Neuroanesthesia and Cerebrospinal Protection

Hiroyuki Uchino
Kazuo Ushijima
Yukio Ikeda *Editors*

With contrib. by
Jeremy Williams
Edward F. Barroga

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Foreword

I am honored and privileged to accept the invitation of the editor and publisher of the textbook *Neuroanesthesia and Cerebrospinal Protection* to write this foreword.

In the past decades, neuroanesthesia underwent a rapid evolution in developing from a curiosity- and expertise-based approach of the early days into a distinguished high profile subspecialty. This merit was possible by pioneer work, the vision of our teachers and the generation of public and political recognition and support ("decade of the brain") with consecutive funding of basic and clinical research throughout the world. Likewise, guidelines, structured subspecialty trainings and fellowship programs were implemented in high- and middle income countries. Today, all of these efforts are expressed in a significant reduction in perioperative morbidity and mortality of patients with neurological disease.

While we do live in a world of almost unlimited availability of information technology, the use of textbooks is still very much justified and appropriate because they represent an important mix of evidence and expertise. Textbooks, written by intellectual, educated, and experienced experts in their field, represent the holistic approach to a clinical problem well ahead of randomized control trials, meta-analyses or guidelines. While I absolutely respect these modules of evidence based medicine, textbooks can incorporate all of the available information into a "perioperative school of neuroanesthesia", representing a symbiosis of the art and science of neuroanesthesia.

The present textbook is a comprehensive, perfectly structured, knowledge-based opus that covers the anatomy, neurophysiology, and neuropharmacology needed to understand the distinguished management of cerebrospinal protection and clinical neuroanesthesia. It represents a profound source of information for physicians that intend to subspecialize in neuroanesthesia but will also serve as a guide for the occasional neuroanesthesiologist. This textbook is a timely and focused share of

evidence and expertise most extensive and accurate in depth and width and it will certainly guide the reader to improve perioperative care of patients with neurological disease.

Mainz, Germany Christian Werner

Preface

The main purpose and aim of neuroanesthesia is not only to perform cerebrospinal protection during neurosurgical and cardiovascular surgeries but also to prevent perioperative cerebrospinal injury. The choice of anesthetics and their management sometimes may not be adequate for the pathogenesis of the patients. How should we select the best anesthetic management to prevent neurological complications for patients who undergo different types of surgeries for conditions such as subarachnoid hemorrhage, stroke, and head trauma, as well as for carotid endarterectomy or cardiovascular surgery under cardiopulmonary bypass? These pathological conditions carry with them the risk of transient cerebrospinal ischemia, and if our management is inept, it may induce serious neurological sequelae. To establish the treatment and elucidate the molecular mechanisms of cerebrospinal injury is urgently needed; however, because their many components are intertwined, some important issues have not yet been resolved.

The title *Neuroanesthesia and Cerebrospinal Protection* represents a knowledge-based book that includes the anatomy, neurophysiology, and neuropharmacology to perform the necessary management and cerebrospinal protection during neuroanesthesia, with perspectives on each of those aspects. Aiming especially to convey readily comprehended information about neuroanesthesia, we have introduced the surgical techniques of neurosurgery, cardiovascular surgery, neuromodulation, and other procedures. In this book we also have tried to facilitate an understanding of the management of neuroanesthesia not only for primary residents but also for specialists. We would like to recommend keeping this book at your side to stay well informed of current perspectives on neuroanesthesia.

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General Consideration: Neuroanatomy for Neuroanesthesia

Chapter 1
Anatomy of Adult Central Nervous System: Structure and Function of the Brain and Spinal Cord

Hirokazu Ohtaki and Seiji Shioda

Abstract The nervous system, which in conjunction with the endocrine system is the most important regulator of homeostasis, is composed mainly of specialized cells known as neurons and their supporting cells, the glia. The function of the neurons is to receive sensory input and to transmit this information to effector organs via a special transmissive system, the synapse. External and internal afferent sensory input is integrated within the nervous system, and efferent impulses are coordinated so that the effector organs work together for the well-being of the individual. The nervous system is divided into two main parts: the central nervous system and the peripheral nervous system. The central nervous system consists of the brain and spinal cord, which together are the primary regulators and integrators of nerve signals. Moreover, the central nervous system in humans has the ability to store sensory information received during past experiences (memory). In this chapter, the anatomical organization of the brain and spinal cord is summarized, together with a brief description of the function of the different regions.

Keywords Central nervous system • Brain • Spinal cord • Neuron

1.1 Introduction

The nervous system, in conjunction with the endocrine system, is the most important regulator of homeostasis through specialized cells known as neurons. The neurons are to receive sensory input and to transmit this information to effector organs. External and internal afferent sensory input is integrated within the nervous system, and efferent impulses are coordinated. The nervous system is divided into two main parts: the central nervous system (CNS) and the peripheral nervous system. The CNS consists of the brain and spinal cord and is the primary regulator and integrator of the nerve signals. In addition to the function of the regulator, the

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CNS, in particular, the brain, has the ability to learn and store sensory information received during past experiences (memory). In this chapter, the anatomical organization of the brain and spinal cord is summarized, together with a brief description of the function of the different regions.

1.2 Nervous System

The nervous system controls homeostasis in conjunction with the endocrine system. The regulation of homeostasis by the endocrine system is a slow response mediated by hormones systemically released into the circulation. In contrast, regulation by the nervous system occurs within seconds and is mediated by the local release of neurotransmitters into the cells via the synaptic cleft. The nervous system is divided into two main parts: the central nervous system, which consists of the brain and spinal cord, and the peripheral nervous system, which consists of the cranial nervous system and its associated ganglia. Sensory input is received by acceptor organs, which connect to the spinal cord and brain via the afferent peripheral nerve system. This information is then processed, and efferent or output impulses are transmitted back to the effector organs via the efferent peripheral nervous system.

1.3 Central Nervous System

The central nervous system consists of the brain and spinal cord, which are neuron-rich tissues that are covered with a system of membranes, known as meninges, and suspended in cerebrospinal fluid. They are located in the cranial cavity and vertebral canal, respectively, with the bone of the skull and the vertebral column providing further protection. The central nervous system is composed of a large number of excitable neurons and their supporting cells, the glia (neuroglia).

The central nervous system can be divided into gray matter, which is made up of neurons and glia, and white matter, which is composed of nerve fibers and glia, and derives its color from lipids in the myelin sheaths of the former.

1.3.1 Brain

The adult brain is divided into five parts: the cerebrum, the diencephalon, the mesencephalon, the metencephalon (which includes the pons and cerebellum), and the myelencephalon (medulla oblongata). The region, including the mesencephalon, pons, medulla oblongata, and sometimes the diencephalon, is also known as the brainstem (Fig. 1.1). The brain lies in the cranial cavity and is connected with the spinal cord through the foramen magnum. The weight of the adult brain is

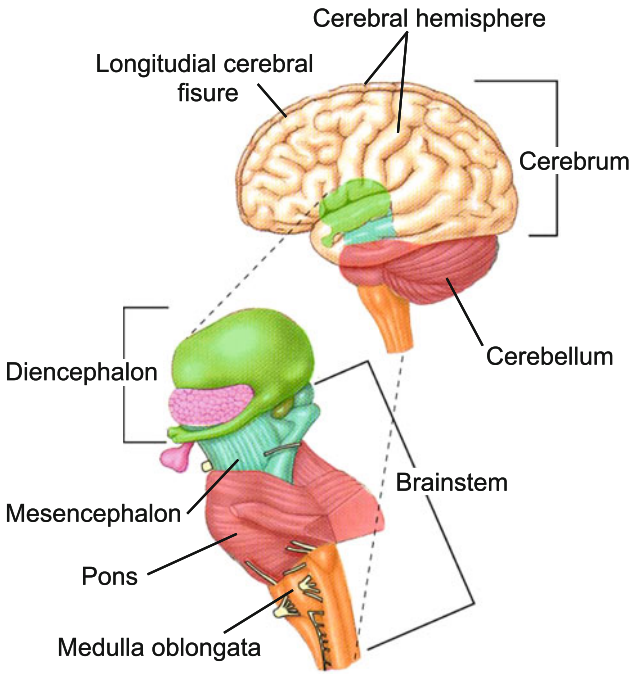

Fig. 1.1 Structure of the brain (Reproduced from [1] with permission)

between 1,300 and 1,500 g in men and 1,150 and 1,350 g in women. It is surrounded by three meninges: the dura mater, the arachnoid mater, and the pia mater, which are continuous with the corresponding meninges of the spinal cord. Cerebrospinal fluid surrounds the brain in the subarachnoid space, which lies between the arachnoid mater and the pia mater (Fig. 1.2). The three meninges, together with the cerebrospinal fluid and the bone of the skull, protect the brain in the event of an impact.

