe spike activity in patients with temporal lobe epilepsy.<sup>229</sup> Untreated rigidity may, itself, also have important CNS consequences. ICP elevation can occur during narcotic-induced rigidity, probably as a consequence of cerebral venous congestion.

## NEONATAL ANESTHETIC NEUROTOXICITY

This subject is discussed in detail in Chapter 78.

## Cerebral Physiology in Pathologic States

### CEREBRAL ISCHEMIA—PATHOPHYSIOLOGIC CONSIDERATIONS

#### Critical Cerebral Blood Flow Thresholds

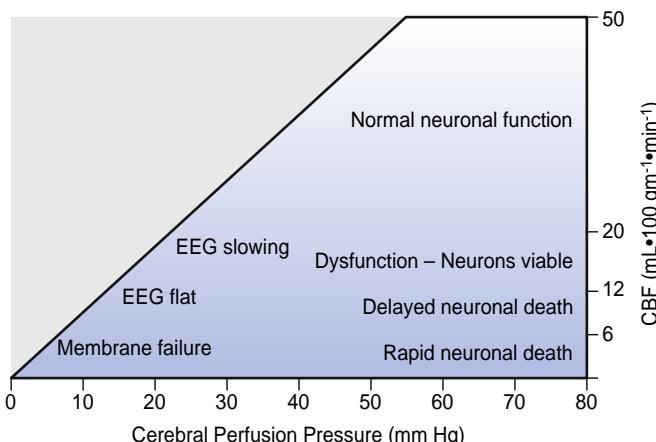
The brain has a high rate of energy utilization and very limited energy storage capacity. The brain is therefore extremely vulnerable in the event of interruption of substrate (e.g., oxygen, glucose) supply. Under normal circumstances, global CBF is maintained at approximately 50 mL/100 g/min. In the face of a declining CBF and therefore oxygen supply, neuronal function deteriorates in a progressive manner rather than in an all-or-none fashion (Fig. 11.18). There is substantial reserve below normal CBF levels, and not until EEG evidence of ischemia begins to appear is CBF decreased to approximately 20 mL/100 g/min. At a CBF level of approximately 15 mL/100 g/min, the cortical EEG is isoelectric. However, only when CBF is reduced to approximately 6 to 10 mL/100 g/min are indications of potentially irreversible membrane failure, such as increased extracellular potassium<sup>230</sup> and a loss of the direct cortical response, rapidly evident. As CBF decreases in the flow range between 15 and 10 mL/100 g/min, a progressive deterioration in energy supply occurs and eventually leads to membrane failure and neuronal death at a time course that may last hours rather than minutes. The brain regions falling within this CBF range (6–15 mL/100 g/min) encompass brain tissue in which neuronal dysfunction is temporarily reversible but within which neuronal death will occur if flow is not restored; such regions are referred to as the *ischemic penumbra*.<sup>230,231</sup> Studies defining progression to cerebral infarction within the penumbra have been performed principally in the cerebral cortex of primates, and the actual CBF levels at which the various decrements in function occur may vary with both anesthetic<sup>232</sup> and species. However, in humans anesthetized with halothane and N<sub>2</sub>O, the CBF threshold for the initial EEG change<sup>233</sup> is similar to that observed in the animal investigations.

#### Models of Cerebral Ischemia

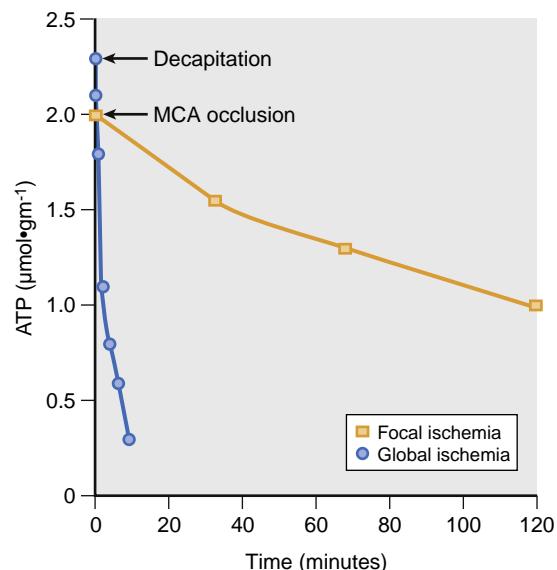
How different is complete cerebral ischemia, as occurs during cardiac arrest, and incomplete cerebral ischemia, as may occur during occlusion of a major cerebral vessel or severe hypotension? From the clinician's vantage, the important difference is that the residual (i.e., collateral) blood flow during incomplete ischemia may result in enough delivery of oxygen to allow some generation of ATP and thereby stave off the catastrophic irreversible membrane failure that occurs within minutes during normothermic complete cerebral ischemia.<sup>234</sup> This difference in the rate of failure of the energy supply (Fig. 11.19)<sup>234,235</sup> can result in significantly greater apparent tolerance for focal or incomplete ischemia than for complete global ischemia (e.g., cardiac arrest).

#### Energy Failure and Excitotoxicity

Energy failure is the central event that occurs during cerebral ischemia.<sup>236</sup> ATP is required for the maintenance of the normal membrane ionic gradient, and energy failure

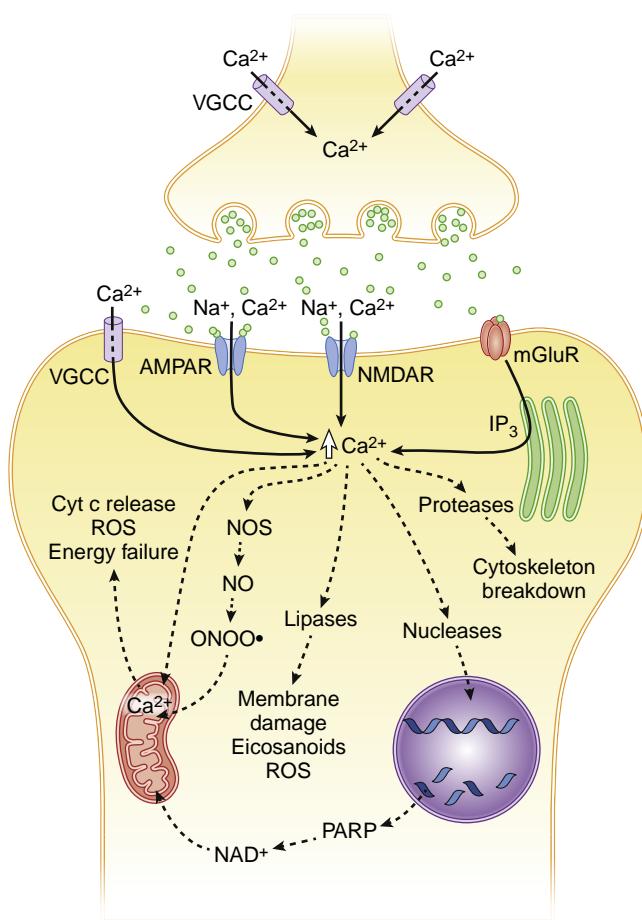


**Fig. 11.18** Relationships between cerebral perfusion, cerebral blood flow (CBF), the electroencephalogram (EEG), and the functional status and viability of neurons. Note that in the approximate CBF range of 6 to 12 mL/100 g/min, the energy supply is insufficient to support electrophysiologic activity (i.e., flat EEG) but can prevent complete membrane failure and neuronal death for extended periods. These areas are referred to as the *ischemic penumbra*.<sup>230</sup> The data are derived from studies on the cerebral cortex of barbiturate-anesthetized baboons<sup>230,359</sup> and nonanesthetized monkeys.<sup>360</sup> The CBF and mean arterial pressure thresholds may vary with anesthetic and species.<sup>232</sup>



**Fig. 11.19** Comparison of rates of failure of energy supply (adenosine triphosphate [ATP]) in complete global ischemia in dogs (produced by decapitation<sup>235</sup>) and in incomplete focal ischemia in monkeys (middle cerebral artery [MCA] occlusion<sup>234</sup>). In the presence of residual cerebral blood flow (CBF), energy supply failure is substantially delayed.

is rapidly attended by membrane depolarization and influx of sodium (Na<sup>+</sup>) and calcium (Ca<sup>2+</sup>) into the neuron. Voltage-dependent Ca<sup>2+</sup> channels are then activated, and Ca<sup>2+</sup> gains entry into the cytosol. Depolarization of presynaptic terminals also results in the release of massive quantities of excitatory neurotransmitters, particularly glutamate, into the synaptic cleft. Activation of glutamatergic receptors, the NMDAR, and the α-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid receptors (AMPARs), adds to the influx of Na<sup>+</sup> and Ca<sup>2+</sup> (Fig. 11.20). Initiation of cellular signaling by the activation of the mGluR leads to the release of stored Ca<sup>2+</sup> from the endoplasmic reticulum (ER) via



**Fig. 11.20** During ischemia, depletion of adenosine triphosphate (ATP) leads to neuronal depolarization and the subsequent release of supranormal quantities of neurotransmitters, especially glutamate. Excessive stimulation of ligand-gated channels and the simultaneous opening of voltage-dependent calcium ( $\text{Ca}^{2+}$ ) channels permit rapid entry of  $\text{Ca}^{2+}$  into neurons. Stimulation of metabotropic glutamate receptors (mGluRs) generates inositol 1,4,5-triphosphate ( $\text{IP}_3$ ), which causes the release of  $\text{Ca}^{2+}$  from the endoplasmic reticulum (ER) and mitochondria. Activation of the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazopropionic acid receptors (AMPAR)-gated subset of glutamate receptors also permits excessive entry of sodium ( $\text{Na}^+$ ). Excessive free  $\text{Ca}^{2+}$  results in the activation of numerous enzymes: protease activation causes the breakdown of the cytoskeleton of the neuron; lipases damage plasma membrane lipids and release arachidonic acid (AA), which is metabolized by cyclooxygenases and lipoxygenases to yield free radicals and other mediators of cell injury; activation of nitric oxide synthase (NOS) leads to the release of nitric oxide (NO) and, in turn, the generation of peroxynitrite ( $\text{ONOO}^\bullet$ ), a highly reactive free radical; and activated endonucleases damage DNA, thereby rendering the neuron susceptible to apoptosis. Injury to the mitochondria leads to energy failure, generation of free radicals, and the release of cytochrome  $\text{c}$  (cyt  $\text{c}$ ) from the mitochondria; the latter is one of the means by which neuronal apoptosis is initiated. mGluR, Metabotropic glutamate receptor; NAD<sup>+</sup>, oxidized form of nicotinamide adenine dinucleotide; NMDAR, N-methyl-D-aspartate receptor; PARP, poly-ADP-ribose polymerase; ROS, reactive oxygen species; VGCC, voltage-gated calcium channel.

inositol 1,4,5-triphosphate ( $\text{IP}_3$ ) receptors. Ionic influx is accompanied by an influx of water, and neuronal swelling rapidly occurs after membrane depolarization. The injury that is initiated by excessive glutamatergic activity is referred to as *excitotoxicity*.

$\text{Ca}^{2+}$  is a ubiquitous second messenger in cells and is a cofactor required for the activation of a number of enzyme systems. The rapid, uncontrolled increase in cytosolic  $\text{Ca}^{2+}$

levels initiates the activation of a number of cellular processes that contribute to injury. Cytoskeletal proteins such as actin are cleaved by activated proteases. These enzymes also degrade a number of the protein constituents of the neuron. Lipases attack cellular lipids and produce membrane damage. An important lipase, phospholipase A<sub>2</sub>, releases fatty acids such as AA from membranes. Metabolism of AA to prostaglandins and leukotrienes by cyclooxygenase and lipoxygenase is accompanied by the generation of superoxide free radicals. The latter, in combination with other free radicals generated in response to mitochondrial injury, can lead to lipid peroxidation and membrane injury. Prostaglandins and leukotrienes also evoke an inflammatory response and are powerful chemotactic drugs. Activation of platelets within cerebral microvessels, as well as an influx of white blood cells into damaged areas, aggravate the ischemic injury by occluding the vasculature.

Deoxyribonucleic acid (DNA) damage is also an important event during ischemic neuronal injury. Generation of free radicals from AA metabolism, from injured mitochondria, and from the production of peroxynitrite from NO leads to oxidative injury to DNA. Activation of endonucleases also produces DNA strand breaks. Under normal circumstances, DNA injury results in the activation of poly-adenosine diphosphate [ADP]-ribose polymerase (PARP), an enzyme that participates in DNA repair. With excessive DNA injury, PARP activity dramatically increases, which can lead to the depletion of nicotinamide adenine dinucleotide (NAD<sup>+</sup>), a substrate of PARP. NAD<sup>+</sup> is also an important coenzyme in energy metabolism, and its depletion further exacerbates energy failure.

Lactate formation is an additional element of the pathophysiological process. Lactic acid is formed as a result of the anaerobic glycolysis that takes place after failure of the supply of oxygen. The associated decrease in pH contributes to the deterioration of the intracellular environment. An increased preischemic serum glucose level may accelerate this process by providing additional substrate for anaerobic glycolysis.

NO, which has emerged as a probable mediator of CBF changes in many normal physiologic states (see the section “Cerebral Metabolic Rate”), is also of relevance to pathophysiological ischemia. NO is, in fact, a weak free radical that in turn leads to the generation of a more reactive species (peroxynitrite), and it is the *killer substance* used by macrophages. In cerebral ischemia, NO is probably both friend and foe. During a period of focal ischemia, the vasodilating effect of NO (probably constitutively elaborated NO of endothelial origin) probably serves to augment collateral CBF. However, in the postischemic phase, NO (probably derived from neurons or macrophages) contributes to neuronal injury.

Collectively, the simultaneous and unregulated activation of a number of cellular pathways overwhelms the reparative and restorative processes within the neuron and ultimately leads to neuronal death.

### The Nature of Neuronal Death

The neuronal death that occurs in response to these processes has been categorized as necrotic or apoptotic in nature. Necrotic death mediated by excitotoxic injury, is characterized by rapid cellular swelling, condensation and

pyknosis of the nucleus, and swelling of the mitochondria and ER. A characteristic of these necrotic neurons is the presence of acidophilic cytoplasm.<sup>237</sup> Necrotic neuronal death results in local infiltration of the brain by inflammatory cells. A considerable amount of collateral damage is a consequence of this inflammation.

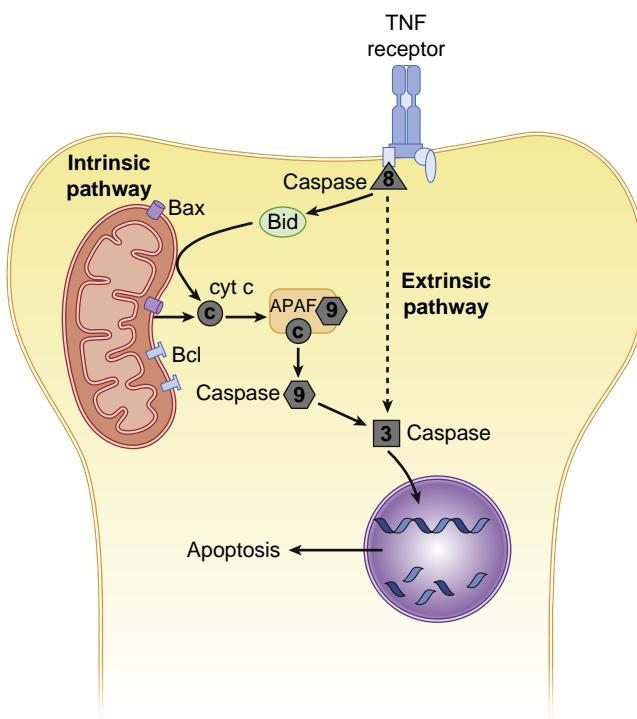
Neuronal apoptosis, a form of *cellular suicide*, has also been demonstrated in a variety of models of cerebral ischemia. Apoptosis is characterized by chromatin condensation, involution of the cell membrane, swelling of mitochondria, and cellular shrinkage. In the later stages of apoptosis, neurons fragment into several apoptotic bodies, which are then cleared from the brain.<sup>237</sup> The lack of a substantial inflammatory response to apoptotic death limits injury to surrounding neurons that have survived the initial ischemic insult.

A number of biochemical pathways that lead to apoptosis have been described. Initiation of apoptosis by the release of cytochrome *c* from injured mitochondria has been studied extensively (Fig. 11.21). Cytochrome *c* is restricted from the cytoplasm by the outer mitochondrial membrane.<sup>238</sup> When mitochondria are injured, pores within the outer membrane allow cytochrome *c* to be released into the cytoplasm, where it interacts with procaspase-9 and apoptosis-activating factor (APAF) to produce an apoptosome. Procaspsase-9 undergoes activation by proteolytic cleavage. Activated caspase-9 then activates caspase-3. The latter serves as an executor of apoptosis by cleaving a number of protein substrates that are essential in DNA repair (such as PARP). Activation of caspase-3 can also occur by inflammatory signaling via tumor necrosis factor alpha (TNF- $\alpha$ ) and the activation of caspase-8.<sup>239</sup> It should be noted that the neuronal injury that occurs in response to ischemia cannot be easily divided into necrosis or apoptosis. The nature of neuronal death probably encompasses a spectrum in which some neurons undergo either necrosis or apoptosis, whereas others undergo cell death that has features of both necrosis and apoptosis.

### Timing of Neuronal Death

The traditional concept of ischemic injury was that neuronal death was restricted to the time of ischemia and during the early reperfusion period. However, more recent data indicate that postischemic neuronal injury is a dynamic process during which neurons continue to die for a long period after the initiating ischemic insult (Fig. 11.22).<sup>240</sup> This delayed neuronal death, which was first demonstrated in models of global cerebral ischemia, has been demonstrated during focal ischemia as well. The extent of delayed neuronal death depends on the severity of the ischemic insult. With severe ischemia, most neurons undergo rapid death. With more moderate insults, neurons that survive the initial insult undergo delayed death. This ongoing neuronal loss contributes to the gradual expansion of cerebral infarction after focal ischemia. In experimental studies, evidence of cerebral inflammation, which can theoretically contribute to further injury, has been demonstrated even 6 to 8 months after the primary ischemia.

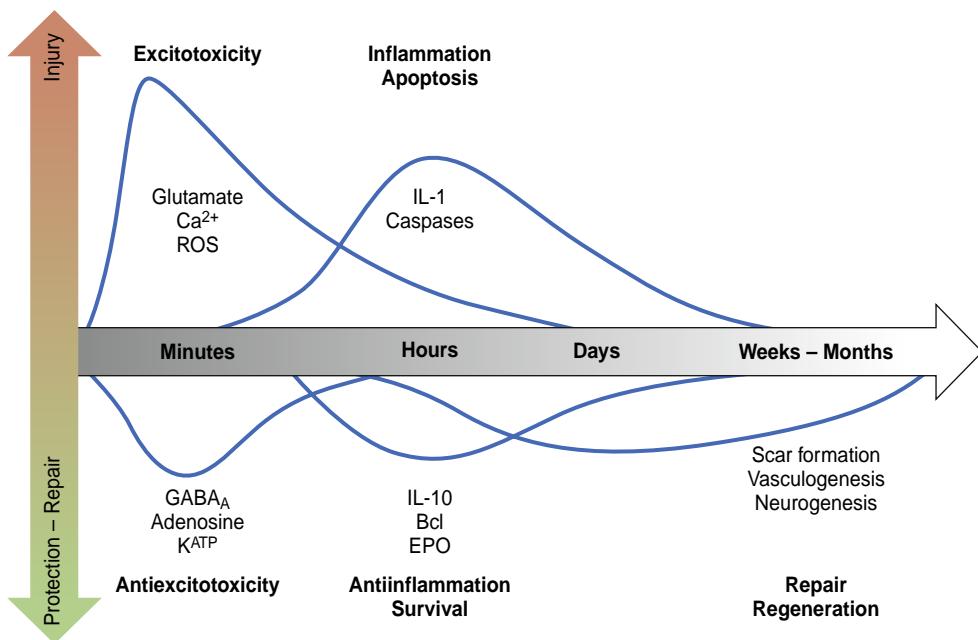
The occurrence of delayed neuronal death has important implications for the evaluation of studies in which neuroprotective strategies are being investigated. A wide variety of interventions have shown neuroprotective



**Fig. 11.21** Cellular processes that lead to neuronal apoptosis. Cytochrome *c* (*cyt c*), which is normally restricted to the space between the inner and outer mitochondrial membranes, is released in response to mitochondrial injury. *Cyt c*, in combination with apoptosis-activating factor (APAF), activates caspase-9 by proteolytic cleavage. Activated caspase-9 then leads to the activation of caspase-3. This enzyme cleaves a number of substrates, including those necessary for DNA repair. Within the mitochondria, Bax augments and Bcl prevents the release of *cyt c*. The release of *cyt c* can also be initiated by Bid, a substance that is activated by caspase-8 via tumor necrosis factor (TNF) signaling. In addition, caspase-8 can directly activate caspase-3. Excessive activation of poly-ADP-ribose polymerase, an enzyme integral to DNA repair, depletes cellular stores of oxidized nicotinamide adenine dinucleotide (NAD<sup>+</sup>). Depletion of NAD<sup>+</sup> further exacerbates the energy failure because of its critical role in energy metabolism.

efficacy in studies in which the extent of injury is evaluated within 3 to 4 days after ischemia. However, this neuroprotective efficacy may not be sustained. Recent data indicate that cerebral infarction undergoes gradual expansion and that a reduction in injury attributed to a particular therapeutic intervention is no longer apparent when the injury is evaluated after a long postischemic recovery period.<sup>240</sup> Long-term (>1 month) evaluation of the efficacy of a particular intervention is therefore important.

Much of the literature on the pathophysiologic process of cerebral ischemia has primarily been focused on neuronal injury. However, recent work has highlighted the importance of the contribution of astrocytes, microglia, vascular cells (e.g., endothelium, smooth muscle cells, pericytes), basement membranes, and extracellular matrix to stroke. These individual components in aggregate form the neurovascular unit. A detailed understanding of the contribution of each component of the neurovascular unit is a prerequisite, not only for the protection of the brain against ischemic and traumatic injury, but also for therapeutic approaches for the regeneration of the CNS.



**Fig. 11.22** Time course of neuronal death. Excitotoxic (glutamate-mediated) injury results in neuronal death within the first few hours after the onset of ischemia. Brain tissue injury elicits an inflammatory response—an important process in the removal of injured tissue and in healing—that leads to a substantial amount of collateral damage. Inflammation-mediated neuronal death can continue for several days. Neuronal apoptosis can occur in injured neurons that survived the initial insult. Apoptotic neuronal death has been demonstrated to occur for many days after the initiating ischemic insult. It is now apparent that ischemic neuronal death is a dynamic process during which neurons continue to die for a long period.  $Ca^{2+}$ , Calcium; *EPO*, erythropoietin; *GABA<sub>A</sub>*, gamma-aminobutyric acid *A*;  $K^{ATP}$ , adenosine triphosphate-regulated potassium; *IL-1*, interleukin 1; *IL-10*, interleukin 10; *ROS*, reactive oxygen species. (Adapted from Dirnagl U, ladecola C, Moskowitz M. Pathobiology of ischaemic stroke: an integrated view. *Trends Neurosci.* 1999;22:391–397.)

## BRAIN PROTECTION

Despite intense investigative efforts, pharmacologic agents that can protect the brain against ischemic injury have not been identified. The mainstay in the reduction of brain injury in the setting of acute ischemic stroke is thrombolysis. Management of thrombolysis has been reviewed in guidelines for the early management of patients with acute ischemic stroke.<sup>241</sup> Intravenous alteplase is recommended for patients in whom the time from onset of symptoms to treatment is less than 3 hours. Contraindications to thrombolysis include inability to identify onset of symptoms, intracranial hemorrhage, previous stroke or head trauma within 3 months, recent intracranial or spinal surgery, gastrointestinal malignancy, or bleeding and coagulopathy.<sup>241</sup> The window of thrombolysis may be extended to 4.5 hours in selected patients.

The narrow window for thrombolysis has limited the number of patients who may benefit from clot removal. Mechanical thrombectomy has recently considerably expanded this window. Previously, endovascular treatment of acute ischemic stroke with large clot in large vessels was restricted to a time period of no more than 6 hours from the time that the patients were last known to be well. Two recent trials demonstrated improved neurologic outcome following internal carotid or proximal MCA thrombectomy in patients up to 16 and 24 hours from the time they were last known well. A key enrollment requirement was the presence of a substantial volume of ischemic, but not yet infarcted, tissue that might be amenable to salvage (substantial mismatch between ischemic and infarcted tissue, indicating that noninfarcted tissue could be salvageable).

The DAWN trial used strictly defined mismatch criteria based upon discrepancy between the clinical neurologic deficit (National Institutes of Health Stroke Scale score) and the volume of infarcted tissue.<sup>242</sup> The DEFUSE 3 trial utilized imaging (computed tomography perfusion or MRI diffusion–perfusion) to identify mismatch between ischemic and infarcted tissue.<sup>243</sup> In both studies, the outcome was more favorable in patients who underwent thrombectomy. These studies will increase the number of patients that are eligible for endovascular treatment following acute ischemic stroke. Consequently, the frequency of involvement of the anesthesiologist in the care of these patients will increase significantly.

The literature on cerebral ischemia and brain protection is vast, and a detailed discourse on this topic is beyond the scope of the present discussion. A number of excellent recent reviews on the subject are available.<sup>244–253</sup>

### Considerations Relevant to Complete Global Ischemia (Cardiac Arrest)

Maintaining adequate perfusion pressure after cardiac arrest is of considerable importance. Hypotension developing after resuscitation from cardiac arrest may aggravate the microcirculatory and vasospastic processes occurring at this time and may increase brain damage. A late phase of intracranial hypertension may occur and is due to the development of extensive cerebral edema (probably both vasogenic and cytotoxic edema) associated with brain necrosis. Attempts to control this type of intracranial hypertension with osmotherapy are particularly effective.

Both barbiturates and CCBs have been administered after cardiac arrest. The former are ineffective. In a small cohort (51 patients) of patients after cardiac arrest, nimodipine was shown to improve CBF but not neurologic outcome.<sup>254</sup> In a second trial with approximately 150 patients after cardiac arrest, no overall benefit in neurologic outcome was observed.<sup>255</sup> However, a subset of patients in whom the initiation of advanced life support was delayed for longer than 10 minutes demonstrated improved survival. This single study cannot serve as justification for the administration of nimodipine after cardiac arrest, especially in the face of the unequivocally negative results of the multicenter lidoflazine cardiac arrest study.<sup>256</sup> Once again, the important therapeutic objectives are the maintenance of normocapnia and normotension, normalization of systemic pH, avoidance of hyperoxia,<sup>257</sup> avoidance of hyperthermia, and prevention and treatment of seizures.

Induced mild hypothermia is effective in reducing mortality and morbidity in patients who sustain a cardiac arrest that is followed by altered mental status with a Glasgow Coma Scale score of 7 or less.<sup>258</sup> Induction of mild hypothermia in the range of 32°C to 34°C for a period of approximately 24 hours improved neurologic outcome and survival 6 months after cardiac arrest in comparison with a normothermic group. Mild hypothermia was induced without difficulty. Passive rewarming of patients was slowly accomplished over a period of 8 hours. The incidence of complications was similar to that in the control normothermic group. This important study is one of the first to demonstrate the feasibility and efficacy of induced hypothermia as a treatment to reduce injury from global ischemia. In neonates who sustained hypoxic-ischemic encephalopathy, induction of whole body hypothermia (33.5°C) for 72 hours resulted in a reduced incidence of mortality.<sup>259</sup> Long-term follow-up of patients enrolled in the study confirmed the potentially beneficial effects of mild hypothermia.<sup>260</sup> In many institutions, induced hypothermia has been added to the armamentarium for the treatment of cerebral complications of cardiac arrest or global neonatal hypoxic-ischemic encephalopathy.

### Considerations Relevant to Focal (Incomplete) Ischemia

Before discussing individual anesthetics, it should be noted that anesthesia, *per se*, is protective. For undefined reasons, reducing the level of systemic stress associated with a standardized experimental insult results in an improved outcome.<sup>261,262</sup> In reviewing the protection-by-anesthetics literature, readers should be conscious of the possibility that the protective benefit ascribed to an intervention with an anesthetic drug may, in fact, be the product of exaggeration of the injury in a high-stress control state, such as N<sub>2</sub>O sedation.

**Barbiturates.** Numerous demonstrations have revealed the protective efficacy of barbiturates in focal cerebral ischemia in animals,<sup>263-265</sup> and a single demonstration confirmed the effectiveness in humans.<sup>266</sup> The effect has been attributed principally to suppression of CMR. However, the effects of CBF redistribution and free radical scavenging<sup>267</sup> may contribute, and evidence indicates that CMR suppression is not the sole mechanism.<sup>268</sup> Suppression of CMR

might logically be expected to be of benefit to brain regions in which oxygen delivery is inadequate to meet normal demands but is sufficient to allow energy consumption by some ongoing electrophysiologic activity (i.e., in which the EEG was abnormal but not flat). Such regions are likely to be limited in size in the setting of focal ischemia, yet several of the animal investigations suggest a very substantial protective effect.<sup>263,264</sup> Review of these experiments reveals that the methods used to monitor and maintain temperature, although accepted at the time, were below the standards that have evolved from a more recent understanding of the effects of both deliberate<sup>269,270</sup> and inadvertent hypothermia. Unrecognized cerebral hypothermia may well have been a factor in some of the cited investigations, and it is therefore possible that the protective efficacy of barbiturates may have been overestimated. Although more recent publications involving suitable temperature control methods do, in fact, indicate a protective effect of barbiturates,<sup>268,271,272</sup> the magnitude of that effect was modest when compared with the results of earlier studies. Barbiturate-induced EEG suppression in an already anesthetized patient may still be logical therapy when it can be applied before or early in the course of a period of temporary focal ischemia (e.g., temporary occlusion during aneurysm surgery). However, the decision to institute such therapy should be made only after considering the risk of the occlusive event, the patient's cardiovascular status, and the physician's willingness to accept the possibility of delayed emergence, together with an objective view of the probable magnitude of the protective effect.