1.3.1.1 Cerebrum

The cerebrum is the largest region in the brain and is divided into two cerebral hemispheres (the telencephalon) by the longitudinal fissure, into which the falx cerebri projects. The cerebral hemispheres are connected by white matter, known as the corpus callosum, and the septum lucidum. The central part between the two cerebral hemispheres forms the diencephalon. The dorsal aspect of each hemisphere is contained within the cranial fossa, while the ventral aspect fits inside the anterior and middle cranial fossa. The cerebrum is divided into two parts: the evolutionarily more recent neocortex and the more primitive limbic system.

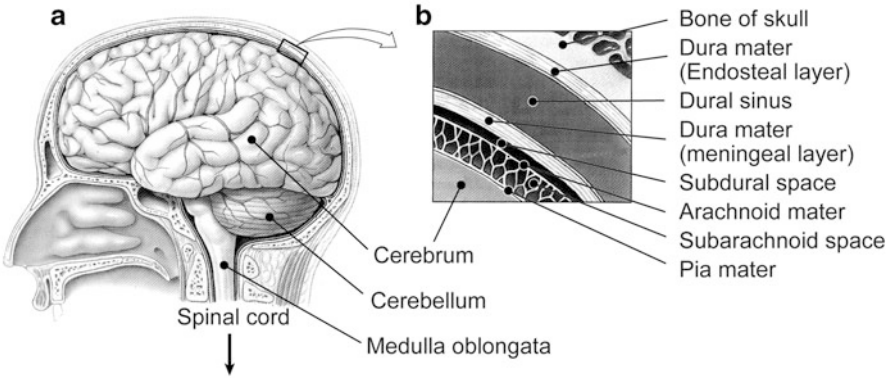

Fig. 1.2 Brain and the outer meninges. (**a**) Lateral view of the brain within the skull. (**b**) Higher magnified images of the meninges and the skull of the brain (Reproduced from [1] with permission)

Cerebral Hemispheres (Telencephalon)

The cerebral hemispheres are highly developed in humans and include motor and sensory centers as well as an association cortex which regulates diverse higher brain functions. Each hemisphere consists of three areas: the pallium, which surrounds the surface layer; the cerebral nuclei (ganglia), which are located deeper in the hemisphere; and the rhinencephalon (olfactory bulb and tract), which is located on the downside of the frontal cortex. The pallium is further divided into the surface area (1.5–4.0 mm from the surface) of the cerebral cortex (gray matter) and the deeper cerebral medulla (white matter). The cerebral cortex contains a huge number of nerve cell bodies, while the white matter consists of a mass of myelinated neuronal fibers (axons). Ninety percent of the cerebral cortex is included in the neocortex which, starting at the surface, consists of six layers: (I) the molecular (plexiform) layer, (II) the external granular layer, (III) the external pyramidal layer, (IV) the internal granular layer, (V) the internal pyramidal (ganglionic) layer, and (VI) the multiform layer (a layer of polymorphic cells) (Fig. 1.3). The cerebral cortex also contains ventricles and blood vessels, which circulate the cerebrospinal fluid and blood, respectively, as well as other components. Blood flow in the gray matter is greater than that in the white matter.

Afferents to a given region of the cortex are derived from five sources: (1) long and short association fibers from small- and medium-sized pyramidal cells occupying other parts of the ipsilateral cortex, (2) commissural fibers from medium-sized pyramidal cells projecting through the corpus callosum from matching areas in the opposite hemisphere, (3) thalamocortical fibers from the appropriate specific or association nucleus, (4) nonspecific thalamocortical fibers from the intralaminar nuclei, and (5) cholinergic and aminergic fibers from the basal forebrain, hypothalamus, and brainstem. These fibers are illustrated in green in Fig. 1.3.

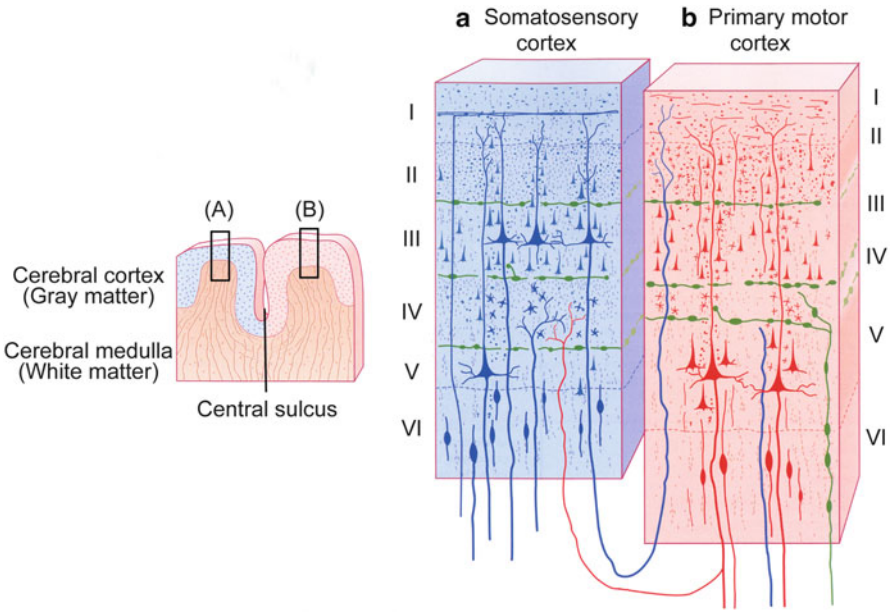

Fig. 1.3 Six layers of cerebral cortex. (**a**) Somatosensory cortex. Cortical laminas I–VI are numbered on the *left*. (**b**) Primary motor cortex. Cortical laminas I–VI are numbered on the *right* (Reproduced from [2] with permission)

All efferent connections from the cerebral cortex are axons of pyramidal cells, and all are excitatory in nature. The axons of some pyramidal cells contribute to short or long association fibers, while others form commissural or projection fibers.

The surface of the cerebral cortex is folded into gyri, which are separated by fissures and sulci (Figs. 1.4 and 1.5), thereby greatly increasing its surface area. The two main sulci are the central sulcus (Rolandic fissure) and the lateral sulcus (Sylvian fissure), which, together with the other sulci, divide the surface of each hemisphere into the frontal, parietal, temporal, and occipital lobes; these lobes are named after the cranial bone under which they lie. There is also a fifth lobe, the limbic lobe, which surrounds the medial margin of the cerebral hemisphere, including the cingulate and parahippocampal gyri (Fig. 1.6).