Numerous investigations in animals and humans have failed to demonstrate any protective effect of barbiturates in the setting of global cerebral ischemia (e.g., cardiac arrest).

Because CMR suppression has been the presumed mechanism of effect, barbiturates have traditionally been administered to produce maximal reduction of the CMR (which is nearly complete when EEG burst suppression has been achieved). However, the same protective benefit (expressed as a reduction of infarct volume) was observed in an animal investigation with one third of the burst-suppression dose.<sup>268</sup> This raises a clinically important issue. The various barbiturates (e.g., thiopental, thiamylal, methohexitol, pentobarbital) have similar effects on the CMR and have generally been assumed to have equal protective efficacy. However, if the mechanism of protection is a pharmacologic effect other than a reduction in the CMR, then is it reasonable to assume equivalence among the barbiturates? Recent data suggest that the neuroprotective efficacy of barbiturates is not similar. In a direct comparison of three clinically used barbiturates, methohexitol and thiopental, but not pentobarbital, reduced injury in an animal model of focal ischemia.<sup>273</sup> These data suggest that mechanisms other than or at least in addition to metabolic suppression may contribute to the protective effect of barbiturates.

**Volatile anesthetics.** Isoflurane is also a potent suppressant of CMR in the cerebral cortex, and EEG evidence suggestive of a protective effect in humans has been reported.<sup>232</sup> In comparison with the awake or N<sub>2</sub>O-fentanyl-anesthetized state, isoflurane is neuroprotective in models of hemispheric,<sup>274</sup> focal,<sup>275</sup> and nearly complete ischemia.<sup>276,277</sup> Of

substantial clinical relevance is the observation in a preclinical investigation that isoflurane's neuroprotective efficacy is not sustained.<sup>278</sup> When injury was evaluated 2 days after ischemia, a robust reduction in injury was observed with isoflurane anesthesia. However, by 14 days, this reduction in injury was no longer apparent. These data indicate that neuronal injury continues well into the postischemic recovery period and that the neuroprotective benefit that is evident shortly after ischemia may not persist for the long term. More recent data have shown that isoflurane treatment can improve neuronal survival when the severity of ischemia is limited and the restoration of blood flow after ischemia is complete.<sup>279</sup> The neuroprotective effect of isoflurane is not substantially different from that of other volatile anesthetics. Sevoflurane reduces ischemic injury in animal models of focal<sup>280</sup> and hemispheric ischemia;<sup>281</sup> its efficacy is not different from that of halothane. Desflurane also reduces neuronal injury to the same extent that isoflurane does.<sup>282</sup> The available data therefore suggest that adequate anesthesia, *per se*, may have a protective effect<sup>261,262</sup> versus the awake state, but there does not appear to be any difference in neuroprotective efficacy among the volatile anesthetics.

**Xenon.** The inert gas xenon exerts its anesthetic action by noncompetitive blockade of NMDAR. As such, it is logical to suspect that it might provide neuroprotection against excitotoxic injury. The neuroprotective efficacy of xenon has been demonstrated against focal ischemia *in vivo* in mice,<sup>283</sup> and cardiopulmonary bypass-induced cognitive dysfunction in rats.<sup>284</sup> Of interest are observations that simultaneous administration of *subanesthetic* doses of xenon in combination with either hypothermia or isoflurane<sup>285</sup> significantly reduces neuronal injury and improves neurologic function in experimental models; this protective effect was apparent as late as 30 days after injury in a model of neonatal asphyxia. Note should be made, however, that long-term neuroprotection with xenon has not yet been demonstrated in experimental adult subjects. Currently, data are not available to support the specific use of xenon for the purpose of neuroprotection in humans.

**Propofol.** EEG suppression can also be achieved with clinically feasible doses of propofol. One case series and informal colleague communications indicate that it is being used to provide *protection* during both aneurysm surgery<sup>286</sup> and carotid endarterectomy (CEA). Cerebral infarction was significantly reduced in propofol-anesthetized animals in comparison with awake animals.<sup>287</sup> Direct comparison of propofol to pentobarbital has also demonstrated that cerebral injury after focal ischemia is similar in animals anesthetized with the two drugs.<sup>288</sup> Similar to the situation with volatile anesthetics, initial investigations revealed that propofol protection is not sustained.<sup>289</sup>

**Etomidate.** Etomidate was proposed as a potential protective anesthetic in the setting of aneurysm surgery.<sup>290</sup> It also produces CMR suppression to an extent equivalent to barbiturates, and similar to the barbiturates, etomidate is an agonist at the (inhibitory) GABA<sub>A</sub> receptor. Nonetheless, in an experimental model of focal ischemia, the

volume of injury was not reduced by etomidate relative to a 1.2 MAC halothane-anesthetized control group. In fact, the volume of injury with etomidate was significantly larger than that in the control group. In patients subjected to temporary intracranial vessel occlusion, the administration of etomidate results in greater tissue hypoxia and acidosis than equivalent desflurane anesthesia. The aggravation of injury produced by etomidate (an imidazole) may be related to direct binding of NO as a consequence of etomidate-induced hemolysis<sup>291</sup> combined with direct inhibition of the NO synthase enzyme by etomidate. Therefore, no scientific studies support the current use of etomidate for cerebral protection and, in fact, suggest that it may actually be deleterious in the setting of focal ischemia.

**Calcium channel antagonists.** Orally administering nimodipine (the intravenous preparation is not approved for clinical use in North America) for 21 days beginning as soon as possible after subarachnoid hemorrhage (SAH) is now established clinical practice.<sup>292</sup> Other CCBs have reduced vasospasm after SAH but have not improved patient outcome, suggesting the benefit of nimodipine is a cellular rather than a vascular effect. However, by contrast with SAH, routinely administering nimodipine or any other CCB after neurologic stroke that has occurred in the surgical unit or in any other environment has not yet become standard practice. Despite favorable results in small trials, not all investigations of those who have sustained stroke have confirmed the benefits of nimodipine.<sup>293</sup> Although the administration of CCBs for the management of blood pressure is reasonable, their administration for the sole purpose of neuroprotection is not currently recommended.<sup>241</sup>

**Other anesthetics.** A remarkable number of anesthetics have shown neuroprotective efficacy in animal studies. However, to date, large-scale randomized trials of a variety of anesthetics in patients with stroke have not demonstrated neuroprotection for any drug. With the exception of tissue plasminogen activator (tPA) for thrombolysis, mechanical thrombectomy, and the CCBs nimodipine and nicardipine for the management of SAH, pharmacologic neuroprotective agents are not available for the treatment of patients with cerebral ischemia. Details about drugs that have undergone clinical trials and those that are currently being investigated in humans can be found at the Stroke Trials Registry ([www.strokecenter.org/trials/clinicalstudies](http://www.strokecenter.org/trials/clinicalstudies)) of Washington University in St. Louis.

### Cerebral Ischemia: Influence of Physiologic Variables

**Cerebral perfusion pressure.** Measures designed to augment CBF (an important determinant of energy supply) are also important. In the *ischemic penumbra* (described in the section “Critical Cerebral Blood Flow Thresholds”), small improvements in CBF have the potential to prolong neuronal survival substantially. Maintenance of high-normal CPP can augment collateral perfusion pressure and maintain CBF<sup>294</sup> and has been shown to result in improvement in neurologic function.<sup>295</sup> By contrast, hypotension can

reduce CBF and exacerbate injury. In trials of nimodipine in patients with acute stroke, a reduction in blood pressure of 10% to 20% increased the probability of an adverse outcome (either death or dependency) fourfold,<sup>296</sup> thus emphasizing the adverse impact of blood pressure reduction on an injured brain. Therefore, in patients with cerebral ischemia, hypotension should be promptly treated and normotension restored. Although the target MAP should obviously be based on knowledge of a patient's preexisting blood pressure, data to provide specific guidelines are insufficient in humans.<sup>241</sup> In the majority of patients, maintenance of the MAP in the 70 to 80 mm Hg range should be adequate. The available data provide support for reducing blood pressure to less than 180/105 mm Hg in patients with stroke who have been treated with thrombolytic agents in the hope of reducing the incidence of hemorrhage into the ischemic brain.<sup>241</sup> In addition, blood pressure augmentation (after ensuring euvoolemia) to a systolic pressure of approximately 180 mm Hg in patients with SAH-induced vasospasm<sup>297</sup> and to a CPP of 60 to 70 mm Hg in patients with traumatic brain injury<sup>298</sup> is reasonable.

**Carbon dioxide tension.** Hypercapnia has the potential to cause intracerebral steal and may worsen intracellular pH. Despite some support for the occurrence of a favorable so-called Robin Hood or inverse steal, hypocapnia has not generally proved effective in either laboratory or clinical settings. Pending further information and in the absence of a means of verifying the perfusion response to the manipulation of  $\text{Paco}_2$ , normocapnia remains standard practice.<sup>298</sup>

**Temperature.** Hypothermia is the principal cerebral protective technique for circulatory arrest procedures. It unequivocally enhances cerebral tolerance for episodes of ischemia. For deep hypothermia, this effect is largely a function of the reduction in the CMR. Although barbiturates reduce only the component of the CMR associated with electrophysiologic work (approximately 60% of the  $\text{CMRO}_2$  in the awake state), hypothermia causes a reduction in both electrophysiologic energy consumption and energy utilization related to the maintenance of cellular integrity; mild hypothermia may preferentially suppress the latter.<sup>299</sup> A substantial number of laboratory studies have demonstrated that mild degree of hypothermia (2°C-4°C) during an episode of ischemia can confer substantial protection as histologically measured.<sup>269,270</sup> In addition, hypothermia initiated in the immediate postischemic period confers a protective benefit.<sup>300</sup>

In light of this dramatic protective effect of mild hypothermia in the laboratory, its use in the surgical setting has been advocated. Proponents of its use argue that hypothermia is readily achieved and not accompanied by significant myocardial depression or arrhythmias. In addition, the patient can be easily rewarmed in the surgical unit after the risk of ischemia has subsided. Results of a pilot study clearly demonstrated a trend toward improved neurologic outcome in hypothermic patients undergoing intracranial aneurysm clipping.<sup>301</sup> Unfortunately, the subsequent definitive Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) did not demonstrate

any improvement in outcome that could be attributable to hypothermia.<sup>302</sup> However, the majority of the patients in that study had SAH of grades I, II, and III. In addition, the number of patients who had temporary clips applied in excess of 20 minutes was quite small (five to six patients). Consequently, an argument has been advanced that mild hypothermia may be of benefit in patients with high-grade aneurysms or in those in whom the complexity of the aneurysm clipping is such that prolonged temporary clipping may be required. Considering that temperature reduction takes time, the decision to induce hypothermia must be made in advance. It is therefore our view that the therapeutic use of hypothermia may be considered in such high-risk patients.<sup>297</sup>

The application of mild hypothermia after head injury reduced ICP<sup>303</sup> and improved neurologic outcome<sup>304</sup> in pilot trials. Complications attributable to hypothermia were not observed. Two subsequent multicenter trials of hypothermia in patients with head injuries, however, failed to confirm the findings of the pilot studies.<sup>305,306</sup> Induction of mild hypothermia did not improve long-term neurologic outcome.

A number of clinical trials of induced hypothermia in a limited number of patients with stroke have been conducted. To date, these trials have demonstrated the feasibility of inducing hypothermia in the range of 33°C to 35°C, even in patients who are not subjected to endotracheal intubation and mechanical ventilation.<sup>307</sup> Hypothermia was associated with improved ICP and CPP. However, complications, particularly thrombocytopenia, bradycardia, ventricular ectopy, hypotension, and infection, are frequent. In addition, an intractable increase in ICP can occur during rewarming, even if the elevation in temperature is gradual and accomplished over a period of several hours. These side effects attest to the need to conduct randomized trials to evaluate properly the efficacy of mild hypothermia in patients with stroke. At the current time, however, hypothermia for purposes of neuroprotection in the setting of acute ischemic stroke is not recommended.<sup>241</sup>

Data regarding the application of mild hypothermia in survivors of cardiac arrest are more positive. Two recent trials have demonstrated that the induction of hypothermia (32°C-34°C) after successful resuscitation from cardiac arrest resulted in a significantly better neurologic outcome 6 months after the arrest.<sup>258,308</sup> These studies demonstrate the clinical efficacy of hypothermia for the purposes of reducing ischemic cerebral injury and provide indirect support for the use of intraoperative hypothermia in patients who are considered to be at high risk.

By contrast, increases in brain temperature during and after ischemia aggravate injury dramatically.<sup>309</sup> An increase of as little as 1°C can increase injury. Ischemia that normally results in scattered neuronal necrosis produces cerebral infarction when body temperature is elevated. Therefore, avoiding hyperthermia in patients who have suffered an ischemic insult or in those who are at risk for cerebral ischemia seems prudent. In the surgical setting, hyperthermia is seldom a problem. In patients at risk of ischemic cerebral injury, treatment of hyperthermia with antipyretics is currently recommended.<sup>241</sup>

**Glucose.** Withholding glucose-containing solutions in situations during which cerebral ischemia may occur is now an established practice. The practice is based on numerous demonstrations in animal models of brain and spinal cord ischemia that elevation of plasma glucose before episodes of either complete or incomplete ischemia results in the aggravation of neurologic injury. However, the majority of investigations involved adult animals and that certainty concerning the adverse effects of hyperglycemia in immature subjects, such as neonates, is less.<sup>310</sup> Furthermore, only some<sup>311,312</sup> and not all<sup>313</sup> of the investigations in humans have provided confirmation of an independent effect of serum glucose on neurologic outcome. Nonetheless, in long-term outcome studies, diabetic and nondiabetic hyperglycemia has been shown to be an independent predictor of poor outcome.<sup>312</sup> In the National Institutes of Health–sponsored recombinant tPA stroke trial, hyperglycemia was associated with significantly lower odds for desirable clinical outcomes and a higher incidence of intracranial hemorrhage.<sup>314</sup> These data prompted a randomized clinical trial of the efficacy of insulin administration to patients with acute stroke. The results showed that the administration of insulin to control blood glucose levels in patients with stroke did not improve outcome 3 months after stroke.<sup>315</sup> A recurrent theme in the discussion of these studies is that glucose elevation may be the *result* of the stress associated with a severe insult, either ischemic or traumatic, rather than its *cause*. In addition, the inevitable questions of whether and how quickly immediate pretreatment of an elevated plasma glucose level with insulin reduces risk to normoglycemic levels have not been thoroughly examined. Based on the lack of the benefit of restoration of glucose within the normal range (referred to as “tight” control), the current recommendations, which call for the maintenance of blood glucose values in the 140 to 180 mg/dL range, represent reasonable clinical objectives.<sup>241</sup>

By contrast, hypoglycemia is also associated with cerebral injury. With a gradual reduction in blood glucose values to approximately 40 mg/dL, a shift in EEG frequencies occurs from alpha and beta toward delta and theta.<sup>316</sup> Below a blood glucose level of 20 mg/dL, suppression of the EEG (flat) is observed. Persistence of this level of hypoglycemia results in seizure activity and neuronal injury, particularly to the hippocampus.