These lobes include several specialized functional areas, although their borders can be difficult to define and many areas can assume multiple functions. Although the anatomical structure of the two hemispheres is mostly the same, higher brain functions are often differently represented between the hemispheres. The most widely used reference map is that of Brodmann. In the early 1900s, Brodmann undertook a detailed histological analysis of the neocortex, based on which he divided it into 47 areas (Fig. 1.7). Although this area map did not always accord with functional subdivisions, clinicopathologic studies in humans and electrophysiologic and ablation studies in animals confirmed that different areas of the cerebral cortex are functionally specialized. From these observations, it has been

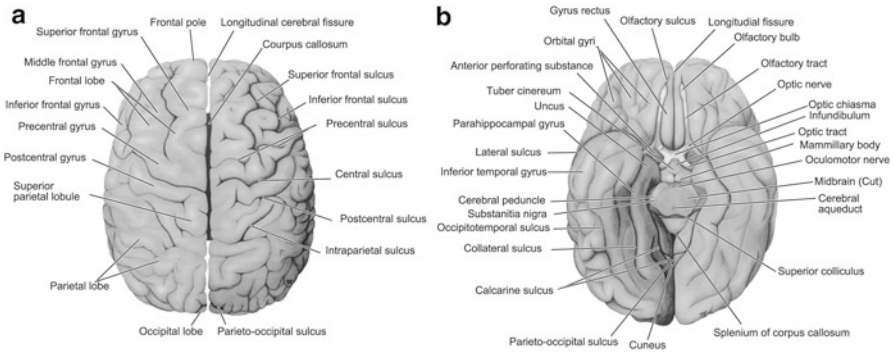

Fig. 1.4 Superior (**a**) and inferior (**b**) views of the brain, depicting the main gyri and sulci. (**a**) The two cerebral hemispheres are observed from the superior view. (**b**) The medulla oblongata, the pons, and the cerebellum have been removed (Reproduced from [3] with permission)

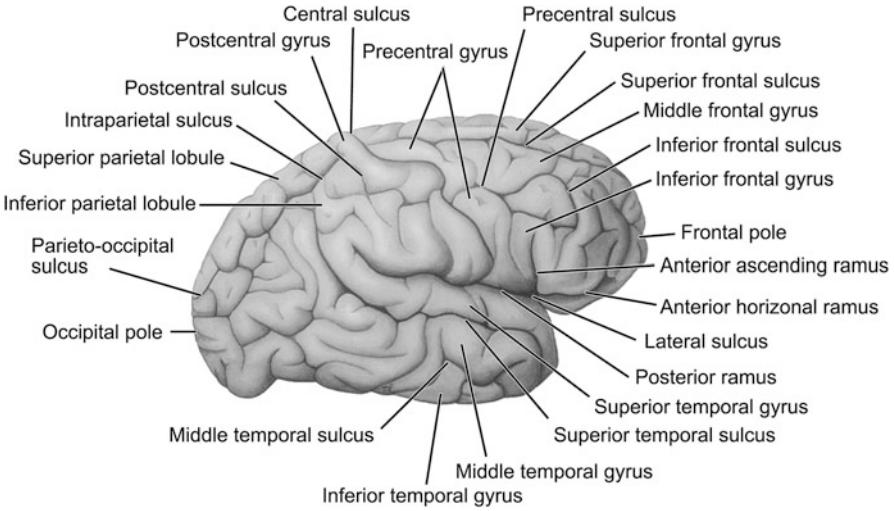

Fig. 1.5 Lateral view of the right cerebral hemisphere, depicting the main gyri and sulci (Reproduced from [3] with permission)

demonstrated that motor, somatosensory, visual, and auditory areas exist in the frontal, temporal, occipital, and parietal lobes (Fig. 1.7).

The somatosensory and motor cortices connect with association areas which analyze input information and coordinate movement responses. The somatomotor association area (premotor cortex) regulates learned motor activity. The somatosensory association area receives information from the primary somatosensory cortex, thalamus, and other regions and integrates and interprets this information.

The integrative center receives information from several different association areas. This center controls very complicated motor activity and undertakes multiple

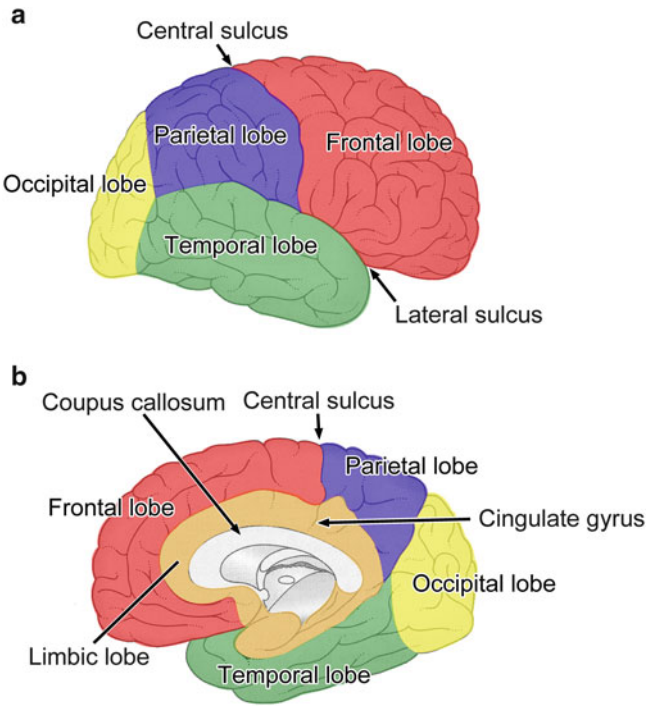

Fig. 1.6 The five lobes of the brain. (**a**) Lateral surface of the right cerebral hemisphere. (**b**) Medial surface of right hemisphere (Reproduced from [2] with permission)

functional analyses. Figure 1.7b shows the cortical association area in the left cerebral hemisphere. The prefrontal cortex, which is highly interconnected with other cortical areas, is responsible for higher-order executive and cognitive functions such as learning, problem solving, and decision making. It also has connections with the limbic system and is associated with the processing of emotion and motivation.

The motor speech area, also known as Broca's area, is located at the lower edge of the prefrontal cortex. This area coordinates the essential respiratory pattern of normal speech and the production of sound.

Figure 1.7c shows the Brodmann reference map. The primary motor cortex corresponds to Brodmann's area 4; Broca's area corresponds to area 44; and areas 17 and 18 correspond closely to the visual cortex and visual association area.

Limbic System

The limbic system, which is embedded in the border zone between the cerebral cortex and the hypothalamus, is involved in the control of emotion, behavior, motivation, and memory. Anatomically, the limbic system comprises the

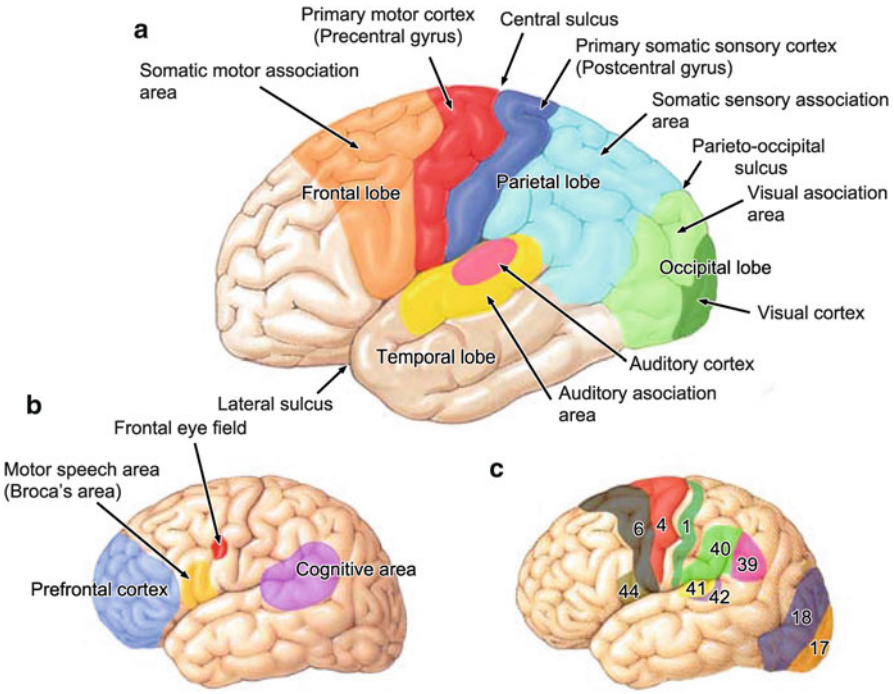

Fig. 1.7 The functional area of the cerebral hemisphere. (**a**) Motor and sensory area of the cerebral cortex. (**b**) Cortical association area of high brain function in the cerebral hemisphere. (**c**) Cytoarchitectural brain map of Brodmann. 1, primary somatosensory cortex; 4, primary motor cortex; 6 and 44, premotor cortex; 17, primary visual cortex; 18, visual association cortex; 39, angular gyrus; 40, secondary somatic sensory cortex; and 41 and 42, primary auditory cortex (Reproduced from [1] with permission)

subcallosal and cingulate gyri, the hippocampal formation, the amygdaloid nucleus (amygdala), the mammillary bodies, and the anterior thalamic nucleus (Fig. 1.8).

The hippocampal formation includes the hippocampus, the dentate gyrus, and the parahippocampal gyrus and is phylogenetically categorized into the three-layered archicortex. The principal cells in the hippocampus are pyramidal cells, while in the dentate gyrus they are granular cells. The dendrites of these cells are studded with dendritic spines. The hippocampal formation also contains abundant GABAergic interneurons and plays important roles in the consolidation of information from short-term memory into long-term memory and spatial navigation.

The amygdaloid nucleus, which is almond shaped and located deep in the uncus of the temporal cortex, consists of a complex of nuclei that can be grouped into a larger basolateral group and a smaller corticomedial group. The amygdaloid nucleus is primarily associated with the processing of fear.

The connecting pathways of the limbic system are the alveus, the fimbria, the fornix, the mammillothalamic tract, and the stria terminalis. The afferent and efferent fibers from and to the hippocampus play a role in the limbic system. This

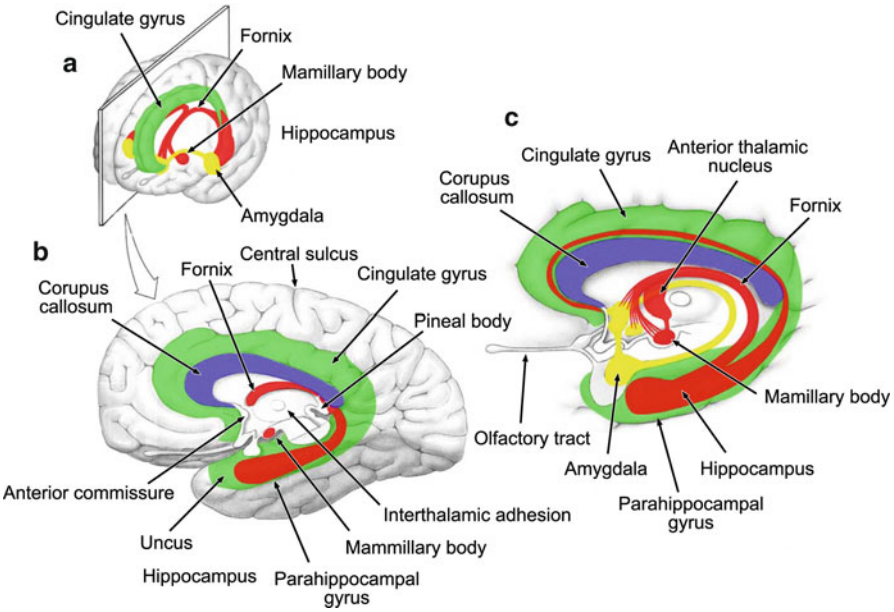

Fig. 1.8 The limbic system of the cerebrum. (**a**) Sagittal section through the cerebral hemisphere. (**b**) Medial view of the right cerebral hemisphere. (**c**) Large image of the limbic system. Same region of the limbic system is highlighted with the same color (Reproduced from [1] with permission)

system is mediated by the hypothalamus and, due to its connection with the output of the autonomic nervous system and its control of the endocrine system, is able to influence many aspects of emotional behavior.

1.3.1.2 Diencephalon

The diencephalon consists of the third ventricle and the structures which connect with the cerebral hemisphere and the brainstem and includes the thalamus, the subthalamus, the epithalamus, and the hypothalamus (Fig. 1.9).

The thalamus is a large ovoid area of gray matter that forms the major part of the diencephalon. The thalamus is a very important processing station that receives and integrates information from all the main sensory tracts apart from the olfactory pathway. This information is then relayed to the cerebral cortex and many other subcortical regions. The thalamus also plays a key role in the integration of visceral and somatic information.

The subthalamus lies inferior to the thalamus and is situated between it and the tegmentum of the midbrain. The subthalamic nucleus has important connections with the corpus striatum and is involved in the control of muscle activity.

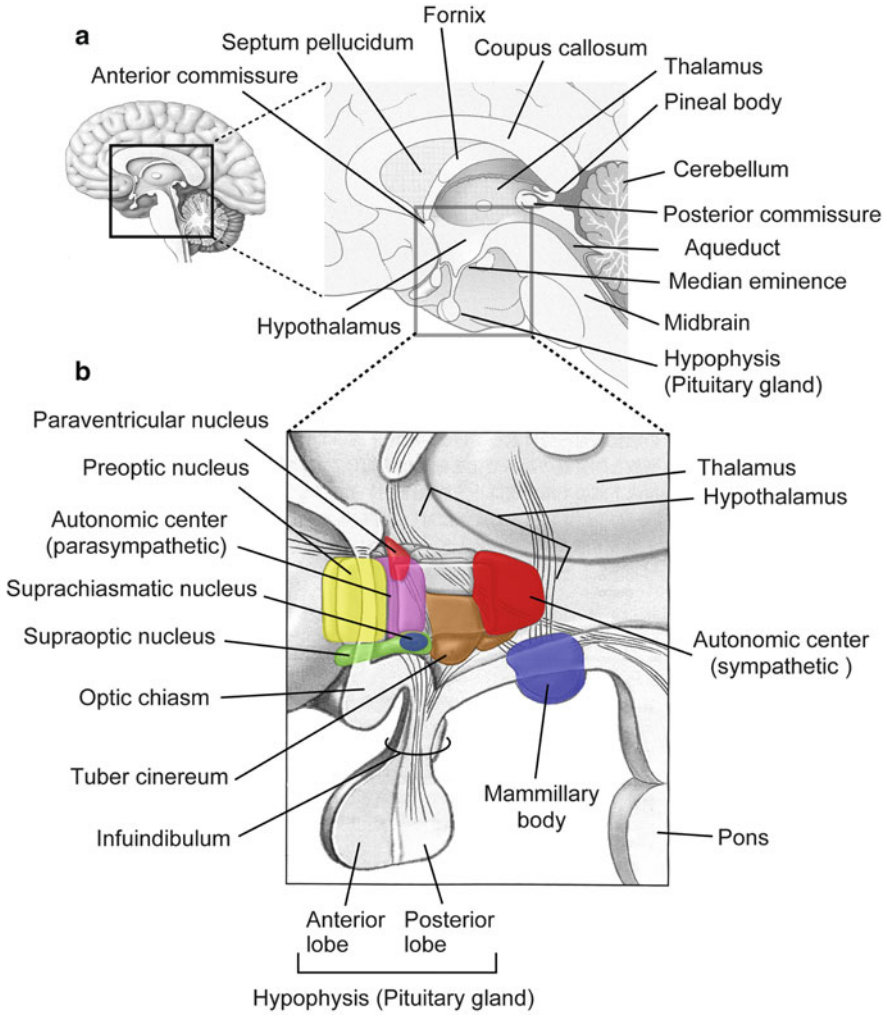

Fig. 1.9 The diencephalon. (**a**) Medial view of the telencephalon and the brainstem. Right figure is enlarged in the *rectangle* in left image. (**b**) The hypothalamus and pituitary gland. Main nerve nuclei are highlighted (Reproduced from [1] and [2] with permission)