**Seizures.** Seizures cause dramatic increases in CMR and CBF. Sustained seizure activity can significantly augment injury in the damaged brain. Accordingly, seizures should be promptly treated with appropriate antiepileptics in the setting of acute stroke (see the section “Coma and Epilepsy” later in the chapter).<sup>241</sup>

**Intravascular volume and hematocrit manipulation.** Hemodilution has not proved effective in studies of human stroke. Although hemodilution was often instituted in patients with ischemia associated with vaso-spasm in SAH with the goal of increasing CBF, current practice is focused more on the maintenance of euvoolemia and induction of modest increases in blood pressure rather than on hemodilution. In addition, the data do not currently justify routine hemodilution (a hematocrit

of 30%-35% is the theoretic optimum) in patients in whom focal ischemia *might* occur in the surgical unit.<sup>317</sup> An increased hematocrit, because of viscosity effects, reduces CBF.<sup>14</sup> In anticipation of a procedure wherein incomplete ischemia might occur, such as CEA, preoperative phlebotomy should be considered when hematocrit is in excess of 55%.

**Hyperoxia.** Hypoxia has repeatedly been shown to adversely affect outcome in patients with brain injury from a variety of causes. In an attempt to prevent hypoxia, administration of supplemental oxygen often leads to relative hyperoxia, with  $\text{PaO}_2$  well in excess of normal values. Hyperoxia is associated with vasoconstriction and reduction in microvascular tissue flow, generation of reactive oxygen species, and augmentation of inflammation.<sup>318</sup> This has led to concerns about the potential adverse effects of excess oxygen in the injured brain.<sup>319</sup>

In patients who had sustained cardiac arrest and who were admitted to an intensive care unit after successful recovery of circulation, hyperoxia increased mortality.<sup>320</sup> The threshold  $\text{PaO}_2$  that leads to this increase in mortality is greater than 300 mm Hg;  $\text{PaO}_2$  in the range of 100 to 300 mm Hg was not associated with increased mortality.<sup>321</sup> By contrast, no adverse effect of hyperoxia on long-term outcome (12 months) was apparent among survivors of cardiac arrest.<sup>322</sup> In the setting of head injury, endothelial and tissue edema can reduce diffusion of oxygen to neurons. Hyperoxia improves cerebral metabolism but only in regions of the brain wherein metabolism has been significantly reduced.<sup>323</sup> Other investigations, however, have shown either worse outcomes in hyperoxic patients,<sup>324</sup> especially in those in whom  $\text{PaO}_2$  was excessive (>487 mm Hg), or no effect on long-term outcome.<sup>325</sup> In acute stroke, oxygen administration by nasal cannula, oxygen mask, and endotracheal tube is not associated with adverse outcomes.<sup>326</sup> Similarly, supplemental oxygen administration to patients with SAH does not impact outcomes.<sup>327</sup>

With these conflicting data, it is difficult to draw firm conclusions that can inform clinical decisions. The available data do not allow for the determination of a target  $\text{PaO}_2$ , and this is not surprising, given the heterogeneous nature of cerebral injury. Consequently, oxygen administration should be customized in each patient, with the goal being the aggressive treatment of hypoxemia and avoidance of hyperoxia (>300 mm Hg) in patients in whom oxygenation is within normal limits.

### Summary of Anesthetics and Neuroprotection

In comparison to the awake or lightly sedated state, the vulnerability of the brain to ischemic injury is reduced under anesthesia. Volatile anesthetics, barbiturates, propofol, xenon, and ketamine reduce injury in experimental models and may reduce injury in comparison with a pure  $\text{N}_2\text{O}$ -narcotic anesthetic. However, direct comparison has not demonstrated the superiority of any one anesthetic (or combination of anesthetics) over another. Therefore, based on the available data, the use of a specific anesthetic or anesthetic regimen for the purpose of brain protection in the clinical setting cannot be recommended.

There is a paucity of information about anesthetic neuroprotection in humans and the lack of clinical trials is understandable, considering the low frequency of stroke and ischemic injury in the perioperative setting. There are, however, a few clinical investigations from which inferences about anesthetic neuroprotection can be made. In the aforementioned IHAST aneurysm trial, a subset of patients received supplemental doses of thiopental, etomidate, or propofol for the purpose of neuroprotection. The neurologic outcome in these patients was no different than those who did not receive these anesthetics.<sup>328</sup> In the general anesthesia versus local anesthesia trial,<sup>329</sup> patients undergoing CEA were randomized to receive either general anesthesia or local anesthesia; in the latter group, patients were lightly sedated but were arousable during surgery. The outcome between the two groups was not different, indicating that the general anesthetic state did not provide any protective benefit.<sup>329</sup> Finally, in a recent retrospective trial of thrombolysis for acute stroke, patients who were anesthetized had a worse outcome than those who were only mildly sedated. Although the worse outcome with general anesthesia was attributed to a lower CPP in that group,<sup>330</sup> the results do not provide evidence of anesthetic neuroprotection. In aggregate, these data suggest that supplemental drugs that produce burst suppression of the EEG do not provide protection in anesthetized patients and that the state of general anesthesia does not improve neurologic outcome measurability.

The neuroprotective efficacy of anesthetic drugs in experimental studies is achieved only by rigorous maintenance of physiologic homeostasis; in fact, the potential for exacerbation of cerebral injury, either traumatic or ischemic, with physiologic mismanagement is significantly greater than the modest protection afforded by pharmacologic drugs—these are important observations. Accordingly, with respect to brain protection, efforts should be focused on the maintenance of physiologic parameters (e.g., perfusion pressure, oxygenation, normocapnia, temperature management, control of hyperglycemia, seizure prophylaxis) within the appropriate ranges and less on pharmacologic or anesthetic drugs to reduce cerebral injury.

### Deferring Elective Procedures After Stroke

The risk of extension of cerebral infarction in the event of subsequent anesthesia and surgery has not been studied systematically. In patients who have suffered a stroke, CBF undergoes significant changes. Areas of both high and low CBF occur, and stabilization of regional CBF and CMR is apparent after approximately 2 weeks.<sup>331</sup> Loss of normal vasoconstrictor responses (e.g., CO<sub>2</sub> responsiveness, autoregulation) in the early postinsult period is very common, and these changes persist beyond 2 weeks in a small percentage of patients with stroke. BBB abnormalities, as reflected by the accumulation of CT contrast material or brain scan isotopes, are still present 4 weeks after the insult,<sup>332</sup> and the histologic resolution of large infarcts is not complete for several months. Early CEA after stroke in patients with large strokes and neurologic disability was accompanied by an increased risk of intracerebral hemorrhage.<sup>333</sup> In a recent large cohort study, the occurrence of adverse cardiovascular events, including new stroke and myocardial infarction, was considerably greater in patients who underwent noncardiac surgery within 3 months of having a stroke;

the complication rate stabilized 9 months after stroke.<sup>334</sup> Based on early experience with CEA, deferring CEA for at least 6 weeks after stroke is recommended.<sup>333</sup> A 6-week delay should give some assurance of the probable recovery of autoregulation, CO<sub>2</sub> responsiveness, and BBB integrity.

A delay in CEA after stroke, however, poses risks. In patients who have sustained a stroke, the incidence of a second stroke is approximately 12%.<sup>335</sup> The risk of a complete carotid occlusion is considerable with delayed surgery. In addition, early CEA can restore cerebral perfusion to the ischemic penumbra, possibly improving long-term functional recovery. However, the size and location of the infarction should be weighed. A small infarction in the silent cortex may offer wider latitudes than a large lesion that has resulted in a paresis that is still resolving. A small prospective study suggests that in patients with non-disabling stroke, early CEA can be performed safely within 2 weeks of the stroke.<sup>336</sup> Candidates for early CEA after stroke may include patients with relatively small cerebral infarctions, with complete or near complete resolution of neurologic symptoms, and those with ipsilateral carotid artery stenosis.<sup>337</sup> Delaying CEA in patients who have had large strokes with significant neurologic disability, reduced level of consciousness, and displaying a midline shift on the CT scan is generally preferable.

Outcome data to inform the decision about surgery for the patient after stroke, other than CEA, is lacking. With the extrapolation of the information from the CEA studies, pending other information, deferring elective surgery for at least 4 weeks after a cerebral vascular accident and preferably for 6 weeks from the point at which a stable postinsult neurologic state has been achieved seems reasonable.<sup>334</sup>

### CHRONIC ARTERIAL HYPERTENSION

A recurrent concern is that of acceptable levels of arterial blood pressure reduction in patients who are chronically hypertensive. Firm guidelines have not been established. However, from the vantage of cerebral well-being, limiting elective MAP reduction 20% to 25% of resting mean levels seems appropriate for both hypertensive and normotensive patients. The same guidelines might apply in both populations, because in chronic hypertension, both the LLA and ULA are shifted to the right with apparently little distortion.<sup>338</sup>

The rationale for a limit of 20% to 25% is as follows. MAP reductions of 50% in nonanesthetized patients, both normotensive and hypertensive, will commonly produce reversible symptoms of cerebral hypoperfusion.<sup>338,339</sup> Although even greater reductions will probably be tolerated provided that exposures are brief, the hematocrit is reasonable, and the cerebral vasculature is patent, the authors counsel against it. A reduction in the MAP of this magnitude will significantly increase the probability of CPP being close to or below the LLA, thereby reducing cerebrovascular reserve. It has been demonstrated that, on average, a 25% reduction in the MAP will bring both normotensive and hypertensive patients to the LLA.<sup>338</sup> As the reduction in the MAP exceeds 25% of baseline, CBF values will be below normal, albeit, in patients free of occlusive vascular disease, above the threshold for neurophysiologic dysfunction or injury (see Fig. 11.6). However, the physiologic reserve is

being encroached upon, thereby leaving little margin for error or for other causes of impaired cerebral oxygen delivery such as low hematocrit or poor collateralization caused by congenital variation or unrecognized cerebrovascular disease.

In animals, treatment of chronic hypertension can restore the LLA to normal.<sup>340, 341</sup> A similar phenomenon has been observed in humans, although restoration was incomplete and had failed to occur after as long as 12 months of treatment in some patients.<sup>338</sup> It is an unexplored possibility that the extent of restoration of the LLA with antihypertensive therapy is agent dependent. Some may restore the LLA more effectively than others. In particular, ACE inhibitors have been shown to decrease the LLA acutely in both normotensive and hypertensive subjects.<sup>342, 343</sup>

### Intracranial Hypertension

Control of intracranial hypertension is discussed in detail in Chapter 57.

### BRAIN TUMORS

There are few data regarding the physiologic function of intracranial tumors. Measurement of CBF in cerebral tumors with laser Doppler technology revealed that tumors had lower CBF than the normal brain.<sup>344</sup> Autoregulation was occasionally apparent. Vascular responsiveness to changes in  $\text{PaO}_2$ <sup>345</sup> and  $\text{PaCO}_2$ <sup>346</sup> are generally preserved in patients with gliomas. Propofol reduces CBF in regions of the brain surrounding the tumor, and quantitatively, the reduction in CBF is similar to that in the contralateral normal hemisphere.<sup>347</sup> Measurement of regional CBF in the area of the tumor might also be a useful predictor of the grade of intracranial gliomas; both regional CBF and regional CBV are greater with high-grade gliomas.<sup>348</sup> Considerable edema is often associated with intracranial tumors, and the radiologic extent of the edema, which presumably represents the extent of abnormal vessel leakiness, correlates with the severity of the elevation in ICP that occurs in association with intubation-related hypertension.<sup>349</sup> Edema formation in the peritumoral region can be characterized as vasogenic with leakage of plasma proteins from the vascular space, hydrocephalic secondary to obstruction of CSF flow, or static as a result of venous obstruction by tumor.<sup>350</sup> Although the precise mechanisms by which edema formation occurs are not clear, the loss of integrity of the tight junctions of components of the BBB, an increased permeability induced by vascular endothelial growth factor expressed by tumors, and an increased expression of leukotriene C4 in peritumoral fluid probably play a role.<sup>351</sup> Osmotherapy with mannitol will effect a reduction in edema; however, with a permeable BBB, mannitol can diffuse into the peritumoral space and lead to rebound edema formation.<sup>350</sup> For acute reduction of ICP in the surgical unit, this concern is not significant. A reduction in osmotherapy-induced neuronal cell volume leads to the intraneuronal accumulation of “idiogenic” osmoles. The consequent increase in intraneuronal osmolarity leads to a reuptake of water into the cell in a compensatory attempt to restore cell volume. This process also contributes to the occurrence of rebound edema. The accumulation of idiogenic osmoles can be reduced significantly by loop diuretics

such as bumetanide.<sup>352</sup> Dexamethasone remains the mainstay of treatment of tumor edema; it causes a reduction in edema formation with little effect on edema reabsorption. See Chapter 57 for a complete discussion.

### COMA AND EPILEPSY

Regardless of its cause, coma reduces brain metabolism. In the case of lesions occurring in the reticular activating system, the reduction in the CMR probably represents a normal physiologic adjustment to reduced functional activity. During generalized seizure activity, CMR and CBF may increase dramatically.<sup>187</sup> The intensive motor and brain activity associated with generalized seizures leads to the development of systemic and cerebral acidosis, often accompanied by a reduction in arterial oxygenation, an increase in  $\text{PaCO}_2$ , and peripheral lactic acidosis. If generalized seizure activity continues unabated, then arterial hypotension ensues. With muscular relaxation and measures ensuring adequate oxygenation and ventilation, the systemic acidosis and hypotension can be avoided and the severity of the cerebral acidosis diminished. During relatively brief episodes of continuous seizures, the brain seems able to meet the high metabolic demands.<sup>204</sup> However, even with effective ventilation and maintenance of perfusion pressure, when seizures continue for a prolonged period, they can lead to the development of irreversible neuronal damage.<sup>353</sup> Therapy aimed at interrupting the seizure and restoring a normal balance between cerebral metabolic demand and blood flow is indicated. Barbiturates, benzodiazepines, or other potent anticonvulsants are appropriate. Adequate ventilation, oxygenation, and maintenance of arterial blood pressure are important adjunctive measures. Muscle relaxants must be viewed as purely symptomatic therapy because they do not alter the abnormal cerebral electrical activity. There is, in addition, the concern that muscle paralysis may mask seizure activity, especially when the EEG is not monitored.

The potentially injurious nature of seizures justifies attention to prevention. Practices vary. However, any patient in whom a substantial cortical incision is planned is at risk, and prophylactic anticonvulsants in the perioperative setting should be considered.

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## KEY POINTS

- The neuromuscular junction contains the distal nerve terminal, Schwann cell, synaptic cleft, and muscle end plate, which together provide an array of receptors and substrates for drug action. Neuromuscular transmission is predominantly dependent on acetylcholine as the natural transmitter. Acetylcholine, when released from the prejunctional nerve terminal, binds to acetylcholine receptors (AChRs) that are present either prejunctionally or postjunctionally within the neuromuscular junction (synapse) and, depending on their structural composition, are classified into the usual muscle subtype AChRs or a variety of neuronal subtype AChRs.
- Muscle relaxants have multiple sites of action. Although the major actions occur by mechanisms and at sites described as agonistic and antagonistic actions at postjunctional receptors for depolarizing and nondepolarizing muscle relaxants (NDMRs), this description of neuromuscular drug action is a simplistic one. Neuromuscular transmission is impeded by NDMRs because they prevent access of acetylcholine to its preferred recognition site on the postjunctional nicotinic AChRs.
- If the concentration of NDMR is increased, another, noncompetitive action—block of the ion channel—is superimposed. The postjunctional paralytic effects of muscle relaxants can be enhanced by the actions of the relaxant on prejunctional AChRs, which modulate the release of acetylcholine. The latter can be documented as *fade* that occurs with increased frequency of stimulation. *Fade* can also be seen when the postjunctional AChRs alone are functionally blocked (e.g., by bungarotoxin) or when the number of AChRs (e.g., myasthenia gravis) is decreased. Hence, the neuromuscular junction is a complex and dynamic system in which the phenomena produced by drugs are composites of actions that vary with the drug, dose, activity at the nerve terminal and muscle, time after administration, presence of anesthetics or other drugs, and age and condition of the patient.
- Inhibition of acetylcholinesterase enzyme by anticholinesterases (e.g., neostigmine) increases the concentration of acetylcholine in the synaptic cleft, which can compete with and displace the NDMRs and thus reverse the paralysis. These anticholinesterase drugs (e.g., neostigmine) also have other effects, including the nerve terminal and the receptor, by an allosteric mechanism. Acute bolus or prolonged administration of anticholinesterases can have deleterious effects on neuromuscular function in otherwise healthy patients. The modified cyclodextrin, sugammadex, is a novel and innovative class of compound that reverses paralysis of only steroid muscle relaxants by encapsulation of this series of compounds.
- Depolarizing compounds (e.g., succinylcholine) initially react with the acetylcholine recognition site and, like the transmitter, open AChR ion channels during depolarization of the end-plate membrane. Unlike the transmitter, they are not subject to hydrolysis by acetylcholinesterase and therefore remain in the junction. Soon after the administration of succinylcholine, some receptors are desensitized, and, although occupied by the agonist, they do not open to allow current to flow to depolarize the muscle membrane area.
- If the depolarizing relaxant is applied in higher-than-usual concentrations or is allowed to remain at the junction for a long time, then other neuromuscular effects occur; depolarizing relaxants in higher concentrations have effects on prejunctional structures, and the combination of prejunctional and postjunctional effects plus secondary ones on muscle and nerve homeostasis results in the complicated phenomenon known as *phase II block*. Some of the other drugs used clinically (e.g., Botox) have effects on the motor nerve and therefore indirectly on muscle. Systemic infection with clostridial toxins (*Clostridium botulinum*, gas gangrene) can lead to systemic paralysis as a result of decreased release of acetylcholine from the nerve terminal. NDMRs administered for 24 hours or longer can have effects on the postsynaptic receptor and simulate denervation state (chemical denervation) manifested by upregulated postsynaptic AChRs. Magnesium given to preeclamptic mothers decreases the release of acetylcholine with a potential for muscle weakness in the mother or newborn. In recognizing these sites and mechanisms, we begin to bring our theoretical knowledge closer to explaining the phenomena observed when these drugs are exposed to living humans.

*Continued*

- Contemporary research work has focused on the control of AChR expression on the postjunctional membrane in normal and diseased states. The presence or absence of the conventional mature and immature isoforms seems to complicate matters further. In certain pathologic states (e.g., denervation, stroke, sepsis, burns, immobilization, chronic use of NDMRs), AChRs are upregulated, with increased expression of the immature isoform and *de-novo* expression of the nicotinic  $\alpha 7$  acetylcholine receptors ( $\alpha 7$  AChRs). Altered functional and pharmacologic characteristics of the immature (fetal or  $\gamma$ -subunit-containing receptors) and  $\alpha 7$  AChRs expressed in pathologic muscle wasting conditions result in increased sensitivity to succinylcholine with hyperkalemia and resistance (insensitivity) to NDMRs.
- An area of increasing attention is control of the expression of mature versus the other two receptor isoforms (immature  $\gamma$ - and  $\alpha 7$  AChRs on the synapse). Re-expression of the immature  $\gamma$ - and  $\alpha 7$  AChRs is probably related to aberrant growth factor signaling.
- Genetic mutations in the AChRs, that result in prolonged or fast open-channel time, can lead to a myasthenia-like state, even in the presence of normal receptor numbers. The weakness is usually related to ineffective depolarization or to the altered open-channel time, or to both.

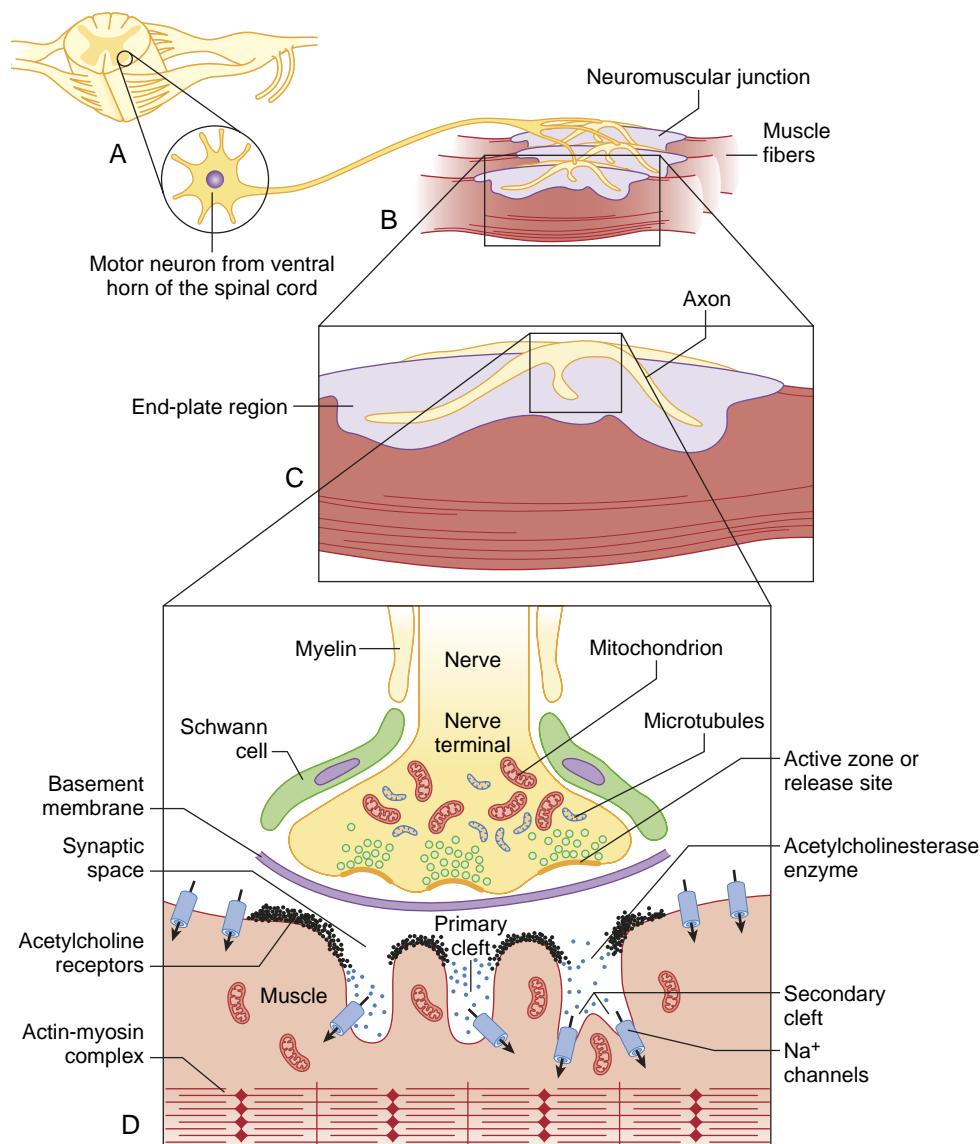
Although cholinergic neurotransmission at the neuromuscular junction is the most widely studied synapse within the nervous system, complete knowledge of its workings has not yet been achieved. The physiology of neuromuscular transmission could be analyzed and understood at the simplest level by using the classic model of nerve signaling to muscle through the acetylcholine receptor (AChR). The mammalian neuromuscular junction and the nicotinic AChRs are the prototypical and most extensively studied synapse and receptor, respectively. Research has provided more detailed information on processes that, within the classic scheme, can modify neurotransmission and response to drugs. One example is the role of qualitative or quantitative changes in AChRs that modify neurotransmission and the response to drugs.<sup>1-3</sup> In myasthenia gravis, for example, the decrease in AChRs results in decreased efficiency of neurotransmission (and therefore muscle weakness)<sup>4</sup> and altered sensitivity to neuromuscular relaxants.<sup>3</sup> Another example is the importance of nerve-related (prejunctional) changes that alter neurotransmission and the response to muscle relaxants.<sup>5-7</sup> Yet, muscle relaxants act in ways that are not encompassed by the classic scheme of a unitary site of action. The observation that muscle relaxants can have prejunctional effects<sup>5</sup> or that some muscle relaxants can also have agonist-like stimulatory actions on the receptor,<sup>8</sup> whereas others have effects not explainable by purely postsynaptic actions on muscle,<sup>9-11</sup> has provided new insight into some previously unexplained observations. Although muscle relaxants are known to have effects on the presynaptic and postsynaptic receptors of the neuromuscular junction, recent evidence indicates that they can react with nicotinic and muscarinic AChRs other than those in muscle, including receptors on the carotid body, on the vagus to the heart, and on bronchial smooth muscle.<sup>9-13</sup> Although this multifaceted action-response scheme makes the physiologic and pharmacologic neurotransmission more complex, these added insights also bring experimentally derived knowledge much closer to clinical observations. This review dwells on the basic physiology and anesthesia-related pharmacology of the neuromuscular junction. Several reviews that provide more detailed insight into the physiological and pathophysiological processes that alter function and pharmacology of the neuromuscular junction are available for the initiated reader.<sup>14-19</sup>

## Neuromuscular Transmission

Neuromuscular transmission occurs by a fairly simple and straightforward mechanism. The nerve synthesizes acetylcholine and stores it in small, uniformly sized packages called *vesicles*. Stimulation of the nerve causes these vesicles to migrate to the surface of the nerve, rupture, and discharge acetylcholine into the cleft separating the nerve from muscle. AChRs in the end plate of the muscle respond by opening their channels for influx of sodium ions into the muscle to depolarize the muscle. The end-plate potential created is continued along the muscle membrane by the opening of sodium channels present throughout the muscle membrane to initiate a muscle contraction.<sup>16,17</sup> The acetylcholine immediately detaches from the receptor and is destroyed by the enzyme, acetylcholinesterase, which is also present in the cleft. Exogenous drugs that activate the nicotinic AChR, that is, agonists such as depolarizing muscle relaxants (e.g., succinylcholine or nicotine), can also act on these receptors and mimic the effect of acetylcholine and cause depolarization of the end plate. Nondepolarizing muscle relaxants (NDMRs) also act on the receptors, but they prevent acetylcholine from binding to the receptor and thus prevent depolarization by agonists. Because these NDMRs prevent the action of agonists (e.g., acetylcholine, carbachol, succinylcholine), they belong to the class of compounds known as *antagonists* at the muscle AChRs. Other compounds, frequently called *reversal drugs* or antagonists of neuromuscular paralysis (e.g., neostigmine, prostigmine), inhibit acetylcholinesterase and therefore impair the hydrolysis of acetylcholine. The increased accumulation of undegraded acetylcholine can effectively compete with NDMRs and thereby displace the latter from the receptor (i.e., law of mass action) and antagonize the effects of NDMRs.

## MORPHOLOGY

The neuromuscular junction is specialized on both the nerve side and on the muscle side to transmit and receive chemical messages.<sup>15-19</sup> Each motor neuron runs without interruption from the ventral horn of the spinal cord or medulla to the neuromuscular junction as a large, myelinated axon (Fig. 12.1A). As the motor neuron approaches the muscle, the neuron repeatedly branches to contact many muscle



**Fig. 12.1** Structure of the adult neuromuscular junction shows the three cells that constitute the synapse: the motor neuron (i.e., nerve terminal), muscle fiber, and Schwann cell. (A) The motor nerve originates in the ventral horn of the spinal cord or brainstem. (B) As the nerve approaches its muscle fibers and before attaching itself to the surface of the muscle fiber, the nerve divides into branches that innervate many individual muscle fibers. (C) Each muscle receives only one synapse. The motor nerve loses its myelin and further subdivides into many presynaptic boutons to terminate on the surface of the muscle fiber. (D) The nerve terminal, covered by Schwann cells, has vesicles clustered about the membrane thickenings, which are the active zones, toward its synaptic side and mitochondria and microtubules toward its other side. A synaptic gutter or cleft made up of a primary and many secondary clefts separate the nerve from the muscle. The muscle surface is corrugated, and dense areas on the shoulders of each fold contain acetylcholine receptors. Sodium ( $\text{Na}^+$ ) channels are present at the bottom of the clefts and throughout the muscle membrane. The acetylcholinesterase and proteins and proteoglycans that stabilize the neuromuscular junction are present in the synaptic clefts.

cells and gather them into a functional group known as a *motor unit* (see Fig. 12.1B). The architecture of the nerve terminal is quite different from that of the rest of the axon. As the terminal reaches the muscle fiber, it loses its myelin, forms a spray of terminal branches against the muscle surface, and is covered by Schwann cells. This arrangement conforms to the architecture on the synaptic area of the muscle membrane (see Fig. 12.1C). The nerve is separated from the surface of the muscle by a gap of approximately 50 nm, called the *junctional cleft* or *synaptic cleft*. The nerve and muscle are held in tight alignment by protein filaments called *basal lamina* that span the cleft between the nerve and end plate. The muscle surface is heavily corrugated, with

deep invaginations of the junctional cleft—the primary and secondary clefts—between the folds in the muscle membrane; thus, the end plate's total surface area is very large. The depths of the folds also vary between muscle types and species. Human neuromuscular junctions, relative to muscle size, are smaller than those of the mouse, although the junctions are located on muscle fibers that are much larger. Human junctions have longer junctional foldings and deeper gutters.<sup>14,17</sup> The sodium channels, which propagate the wave of depolarization, are located in the depths of the folds (see Fig. 12.1D). The shoulders of the folds are densely populated with AChRs, approximately 5 million of them in each junction. AChRs are sparse in the depths between the folds.