The epithalamus consists of the habenular nuclei and their connections and the pineal gland. The habenular nuclei lie on the posterior surface of the thalamus and are believed to comprise a center for the integration of information from the olfactory, visceral, and somatic afferent pathways. The pineal gland is an endocrine gland that produces melatonin from its pinealocytes. This melatonin is released into the blood or into the cerebrospinal fluid of the third ventricle and inhibits the action of gonadotrophic hormone in the pituitary gland. In humans and animals, the

plasma level of melatonin rises at night and falls during the day. It would appear that the pineal gland plays a role in the regulation of reproductive function.

The hypothalamus extends from the region of the optic chiasma to the caudal border of the mammillary bodies. The hypothalamus refines and integrates the functions of the autonomic nervous system and the endocrine system and plays a vital role in maintaining homeostasis, including body temperature, body fluids, appetite, sexual behavior, and emotion.

1.3.1.3 Brainstem

The brainstem regulates autonomic function and is directly involved in several processes that are essential for life. The brainstem consists of the medulla oblongata (myelencephalon), the pons (part of the metencephalon), and the midbrain (mesencephalon) and occupies the posterior cranial fossa of the skull (Fig. 1.10). Less frequently, parts of the diencephalon are also included. All the cranial nerves apart from the olfactory and optic nerves originate in the brainstem, which is structurally continuous with the spinal cord. The cranial nerve is positioned on the dorsal part of the tegmentum, and the sensory and motor nuclei are located on its lateral and medial sides, respectively.

Midbrain (Diencephalon)

The midbrain, which connects the pons and cerebellum with the forebrain, is approximately 2 cm in length. The midbrain adjoins the third ventricle rostrally, the pons and cerebellum caudally, and the diencephalon laterally. The cerebral peduncles are paired structures present on the ventral side of the midbrain. On the posterior surface are four colliculi (the corpora quadrigemina). These are rounded eminences that are divided into superior and inferior pairs by a vertical and a transverse groove. The superior colliculi are centers for visual processing, and the inferior colliculi are lower auditory centers (Fig. 1.11).

The cerebral peduncles are divided into an anterior part, the crus cerebri, and a posterior part, the tegmentum, by a pigmented band of gray matter, the substantia nigra. At the level of the superior colliculi lies the red nucleus, a rounded mass of gray matter which appears light pink in color due to the abundant blood vessels situated in the superior part of the substantia nigra. These two regions play an important role in reward, addiction, and movement.

Pons

The pons, which lies anterior to the cerebellum and connects the medulla oblongata to the midbrain, measures approximately 2.5 cm in length. Many transverse fibers converge on each side of its ventral surface to form the middle cerebellar peduncle.

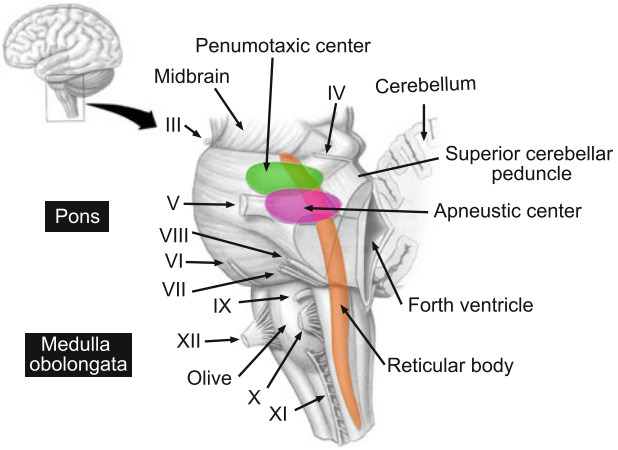

Fig. 1.10 The brainstem. *Rectangle* shows enlargement of the lateral view of the right hemisphere in the brain. Main centers and structures located inside the brainstem are highlighted. Twelve pairs of cranial nerves are shown as I to XII. I, olfactory nerve; II, optic nerve; III, oculomotor nerve; IV, trochlear nerve; V, trigeminal nerve; VI, abducens nerve; VII, facial nerve; VIII, vestibulocochlear nerve; IX, glossopharyngeal nerve; X, vagus nerve; XI, accessory nerve; and XII, hypoglossal nerve (Reproduced from [1] with permission)

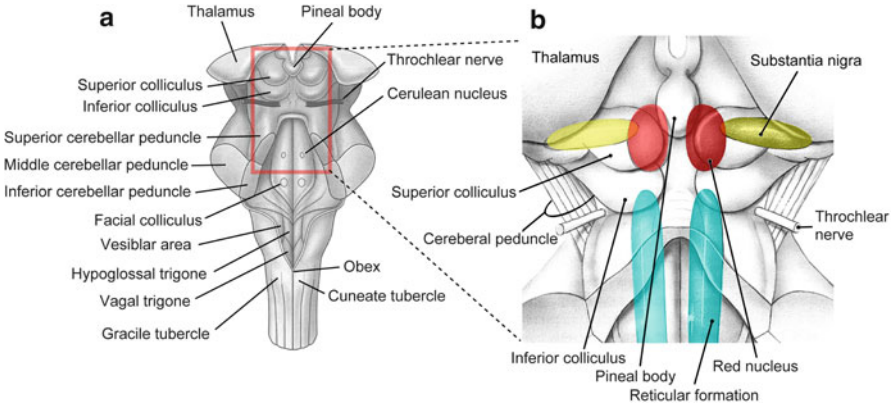

Fig. 1.11 The midbrain. (**a**) Posterior view of the midbrain and brainstem. (**b**) *Rectangle* shows same area enlarged. Main centers and structures located inside the midbrain are highlighted (Reproduced from [1] and [2] with permission)

In the middle, the basilar artery is embedded in the shallow basilar groove. The dorsal surface of the pons is covered by the cerebellum, with which it forms the triangular fourth ventricle.

Cerebellum

The cerebellum, which is cauliflower-like in appearance, lies within the posterior cranial fossa of the skull, posterior to the pons and the medulla oblongata of the brainstem, and is covered superiorly by the tentorium cerebelli (Fig. 1.12). Together with the brainstem, the cerebellum forms the fourth ventricle, a cavity filled with cerebrospinal fluid. The adult cerebellum weighs between 120 and 140 g and accounts for 10 % of the total volume of the brain. Macroscopically, the cerebellum is divided into three sections: the flocculonodular lobe, which belongs to the archicerebellum and is also known as the vestibulocerebellum; the anterior lobe, which belongs to the paleocerebellum and is also called the spinocerebellum; and the posterior lobe, which belongs to the neocerebellum and is also known as the pontocerebellum. The latter two are further subdivided into the median cerebellar vermis and the laterally symmetric cerebellar hemispheres.

The cerebellum is composed of an outer covering of gray matter, called the cortex, and inner white matter, known as the intracerebellar nuclei. The cerebellar cortex is a sheetlike structure with fissures lying in the coronal plane. The gray matter of the cortex is uniform in structure and, from the surface, is divided into three layers: the molecular layer, the Purkinje cell layer, and the granular layer. Purkinje cells, some of the largest cells in the body, are large Golgi type I neurons arranged in a single layer. They are considered to be the output cells of the cerebellum (Fig. 1.12).

At the midline, underneath the gray matter of the cortex, lie white matter and the four intracerebellar nuclei: the dentate, the emboliform, the globose, and the fastigial. The intracerebellar nuclei are composed of large, multipolar neurons with simple branched dendrites. The axons of these neurons are myelinated and form the cerebellar outflow in the superior and inferior cerebellar peduncle.

1.3.1.4 Medulla Oblongata

The medulla oblongata (the medulla) is the lower half of the brainstem and connects the pons superiorly with the spinal cord inferiorly. The medulla forms the cavity of the fourth ventricle (rhomboid fossa). On the anterior surface of the medulla oblongata is the anterior median fissure, which is continuous with that of the spinal cord. On either side of the median fissure are the pyramids, a bundle of corticospinal fibers that tapers to form a decussation. Posterolateral to the pyramids are the olives, which are prominent oval areas produced by the inferior olivary nuclei (Fig. 1.10).

The medulla oblongata controls autonomic functions and connects the higher levels of the brain to the spinal cord. It is also responsible for regulating several basal functions of the autonomic nervous system, including respiration, cardiac function, vasomotor control, and reflex actions such as vomiting, coughing, sneezing, and swallowing.

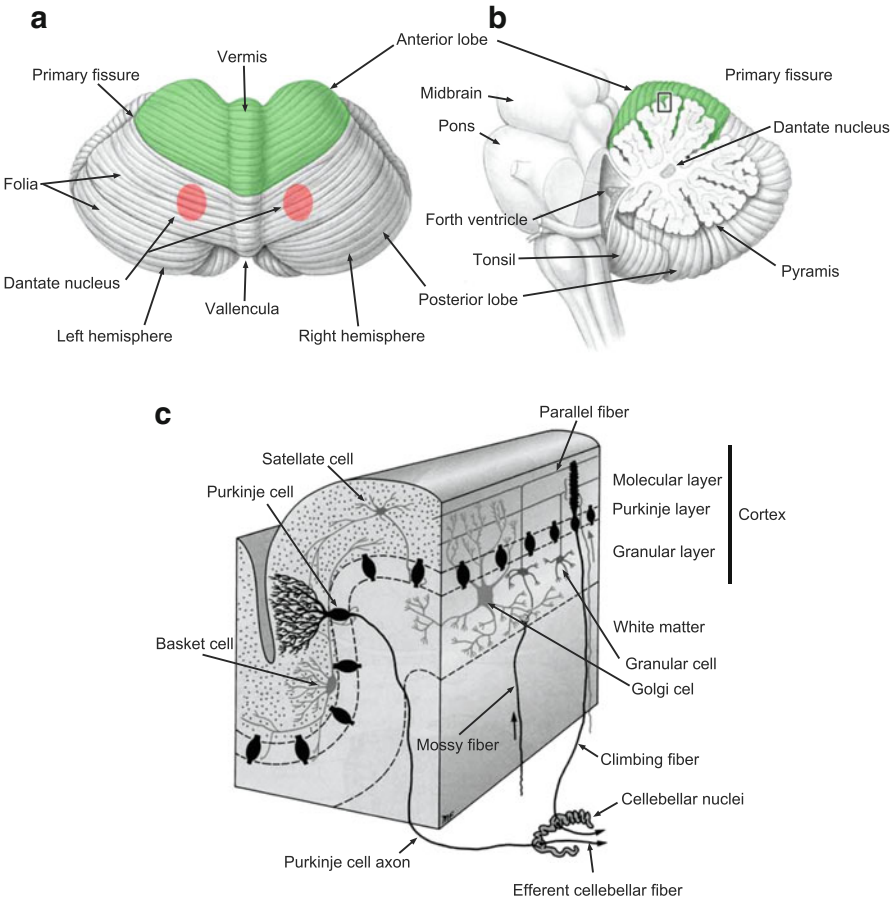

Fig. 1.12 The cerebellum. (**a**) View from above. (**b**) Sagittal section of the hindbrain. Anterior lobe in the cerebellum is highlighted in *green*. The dentate nuclei, which are located deeper in the cerebellum, are highlighted in *red*. (**c**) Cellular organization of the cerebellar cortex shown enlarged in *rectangle* in (**b**) (Reproduced from [1] and [3] with permission)

1.3.2 Spinal Cord

The spinal cord is situated within the upper two thirds of the vertebral canal of the vertebral column. The lower part of the spinal cord tapers gradually and terminates at the first caudal vertebra. The spinal cord is surrounded by three meninges: the dura mater, the arachnoid mater, and the pia mater. The subarachnoid space is suffused with spinal fluid for protection. The vertebral column is composed of 33 vertebrae: 7 cervical (C); 12 thoracic (Th); 5 lumbar (L); 5 sacral (S), which form the sacrum; and 4 coccygeal (the lower three of which are ordinarily fused). Fibrocartilaginous pads form intervertebral disks and are situated between the