The trophic function of the nerve is vital for the development and maintenance of adequate neuromuscular function. Before birth, each muscle cell commonly has contacts with several nerves and has several neuromuscular junctions.<sup>14,19</sup> At birth, all but one of the nerves retract, and a single end plate remains (see section on “Neuromuscular Junction at the Extremes of Age”). Once formed, the nerve-muscle contact, especially the end plate, is durable. Even if the original nerve dies, the one replacing it innervates exactly the same region of the muscle. The nerve endings on fast muscles are larger and more complicated than those on slow muscles. The reason for this is unclear. These differences in the nerve endings on muscle surfaces may play a role in the difference in response of fast- and slow-twitch muscle fibers to muscle relaxants.

Because all the muscle cells in a unit are excited by a single neuron, stimulation of the nerve electrically or by an action potential originating from the ventral horn or by any agonist, including depolarizing relaxants (e.g., succinylcholine), causes all muscle cells in the motor unit to contract synchronously. Synchronous contraction of the cells in a motor unit is called *fasciculation* and is often vigorous enough to be observed through the skin. Although most adult human muscles have only one neuromuscular junction per cell, an important exception is some of the cells in extraocular muscles. The extraocular muscles are *tonic* muscles, and, unlike other mammalian striated muscles, they are multiply innervated with several neuromuscular junctions strung along the surface of each muscle fiber.<sup>20-23</sup>

Quite in contrast to other muscles, even the adult ocular muscle contains mature and immature fetal receptors (see section on “Biology of Prejunctional and Postjunctional Nicotinic Acetylcholine Receptors”) segregated into distinct synapses on different fibers.<sup>20-22</sup> The ocular muscles slowly contract and relax rather than quickly as do other striated muscles; they can maintain a steady contraction, or contracture, the strength of which is proportional to the stimulus received. Physiologically, this specialization apparently holds the eye steadily in position. Ocular muscles are important to an anesthesiologist because depolarizing muscle relaxants (e.g., succinylcholine) affect them differently than they do on most skeletal muscles. Instead of causing a brief contraction, followed by paralysis, the depolarizing drug causes a long-lasting contracture response that pulls the eye against the orbit and could contribute to an increase in intraocular fluid pressure.<sup>22,23</sup> The clinical significance of the succinylcholine-induced increase in intraocular pressure has been questioned. Although many textbooks invoke the reported extrusion of intraocular contents with succinylcholine, the basis for this effect seems to be anecdotal.<sup>24</sup> Clinical studies, however, have indicated that succinylcholine-induced contractions of the extraocular muscles can last as long as 1 to 2 minutes and isometric tensions larger than 12 g can develop for each extraocular muscle.<sup>23</sup> Thus, succinylcholine probably should not be given to patients with open eye injuries.

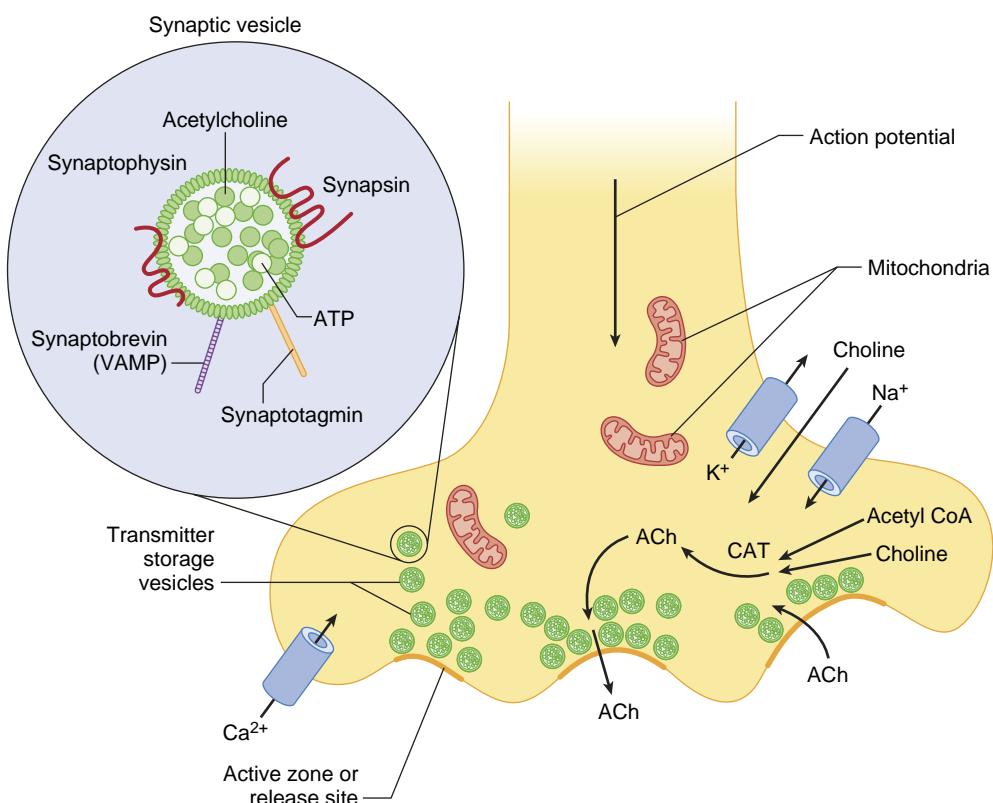
The perijunctional zone is the area of muscle immediately beyond the junctional area and is critical to the function of the neuromuscular junction. The perijunctional zone contains a mixture of receptors, including a smaller density of AChRs and a high density of sodium channels (see Fig. 12.1D). The admixture enhances the capacity of the

perijunctional zone to respond to the depolarization (i.e., end-plate potential) produced by the AChRs and to transduce it into the wave of depolarization that travels along the muscle to initiate muscle contraction. The density of sodium channels in the perijunctional area is richer than in more distal parts of the muscle membrane.<sup>25,26</sup> The perijunctional zone is close enough to the nerve ending to be influenced by transmitter released from it. Moreover, special variants (i.e., isoforms) of receptors and sodium channels can appear in this area at different stages of life and in response to abnormal decreases in nerve activity (see section on “Biology of Prejunctional and Postjunctional Nicotinic Acetylcholine Receptors”). Congenital abnormalities in the AChRs or in the sodium and calcium channels (i.e., mutations) are also known.<sup>25-27</sup> These variabilities seem to contribute to the differences in response to relaxants that are observed in patients with different pathologic conditions and ages.<sup>17,27</sup>

## QUANTAL THEORY

The contents of a nerve ending are not homogeneous. As illustrated in Figs. 12.1C and 12.2, vesicles are congregated in the portion toward the junctional surface, whereas microtubules, mitochondria, and other support structures are located toward the opposite side. The vesicles containing transmitter are ordered in repeating clusters alongside small, thickened, electron-dense patches of membrane referred to as *active zones* or *release sites*. This thickened area is a cross section of a band running across the width of the synaptic surface of the nerve ending that is believed to be the structure to which vesicles attach (active zones) before they rupture into the junctional cleft (see section on “Process of Exocytosis”). High-resolution scanning electron micrographs reveal small protein particles arranged alongside the active zone between vesicles. These particles are believed to be special channels—voltage-gated calcium channels—that allow calcium to enter the nerve and cause the release of vesicles.<sup>28,29</sup> The rapidity with which the neurotransmitter is released (200  $\mu$ s) suggests that voltage-gated calcium channels are close to the release sites. Proteomic studies suggest that at least 26 genes encode presynaptic proteins, and mutations in 12 of them cause defects in presynaptic structure that can lead to decreased acetylcholine release and muscle weakness.<sup>30</sup> These defects can be related to exocytosis, endocytosis, formation of active and periactive zones, vesicle transport, and neuropeptide modulation.<sup>30</sup>

When observing the electrophysiologic activity of a skeletal muscle, small, spontaneous depolarizing potentials at neuromuscular junctions can be seen. These potentials have only one hundredth the amplitude of the evoked end-plate potential produced when the motor nerve is stimulated. Except for amplitude, these potentials resemble the end-plate potential in the time course and manner they are affected by drugs. These small-amplitude potentials are called *miniature end-plate potentials* (MEPPs). Statistical analysis led to the conclusion that they are unitary responses; that is, there is a minimum size for the MEPP, and the sizes of all MEPPs are equal to or multiples of this minimum size. Because MEPPs are too large to be produced by a single molecule of acetylcholine, it was deduced that they are produced by uniformly sized packages, or quanta, of transmitter released from the



**Fig. 12.2** The working of a chemical synapse, the motor nerve ending, including some of the apparatus for synthesis of transmitter, is illustrated. The large intracellular structures are mitochondria. Acetylcholine (ACh), synthesized from choline and acetate by acetyl coenzyme A (CoA), is transported into coated vesicles, which are moved to release sites. A presynaptic action potential that triggers the influx of calcium ( $\text{Ca}^{2+}$ ) through specialized proteins (i.e.,  $\text{Ca}^{2+}$  channels) causes the vesicles to fuse with the membrane and discharge transmitter. Membrane from the vesicle is retracted from the nerve membrane and recycled. Each vesicle can undergo various degrees of release of contents—from incomplete to complete. The transmitter is inactivated by diffusion, catabolism, or reuptake. The inset provides a magnified view of a synaptic vesicle. Quanta of ACh, together with adenosine triphosphate (ATP), are stored in the vesicle and covered by vesicle membrane proteins. Synaptophysin is a glycoprotein component of the vesicle membrane. Synaptotagmin is the vesicle's calcium sensor. Phosphorylation of another membrane protein, synapsin, facilitates vesicular trafficking to the release site. Synaptobrevin (vesicle-associated membrane protein [VAMP]) is a SNARE protein involved in attaching the vesicle to the release-site proteins at the nerve terminal (see also Fig. 12.3). CAT, Choline acetyltransferase;  $\text{K}^+$ , potassium;  $\text{Na}^+$ , sodium.

nerve (in the absence of stimulation). The stimulus-evoked end-plate potential is the additive depolarization produced by the synchronous discharge of quanta from several hundred vesicles. The action potential that is propagated to the nerve ending allows the entry of calcium into the nerve through voltage-gated calcium channels, which causes vesicles to migrate to the active zone, fuse with the neural membrane at release sites, and discharge their acetylcholine into the junctional cleft.<sup>28,29</sup> Because the release sites are located immediately opposite the receptors on the postjunctional surface, little transmitter is wasted, and the response of the muscle is coupled directly with the signal from the nerve.<sup>17,28</sup>

Alignment of the presynaptic receptor site is achieved by adhesion molecules or specific cell-surface proteins located on both sides of the synapse that grip each other across the synaptic cleft and hold together the prejunctional and postjunctional synaptic apparatuses.<sup>14,19,31</sup> One such protein implicated in synapse adhesion is neurexin, which binds to neuroligins on the postsynaptic membrane. The amount of acetylcholine released by each nerve impulse is large, at least 200 quanta of approximately 5000 molecules each, and the number of AChRs activated by transmitter released by a nerve impulse is also large, approximately 500,000 molecules. The ions (mostly sodium and some calcium) that flow through the channels of activated (open) AChRs cause maximum depolarization of

the end plate, which results in an end-plate potential that is greater than the threshold for stimulation of the muscle. This system is extremely vigorous. The signal is carried by more molecules of transmitter than are needed, and they evoke a response that is larger than needed. At the same time, only a small fraction of the available vesicles and receptors or channels are used to send each signal. Consequently, transmission has a substantial margin of safety, and, at the same time, the system has substantial capacity in reserve.<sup>16-18,32</sup>

## Neuromuscular Junction

### FORMATION OF NEUROTRANSMITTER AT MOTOR NERVE ENDINGS

The axon of the motor nerve carries electrical signals from the spinal cord to muscles and has all the biochemical apparatus needed to transform the electrical signal into a chemical one. All the ion channels, enzymes, other proteins, macromolecules, and membrane components needed by the nerve ending to synthesize, store, and release acetylcholine and other trophic factors are made in the cell body and transmitted to the nerve ending by axonal transport (see Fig. 12.2).<sup>15,28,29</sup> The simple molecules, choline and

acetate, are obtained from the environment of the nerve ending, where choline is transported by a special system from extracellular fluid to the cytoplasm and acetate in the form of acetyl coenzyme A from mitochondria. The enzyme choline acetyltransferase brings about the reaction of choline and acetate to form acetylcholine. After synthesis, acetylcholine is stored in cytoplasm until it is transported and incorporated into vesicles, which are better positioned for release when an action potential reaches the nerve terminal.

## NERVE ACTION POTENTIAL

During a nerve action potential, sodium from outside flows across the membrane, and the resulting depolarizing voltage opens the calcium channels, which allows entry of calcium ions into the nerve and causes acetylcholine to be released. A nerve action potential is the normal activator that releases the transmitter acetylcholine. The number of quanta released by a stimulated nerve is greatly influenced by the concentration of ionized calcium in extracellular fluid. If calcium is not present, then depolarization of the nerve, even by electrical stimulation, will not produce the release of transmitter. Doubling the extracellular calcium results in a 16-fold increase in the quantal content of an end-plate potential.<sup>33</sup> The calcium current persists until the membrane potential is returned to normal by outward fluxes of potassium from inside the nerve cell. Along with calcium channels on the nerve terminal are potassium channels, including the voltage-gated and calcium-activated potassium channels, whose function is to limit entry of calcium into the nerve and therefore depolarization.<sup>26,32</sup> The calcium current can be prolonged by potassium channel blockers (e.g., 4-aminopyridine, tetraethylammonium), which slow or prevent the efflux of potassium out of the nerve. The increase in quantal content produced in this way can reach astounding proportions.<sup>17,34</sup> An effect of increasing calcium in the nerve ending is also clinically observed as the so-called *posttetanic potentiation* (PTP), which occurs after a nerve of a patient paralyzed with an NDMR is stimulated at high, tetanic frequencies. Calcium enters the nerve with every stimulus, but it accumulates during the tetanic period because it cannot be excreted as quickly as the nerve is stimulated. Because the nerve ending contains more than the normal amount of calcium for some time after the tetanus, a stimulus applied to the nerve during this time causes the release of more than the normal amount of acetylcholine. The abnormally large amount of acetylcholine antagonizes the relaxant (temporarily) and causes the characteristic increase in the size of the twitch (i.e., post tetanic facilitation).