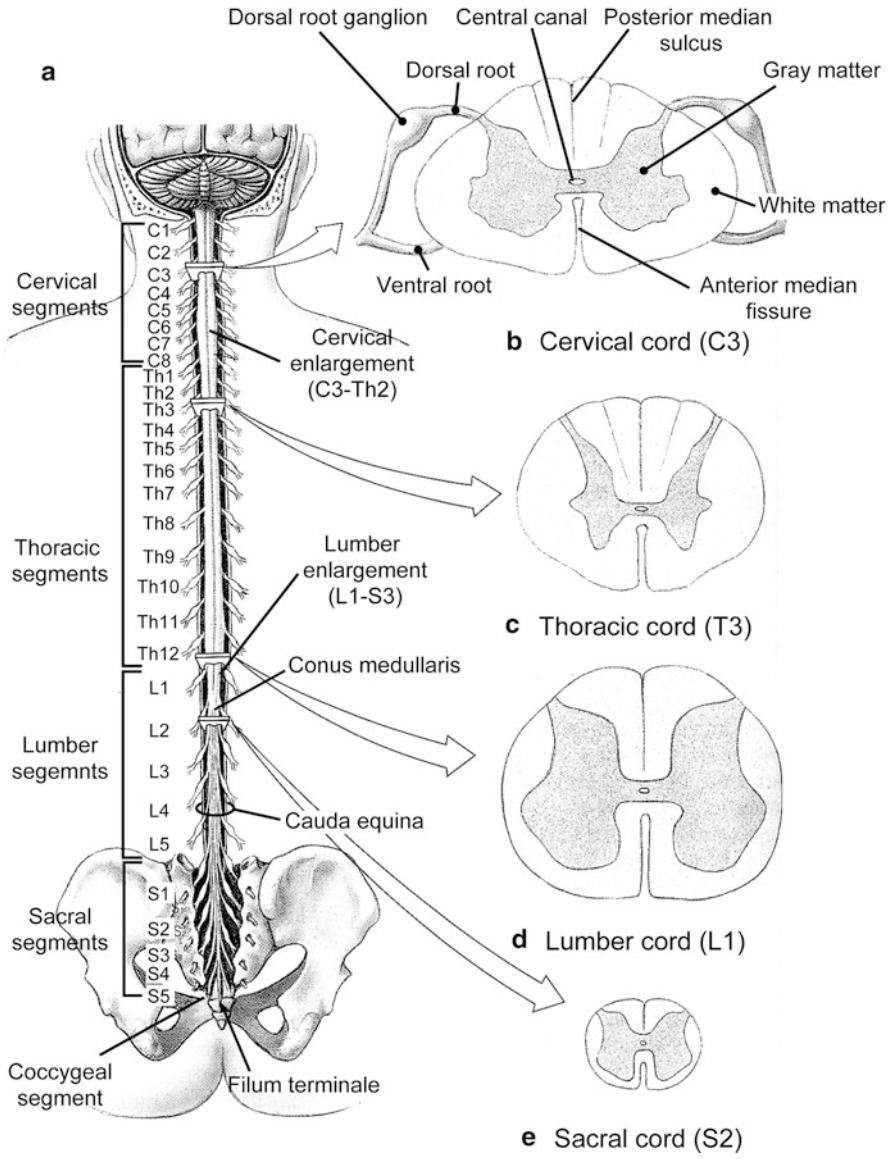

Fig. 1.13 The spinal cord. (**a**) Posterior view of the spinal cord. (**b**–**e**) Representative transverse sections of the spinal cord (Reproduced from [1] with permission)

vertebrae along approximately one fourth of the length of the column, thereby producing a flexible structure (Fig. 1.13).

The length of the spinal cord is approximately 44 cm in men and 43 cm in women, and its lateral diameter is approximately 1 cm. The spinal cord is enlarged at the level of the fifth and sixth cervical vertebrae and the 12th thoracic vertebra,

forming the cervical and lumbar enlargement, respectively. The lower border of the spinal cord (conus medullaris) in adults is at the level of the first lumbar or 12th thoracic vertebra, with the region below this being known as the cauda equina, which is formed by a vertical leash of nerves around the filum terminale. The spinal cord is embedded within a deep longitudinal fissure, called the anterior median fissure, anteriorly at the midline, and a shallow furrow, called the posterior median sulcus, on the posterior surface. It extends 31 pairs of spinal nerves with anterior (motor) and posterior (sensory) roots, which are classified into 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal segments (Fig. 1.13).

1.3.2.1 Gray Matter

The spinal cord is composed of an inner core of gray matter, which forms a butterfly-like or "H" shape, and an outer covering of white matter. The gray matter consists of a central gray commissure with symmetrical dorsal and ventral projections known as the anterior and posterior horns (or columns), respectively. The lateral gray horn presents at the level of the thoracic and upper lumbar segments of the cord. The sacral autonomic nuclei form a cellular cluster resembling a lateral gray horn at the second to fourth levels of the sacral segments; the parasympathetic nerve fibers extend from these nuclei.

The gray matter of the spinal cord consists of a mixture of nerve cells and their fibers, glia, and blood vessels. The nerve cells are multipolar. The glia give rise to an intricate network around the nerve cell bodies and neurites.

1.3.2.2 White Matter

The white matter is divided into the posterior, anterior, and lateral funiculi (fasciculus), the latter two of which are often called the anterolateral funiculi. The anterior funiculus on each side lies between the midline and the point of emergence of the anterior nerve root. The lateral funiculus lies between the point at which the anterior nerve root emerges and that at which the posterior nerve root enters; the posterior funiculus lies between the point at which the posterior nerve root enters and the midline.

The white matter of the spinal cord consists of a mixture of nerve fibers, glia, and blood vessels. Its color is due to the high proportion of myelinated nerve fibers.

1.4 Nervous Tissue and Function

Nervous tissue consists of two kinds of cells: neurons (nerve cells) and their supporting glial cells (neuroglia).

1.4.1 Neurons

Neurons, the basic units of the nervous system, are specialized for the reception of stimuli and the conduction of nerve impulses. They are composed of a cell body (or soma), which contains the nucleus and its surrounding cytoplasm, and two kinds of neurites: dendrites and axons (Fig. 1.14). One or more dendrites project from the cell body and are responsible for receiving information and conducting it toward the soma, while the axon, a single long tubular neurite, transmits impulses away from the cell body to other neurons. The end of the axon (telodendron) branches to form the synaptic terminal, or bouton, from which information is communicated to other neurons via a structure known as a synapse. Most neurons make synaptic connections with 1,000 or more other neurons and can receive up to 10,000 connections from other neurons. Dendrites and axons are often referred to as nerve fibers. Neurons are found in the brain, spinal cord, and ganglia. Unlike most cells in the body, neurons in the mature individual do not undergo cell division and replication. Different types of neurons can be identified on the basis of the number and length of the processes emerging from the cell body (Fig. 1.15). According to the number of processes, neurons can be classified as (1) multipolar neurons which display many processes attached to a polygonal-shaped soma (these are the most abundant neurons and include the pyramidal cells of the cerebral cortex, the Purkinje cells, and neurons of the cerebellar cortex); (2) bipolar neurons, which have two processes and are typically found in the visual, auditory, and vestibular systems; and (3) pseudounipolar neurons, which have only one short process and are located in the sensory ganglia of the cranial and spinal nerves. Based on the length of their axons relative to the dendritic tree, multipolar neurons can be subclassified into Golgi type I neurons and Golgi type II neurons. Golgi type I neurons extend a single long axon and are observed in the fiber tracts of the brain and spinal cord and the peripheral nerves; they are represented by the motor cells of the spinal cord.

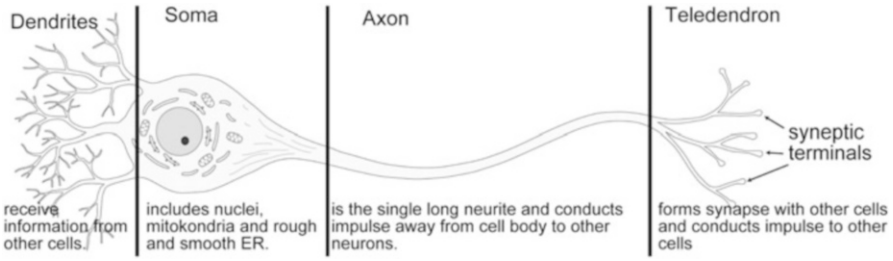

Fig. 1.14 The neuron and its structure (Reproduced from [1] with permission)

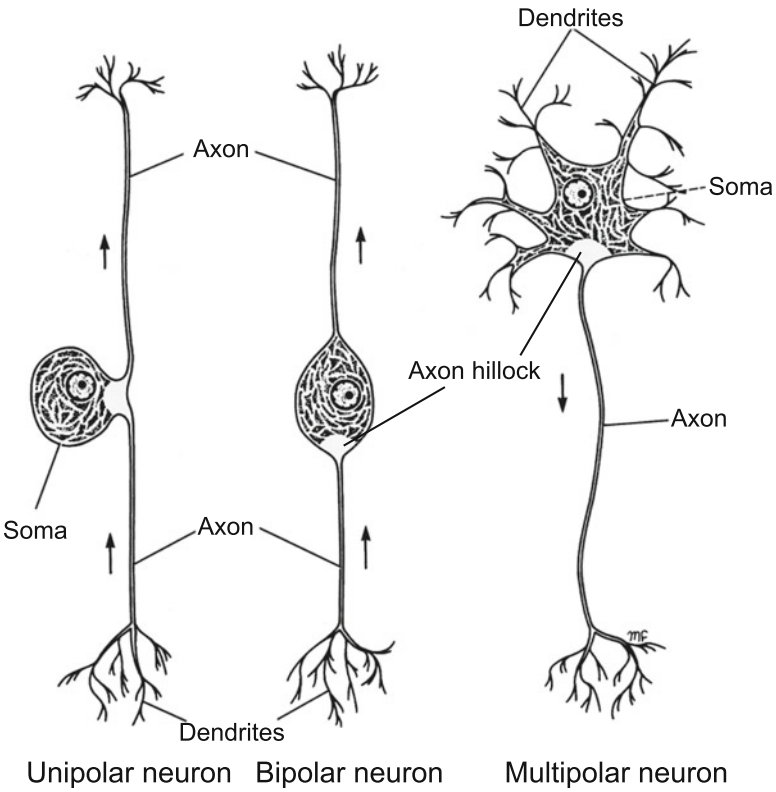

Fig. 1.15 The classification of neurons according to the number, length, and mode of branching of the neurites (In reference to [3], with permission)