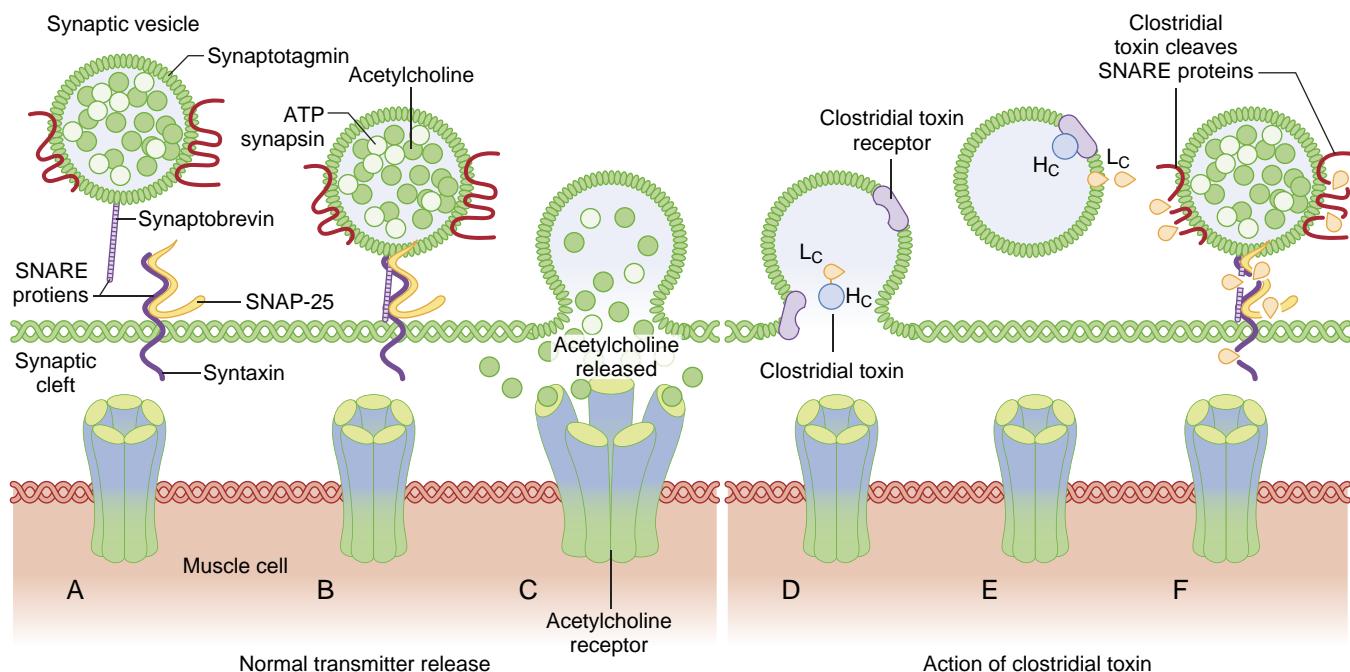
Calcium enters the nerve through specialized proteins called *calcium channels*.<sup>15,35</sup> Of the several types of calcium channels, two seem to be important for the release of transmitter: P channels and the slower L channels. P channels, probably the type responsible for the normal release of transmitter, are found only in nerve terminals.<sup>13,35</sup> In motor nerve endings, the calcium channels are located immediately adjacent to the active zones (see Fig 12.2). They are voltage-dependent and are opened and closed by changes in membrane voltage caused by the nerve action potential. In addition to calcium channels, several forms of potassium channels are present in the nerve terminal,

including voltage-gated and calcium-activated potassium channels. Potassium channels limit the duration of nerve terminal depolarization and hence the entry of calcium and the release of transmitter.<sup>26</sup> Alterations in entry of calcium into the nerve ending can also alter the release of transmitter. The Eaton-Lambert myasthenic syndrome, which should not be confused with myasthenia gravis, is an acquired autoimmune disease in which antibodies are directed against voltage-gated calcium channels at nerve endings.<sup>36</sup> In this syndrome, decreased function of the calcium channel causes decreased release of transmitter, which results in inadequate depolarization and muscle weakness. Patients with Eaton-Lambert myasthenic syndrome exhibit increased sensitivity to depolarizing and nondepolarizing relaxants.<sup>37</sup>

Higher-than-normal concentrations of bivalent inorganic cations (e.g., magnesium, cadmium, manganese) can also block the entry of calcium through P channels and profoundly impair neuromuscular transmission. This mechanism is behind the typical muscle weakness and potentiation of the effect of muscle relaxants in a mother and fetus when magnesium sulfate is administered to treat preeclampsia. P channels, however, are not affected by calcium entry-blocking drugs such as verapamil, diltiazem, and nifedipine. These drugs have profound effects on the slower L channels present in the cardiovascular system. As a result, the L-type calcium channel blockers have no significant effect at therapeutic doses on the normal release of acetylcholine or on the strength of normal neuromuscular transmission. However, calcium entry-blocking drugs may increase the block in neuromuscular transmission induced by NDMRs. The effect is small, and not all investigators have been able to observe it. The explanation may lie in the fact that nerve endings also contain L-type calcium channels. The effects of calcium channels on depolarizing relaxants, if any, are unknown.

## SYNAPTIC VESICLES AND RECYCLING

Two pools of vesicles seem to release acetylcholine, a readily releasable pool and a reserve pool, sometimes called VP1 and VP2, respectively.<sup>38,39</sup> Electron microscopic studies have demonstrated that the majority of synaptic vesicles (VP1) are sequestered in the reserve pool and tethered to the cytoskeleton in a filamentous network made up of primarily actin, synapsin (an actin-binding protein), synaptotagmin, and spectrin.<sup>38,39</sup> Vesicles in VP2 are a bit smaller and limited to an area very close to the nerve membrane, where they are bound to the active zones. These vesicles are the ones that ordinarily release transmitter. Release occurs when calcium ions enter the nerve through the P channels lined up on the sides of the active zones by soluble N-ethylmaleimide-sensitive attachment protein receptor (SNARE) proteins.<sup>38,39</sup> The SNARE proteins are involved in fusion, docking, and release of acetylcholine at the active zone. Calcium needs to move only a very short distance (i.e., a few atomic radii) to encounter a vesicle and activate the proteins in the vesicle wall involved in a process known as *docking* (see section on “Process of Exocytosis”).<sup>39</sup> The activated proteins seem to react with the nerve membrane to form a pore through which the vesicle discharges its acetylcholine into the junctional cleft. Studies using fluorescent proteins



**Fig. 12.3** Model of protein-mediated membrane fusion and exocytosis. (A) Release of acetylcholine from vesicles is mediated by a series of proteins collectively called SNARE proteins. Synaptotagmin is the neuronal calcium receptor that detects entry of calcium. Synaptobrevin (i.e., vesicle-associated membrane protein [VAMP]) is a filament-like protein on the vesicle. (B) During depolarization and entry of calcium, synapsin is also present on the vesicle membrane. Synaptobrevin on the vesicle unfolds and forms a ternary complex with syntaxin/SNAP-25 on the nerve terminal membrane. (C) Assembly of the ternary complex forces the vesicle in close apposition to the nerve membrane at the active zone with release of its contents, acetylcholine. The fusion is disassembled, and the vesicle is recycled. (D) Clostridial toxin, botulinum, inhibits the release of acetylcholine and causes paralysis of muscles. The toxin consists of a light chain ( $L_c$ ) and a heavy chain ( $H_c$ ). The first stage in intoxication is the interaction of the toxin with a thus far unidentified receptor. (E) This interaction is followed by internalization of the toxin within the vesicle and the release of the  $L_c$  of toxin from the vesicle. (F) The liberated  $L_c$  cleaves a variety of SNARE proteins, depending on the type of toxin released, thereby preventing assembly of the fusion complex and thus blocking the release of acetylcholine. ATP, Adenosine triphosphate; SNAP-25, synaptosome-associated protein of 25-kd.

have visualized how synaptic vesicles fuse with release sites and release their contents, which are then retrieved. Some vesicles stay open briefly before retrieval and do not completely collapse into the surface membrane (“kiss and run”). Others stay open longer and probably do not completely collapse (“compensatory”). Still others completely collapse and are not retrieved until another stimulus is delivered (“stranded”).<sup>38,39</sup>

The larger reserve (VP1) vesicles, from their position deep from the nerve ending and firmly tethered to the cytoskeleton by many proteins, including actin, synapsin (an actin-binding protein), synaptotagmin, and spectrin,<sup>37,38</sup> may be moved to the readily releasable store to replace worn-out vesicles or to participate in transmission when the nerve is called on to work especially hard (e.g., when it is stimulated at very high frequencies or for a very long time). Under such strenuous circumstances, calcium may penetrate more deeply than normal into the nerve or may enter through L channels to activate calcium-dependent enzymes that break the synapsin links holding the vesicles to the cytoskeleton, thereby allowing the vesicles to be moved to the release sites. Repeated stimulation requires the nerve ending to replenish its store of vesicles filled with transmitter, a process known as *mobilization*. The term is commonly applied to the aggregate of all steps involved in maintaining the nerve ending’s capacity to release transmitter—everything from the acquisition of choline and the synthesis of acetate to the movement of filled vesicles to release sites. Uptake of choline and the activity of choline acetyltransferase, the

enzyme that synthesizes acetylcholine, are probably the rate-limiting steps.<sup>15,29</sup>

## PROCESS OF EXOCYTOSIS

The readily releasable pool of synaptic vesicles constitutes the vesicles directly available for release. During an action potential and calcium influx, neurotransmitter is released. Studies have shed some light on the inner workings by which the vesicle releases its contents. The whole process is called *exocytosis*. The SNARE proteins include (Fig. 12.3A) the synaptic-vesicle protein, synaptobrevin; the plasma-lemma-associated protein, syntaxin; and the synaptosome-associated protein of 25-kd (SNAP-25).<sup>38,39</sup> The current model of protein-mediated membrane fusion in exocytosis is as follows. When there is an action potential and calcium ions enter, synapsin becomes phosphorylated, which frees the vesicle from its attachment to the cytoskeleton. Syntaxin and SNAP-25 are complexes attached to the plasma membrane. After the initial contact, the synaptobrevin on the vesicle forms a ternary complex with syntaxin and SNAP-25. Synaptotagmin is the protein on the vesicular membrane that acts as a calcium sensor, localizes the synaptic vesicles to synaptic zones rich in calcium channels, and stabilizes the vesicles in the docked state.<sup>38</sup> Assembly of the ternary complex forces the vesicle to move close to the underlying nerve terminal membrane (i.e., the active zone), and the vesicle is then ready for release (see Fig. 12.3B). The close proximity of release sites, calcium channels, and

synaptic vesicles and the use of the calcium sensor lead to a burst of release of new transmitter synchronous with the stimulus (see Fig. 12.3C).<sup>37-40</sup> The vesicle can release part or all of its contents, some of which can be recycled to form new vesicles as previously described (“kiss and run,” “compensatory,” “stranded”).<sup>37-40</sup>

Botulinum neurotoxin selectively digests one or all these SNARE proteins and blocks exocytosis of the vesicles,<sup>41,42</sup> which ultimately results in muscle weakness or more profound muscle paralysis. This toxin may produce a partial or complete chemical denervation. Botulinum toxin is therapeutically used to treat spasticity or spasm in several neurologic and surgical diseases, to prevent hyperhidrosis in patients with excessive sweating, and cosmetically to correct wrinkles.<sup>43,44</sup> Botulinum toxin consists of two protein segments known as heavy and light chains (see Fig. 12.3D and E). The heavy chain interacts with lipid molecules called *polysialogangliosides* in the cell membrane and synaptotagmin on the vesicle to enter the vesicle. Once in the vesicle, the light chain inactivates neuromuscular transmission by breakdown and thereby inhibits the function of SNARE proteins (see Fig. 12.3F). Some reports indicate an increased incidence of clostridial infections in both Canada and the United States, with *Clostridium botulinum* infection being particularly common after traumatic injuries, in drug abusers, and after musculoskeletal allografts.<sup>6,7</sup> Thus, systemic paralysis can occur after clostridial infection. Local injection for therapeutic purposes will usually result in localized paresis, although systemic effects have been reported.<sup>7,45</sup>

## ACETYLCHOLINESTERASE

The acetylcholine released from the nerve diffuses across the junctional cleft and reacts with nicotinic AChRs in the end plate to initiate muscle contraction. Transmitter molecules that do not immediately react with a nicotinic AChR or those released after binding to the receptor are almost instantly destroyed by acetylcholinesterase in the junctional cleft. Acetylcholinesterase at the junction is the asymmetric or A12 form protein made in the muscle under the end plate. Acetylcholinesterase (enzyme classification 3.1.1.7) is type B carboxylesterase enzyme. A smaller concentration of the enzyme is found in the extrajunctional area. The enzyme is secreted from the muscle but remains attached to it by thin stalks of collagen fastened to the basement membrane.<sup>15,37</sup> Most of the molecules of acetylcholine released from the nerve initially pass between the enzymes to reach the postjunctional receptors; however, as they are released from the receptors, they invariably encounter acetylcholinesterase and are destroyed. Under normal circumstances, a molecule of acetylcholine reacts with only one receptor before it is hydrolyzed. Acetylcholine is a potent messenger, but its actions are very short lived because it is destroyed in less than 1 ms after it is released.

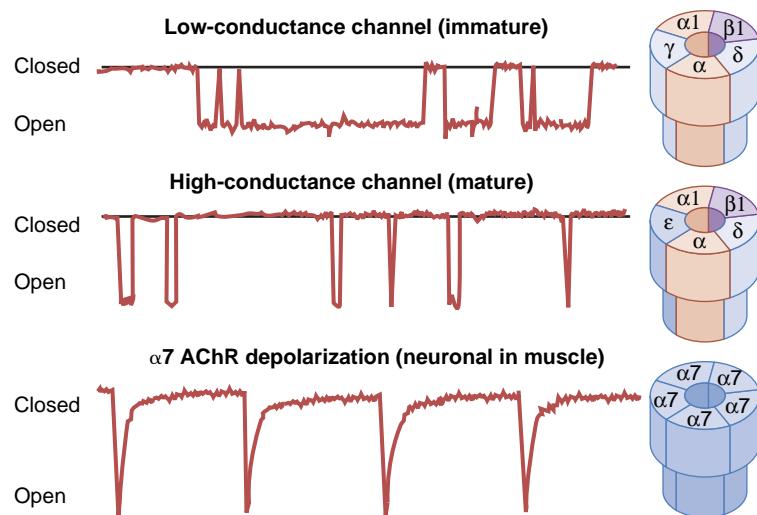
Some congenital and acquired diseases are caused by altered activity of acetylcholinesterase. The congenital absence of the secreted enzyme (in knock-out mice) leads to impaired maintenance of the motor neuronal system and organization of nerve terminal branches.<sup>46</sup> Many syndromes caused by congenital abnormalities in cholinesterase function have been described and result in neuromuscular disorders whose symptoms and signs usually

resemble those of myasthenia gravis or myasthenic syndromes.<sup>27,47</sup> Denervation decreases acetylcholinesterase at the junctional and extrajunctional areas.<sup>37</sup> Other acquired diseases involving cholinesterases are related to chronic inhibition of acetylcholinesterase by organophosphate pesticides or nerve gas (e.g., sarin) or to chronic pyridostigmine therapy given as prophylaxis against nerve gas poisoning.<sup>48,49</sup> Symptoms ranging from chronic fatigue to muscle weakness have been attributed to chronic cholinesterase inhibition, thus underscoring the importance of acetylcholinesterase in normal and abnormal neuromuscular function. A rodent study confirms that the muscle weakness associated with chronic pyridostigmine therapy is related to both AChRs downregulation and to receptor-independent factors.<sup>50</sup>

## POSTJUNCTIONAL ACETYLCHOLINE RECEPTORS

The similarity of AChRs among many species and the abundance of AChRs from *Torpedo electric fish* have greatly facilitated research in this area. The availability of messenger RNA from humans and other species and DNA has allowed the study of the receptor in artificial systems such as oocytes from frogs and in mammalian cells that do not express the receptor, such as COS or fibroblast cells. Receptors can also be mutated by molecular techniques to simulate pathologic states; the receptor function in these artificial systems can then be studied. By using these and related techniques, much has been learned about the synthesis, composition, and biologic function and mechanisms that underlie the physiologic and pharmacologic responses in AChRs.<sup>51-53</sup> Three isoforms of postjunctional nicotinic AChRs exist: a junctional or mature receptor, an extrajunctional or immature (fetal) receptor, and the more recently described neuronal  $\alpha 7$  nicotinic receptor (see section on “Biology of Prejunctional and Postjunctional Nicotinic Acetylcholine Receptors”).<sup>2,16,18</sup> The differences between receptor subtypes, however, can be neglected in a general discussion of the role of receptors in neuromuscular transmission.

AChRs are synthesized in muscle cells and are anchored to the end-plate membrane by a special 43-kd protein known as *rpasyn*. This cytoplasmic protein is associated with the AChR in a 1:1 ratio.<sup>16-19</sup> The receptors, formed of five subunit proteins, are arranged like the staves of a barrel into a cylindrical receptor with a central pore for ion channeling (the key features are illustrated in Fig. 12.4). The receptor protein has a molecular mass of approximately 250,000 daltons. The mature receptor consists of  $\alpha 1$ -,  $\beta 1$ -,  $\delta$ -, and  $\epsilon$ -subunits, and the fetal (immature, extrajunctional) receptor consists of  $\alpha 1$ -,  $\beta 1$ -,  $\delta$ -, and  $\gamma$ -subunits; there are two subunits of  $\alpha$  and one each of the others. The neuronal  $\alpha 7$  AChR consists of five  $\alpha 7$ -subunits.<sup>16,18</sup> Each of all receptor subunits consists of approximately 400 to 500 amino acids. The receptor-protein complex passes entirely through the membrane and protrudes beyond the extracellular surface of the membrane and into the cytoplasm. The binding site for acetylcholine is on each of the  $\alpha 1$ - or  $\alpha 7$ -subunits, is located on the extracellular component of the  $\alpha$ -subunit protein, and these are the sites of competition between receptor agonists and antagonists. Agonists and antagonists are attracted to the binding site, and either may occupy the site, which is located near cysteine residues



**Fig. 12.4** Schematic illustration depicts acetylcholine receptor (AChR) channels (right) and tracings of cell-patch records of receptor channel openings (left). The mature or junctional receptor consists of two  $\alpha 1$ -subunits and one each of  $\beta 1$ -,  $\delta$ -, and  $\epsilon$ -subunits. The immature, extrajunctional, or fetal form consists of two  $\alpha 1$ -subunits and one each of  $\beta 1$ -,  $\delta$ -, and  $\gamma$ -subunits. The latter is thus called the  $\gamma$ -subunit receptor. Recently, a neuronal receptor consisting of five  $\alpha 7$ -subunits has been described in muscle. All the subunits are arranged around the central cation channel. The immature isoform containing the  $\gamma$ -subunit has long open times and low-amplitude channel currents. The mature isoform containing the  $\epsilon$ -subunit has shorter open times and high-amplitude channel currents during depolarization. Substitution of the  $\epsilon$ -subunit for the  $\gamma$ -subunit gives rise to the fast-gated, high-conductance channel type. As expected, application of acetylcholine to the  $\alpha 7$  AChR also results in a fast, rapidly decaying inward current. All these depolarizing events are insensitive to treatment with muscarinic acetylcholine receptor antagonist, atropine, but sensitive to treatment with  $\alpha$ -bungarotoxin or muscle relaxants, which block the flow of current. The affinity of the muscle relaxants to each of the three isoforms may be different,  $\alpha 7$  AChR being the least sensitive to block.

(unique to the  $\alpha$ -chain) at amino acid positions 192 to 193 of the  $\alpha$ -subunit.<sup>16-18</sup> Radiolabeled  $\alpha$ -bungarotoxin from the cobra, used to quantitate or fluorescent stain the receptor, binds to heptapeptide region 185 to 199 of the  $\alpha$ -subunit.<sup>54</sup> Motor neuron-derived neuregulin-1 $\beta$  (NR $\beta$ -1), originally described as AChR-inducing activity (ARIA), induces AChR gene transcription in subsynaptic myonuclei by activating ErbB receptors.<sup>16-19</sup>

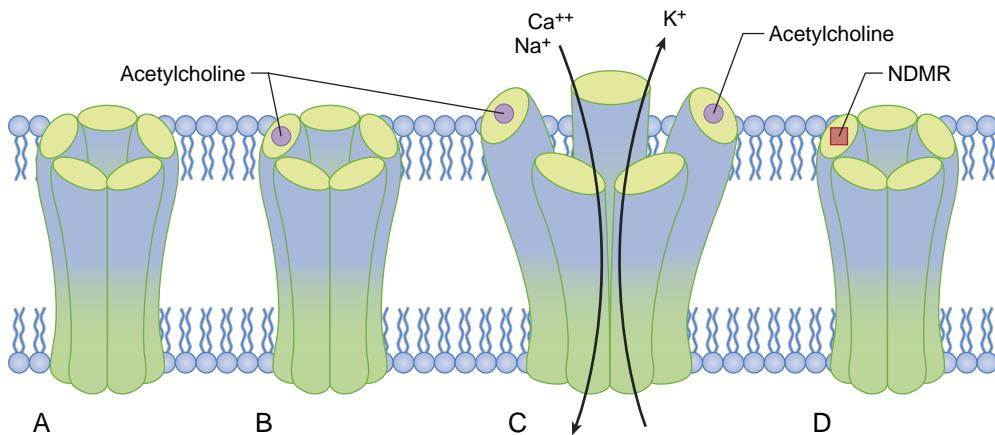
## SYNTHESIS AND STABILIZATION OF POSTJUNCTIONAL RECEPTORS

Muscle tissue is formed from the mesoderm and initially appears as myoblasts. Myoblasts fuse to produce myotubes, which therefore have multiple nuclei. As the myotubes mature, the sarcomere, which is the contractile element of the muscle consisting of actin and myosin, develops.<sup>55</sup> The protein  $\beta$ -integrin seems to be essential for myoblast fusion and sarcomere assembly.<sup>55</sup> Shortly afterward, motor nerve axons grow into the developing muscle, and these axons bring in nerve-derived signals (i.e., growth factors), including agrin and neuregulins (NR $\beta$ -1 and NR $\beta$ -2), which are key to the maturation of myotubes to muscle.<sup>19</sup> Agrin is a protein from the nerve that stimulates postsynaptic differentiation by activating muscle-specific tyrosine kinase (MuSK), a tyrosine kinase expressed selectively in muscle. With signaling from agrin, the AChRs, which have been scattered throughout the muscle membrane, cluster at the area immediately beneath the nerve. Agrin, together with neuregulins and other growth factors, induce the clustering of other critical muscle-derived proteins, including MuSK, rapsyn, and ErbB proteins, all of which are necessary for maturation and stabilization of AChRs at the junction. In addition to the effects on postsynaptic differentiation, agrin

and MuSK display effects on presynaptic differentiation as well. Agrin and MuSK induce retrograde signals that instruct axons to undergo neuron outgrowth and terminal differentiation.<sup>19</sup> Current understanding of presynaptic development of the neuromuscular junction, however, is significantly less advanced than the understanding of postsynaptic development. Just before and shortly after birth, the immature,  $\gamma$ -subunit-containing AChRs are replaced by the mature,  $\epsilon$ -subunit-containing receptors. Although the mechanism of this change is unclear, a neuregulin, NR $\beta$ -1, also called ARIA, that binds to one of the ErbB receptors seems to play a role.<sup>19,56</sup>

## BASIC ELECTROPHYSIOLOGY OF NEUROTRANSMISSION

**Fig. 12.5** illustrates the results of the classic depolarizing action of acetylcholine on end-plate receptors. Normally, the pore of the channel is closed by approximation of the cylinders (i.e., subunits). When an agonist occupies both  $\alpha$ -subunit sites, the protein molecule undergoes a conformational change with a twisting movement along the central axis of the receptor that results in the opening of the central channel through which ions can flow along a concentration gradient. When the central channel is open, sodium and calcium flow from the outside of the cell to the inside and potassium flows from the inside to the outside. The channel in the tube is large enough to accommodate many cations and electrically neutral molecules, but it excludes anions (e.g., chloride). The current transported by the ions depolarizes the adjacent membrane. The net current is depolarizing and creates the end-plate potential that stimulates the muscle to contract. In this instance, downward-going (i.e., depolarizing) current can be recorded by



**Fig. 12.5** Actions of acetylcholine or non-depolarizing muscle relaxant (NDMR) on end-plate receptors. (A) The ion channel is inactive and does not open in the absence of acetylcholine. (B) Although one acetylcholine molecule (filled circle) is binding to one of two binding sites, the central channel does not open. (C) When acetylcholine simultaneously binds to the recognition sites of both  $\alpha$ -subunits (filled circles), a conformation change is triggered that opens the channel and allows the cations to flow across the membrane. (D) Action of antagonists such as an NDMR (filled square). Acetylcholine is in competition with NDMR for the receptor's recognition site but may also react with acetylcholinesterase. Inhibiting the acetylcholinesterase enzyme increases the lifetime of acetylcholine and the probability that it will react with a receptor. When one of the two binding (recognition) sites is occupied by an NDMR, the receptor will not open, even if the other binding site is occupied by acetylcholine.  $Ca^{2+}$ , Calcium ion;  $K^+$ , potassium ion;  $Na^+$ , sodium ion.

the patch-clamp electrophysiologic technique previously described (see Fig. 12.4).

The pulse stops when the channel closes by a reversed mechanical conformation (see earlier discussion), which is typically initiated when one or both agonist molecules detach from the receptor. In the activated, open state, the current that passes through each open channel is minuscule, only a few picoamperes (approximately  $10^4$  ions/ms). However, each burst of acetylcholine from the nerve normally opens approximately 500,000 channels simultaneously, and the total current is more than adequate to produce depolarization of the end plate and contraction of muscle. Opening of a channel causes conversion of chemical signals from a nerve to the flow of current on the muscle disease to cause end-plate potentials, thereby leading to muscle contraction. The end-plate potential has been viewed as a graded event that may be reduced in magnitude or extended in time by drugs, but, in reality, the end-plate potential is the summation of many all-or-nothing events simultaneously occurring at myriad ion channels. It is these tiny events that are affected by drugs.

Receptors that do not have two molecules of agonist (e.g., acetylcholine) bound remain closed. Both  $\alpha$ -subunits must be simultaneously occupied by agonist; if only one of them is occupied, then the channel remains closed (see Fig. 12.5). This is the basis for preventing depolarization by antagonists. NDMRs act by binding to either or both  $\alpha$ -subunits and thus preventing acetylcholine from binding and opening the channel. This interaction between agonists and antagonists is competitive, and the outcome—transmission or block—depends on the relative concentrations and binding characteristics of the drugs involved (see section on “Drug Effects on Postjunctional Receptors”).

Individual channels are also capable of a wide variety of conformational states.<sup>17,57</sup> They may stay open or remain closed and thereby affect total current flow across the membrane, but they can do more. They may open for a longer or shorter time than normal, open or close more gradually than usual, open briefly and repeatedly (i.e., flickering), or

pass fewer or more ions per opening than they usually do. Their function is also influenced by drugs, changes in fluidity of the membrane, temperature, electrolyte balance in the milieu, and other physical and chemical factors.<sup>38,39</sup> Receptor channels are dynamic structures that are capable of a wide variety of interactions with drugs and of entering a wide variety of current-passing states. All these influences on channel activity are ultimately reflected in the strength or weakness of neuromuscular transmission and contraction of a muscle.

## Drug Effects on Postjunctional Receptors

### CLASSIC ACTIONS OF NONDEPOLARIZING MUSCLE RELAXANTS

Neurotransmission occurs when acetylcholine released by the nerve action potential binds to nicotinic AChRs. All NDMRs impair or block neurotransmission by competitively preventing the binding of acetylcholine to the muscle AChR. The final outcome—block or transmission—depends on the relative concentrations of the chemicals and their comparative affinities for the receptor. Fig. 12.5 shows a system exposed to acetylcholine and the nondepolarizing neuromuscular blocking compound. One receptor has attracted two acetylcholine molecules and has opened its channel, where current will flow to depolarize that segment of membrane. Another has attracted one molecule of NDMR; its channel will not open, and no current will flow, even if one acetylcholine molecule binds to the other site. The third receptor has acetylcholine on one  $\alpha$ -subunit and nothing on the other. What will happen depends on which of the molecules binds. If acetylcholine binds, then the channel will open and the membrane will be depolarized; if a NDMR binds, then the channel will remain closed and the membrane will not be depolarized. At other times, one or two