1.4.2 Glia (Neuroglia)

The neurons of the central nervous system are supported by several varieties of non-excitable cells, which together are known as glia (glial cells, neuroglia). The glia are five- to tenfold more numerous than neurons and occupy half of the total volume of the brain and spinal cord. They are generally smaller than neurons and retain the ability to proliferate. There are four types of glia: (1) astrocytes (astroglia); (2) oligodendrocytes (oligodendroglia); (3) ependymal cells, collectively known as macroglia; and (4) microglial cells, or microglia (Fig. 1.16).

1.4.2.1 Astrocytes

There are two types of astrocytes: fibrous astrocytes, which are found mainly in the white matter, and protoplasmic astrocytes, which are found mainly in the gray matter. Fibrous astrocytes have long thin processes with few branches, while

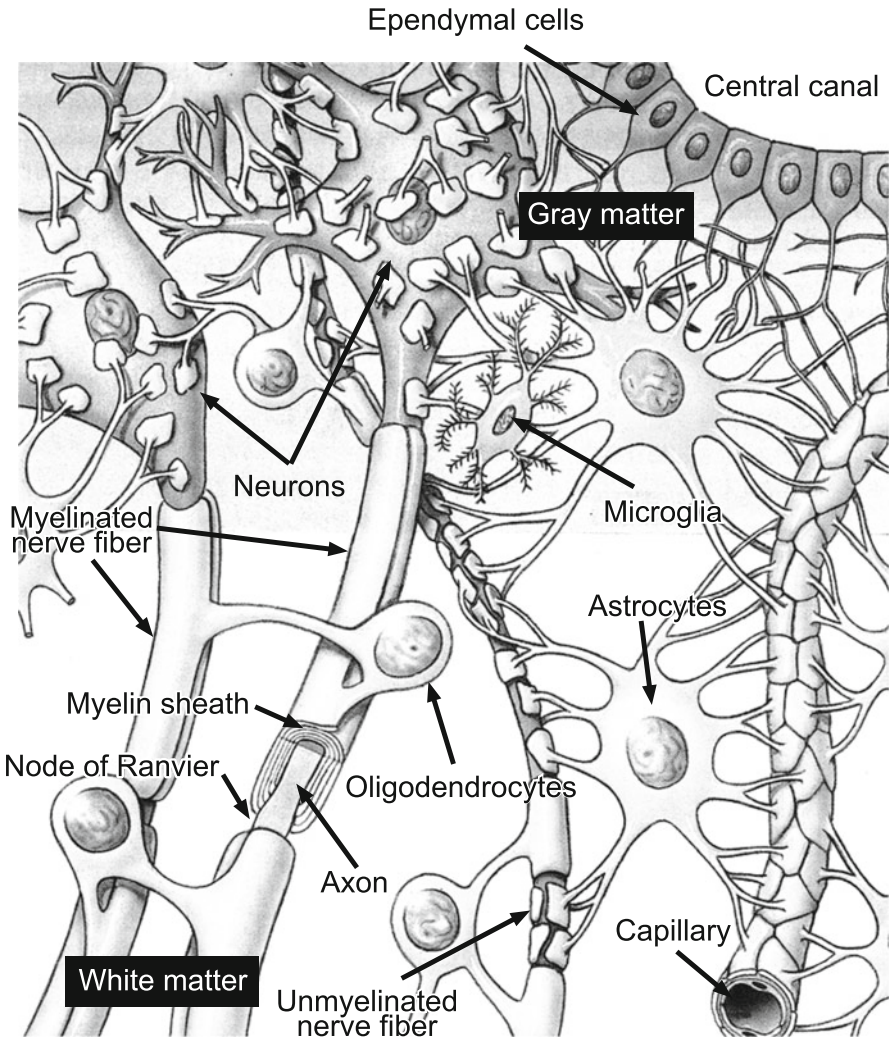

Fig. 1.16 Illustration of the central nervous system (Reproduced from [1] with permission)

protoplasmic astrocytes have shorter processes with many short branches. Astrocytic processes terminate in expansions known as end feet, most of which (perivascular feet) form the glial limitation, which almost completely covers the surface of the capillaries. This close association between astrocytes and brain capillaries suggests a role in the regulation of brain metabolism. Astrocytes also surround neurons and neuronal processes in areas devoid of myelin sheaths and help form the structural matrix of the nervous system.

1.4.2.2 Oligodendrocytes

Oligodendrocytes, which have small cell bodies and a few delicate processes, are frequently found in rows together with myelinated nerve fibers and surrounding neuronal somata. Oligodendrocytes are responsible for the formation of the myelin sheaths in the central nervous system. The formation and maintenance of myelin around many axons provides them with an insulating coat and greatly increases their speed of nerve conduction.

1.4.2.3 Microglia

Microglia, the smallest of the glia, are the resident macrophages of the central nervous system and are responsible for host defense and the removal of dead cells. Microglia are mesodermal cells that migrate into the nervous system during fetal life.

1.4.2.4 Ependymal Cells

Ependymal cells, which are cuboidal or columnar cells that possess microvilli and cilia, form a single layer lining the cavity of the brain and the central canal of the spinal cord. These cells assist in the circulation of the cerebrospinal fluid in these regions through the movement of their cilia, while the presence of microvilli on their free surface suggests that they also have an absorptive function. Ependymal cells also circulate cerebrospinal fluid to the hypophyseal portal system.

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Part II
General Consideration: Neurophysiology for Neuroanesthesia

Chapter 2
Cerebrospinal Blood Flow and Its Regulation

Toru Yamashita, Kazunori Miyazaki, and Koji Abe

Abstract The human brain utilizes large amounts of O_2, which means that the rate of blood flow has to be maintained at a consistently high level. This is made possible by "cerebral autoregulation," the process by which the cerebral and spinal blood vessels keep cerebral blood flow constant, even under change in systemic blood pressure. In addition, cerebral and spinal blood flow and its regulation appear to be closely related not only to vascular disease phenotype but also the pathophysiology of various neurodegenerative disorders, including Alzheimer's disease and amyotrophic lateral sclerosis. In this review, we briefly highlight cerebral and spinal blood flow and its autoregulation and show its relationship to neurological diseases.

Keywords Amyotrophic lateral sclerosis (ALS) • Cerebral autoregulation • Cerebral blood flow • Flow-metabolism coupling

2.1 Introduction

The adult human brain weighs approximately 1,350 g, representing approximately only 2 % of total body weight. However, the brain receives 12–15 % of cardiac output. In addition, whole-brain O_2 consumption can be approximately 20 % of that of the body as a whole. This high blood flow rate and level of O_2 utilization indicate high metabolic demand, showing that the brain constantly requires adequate nutritional and oxygenated blood flow. Cerebral blood vessels have the inherent ability, termed "cerebral autoregulation," to keep cerebral blood flow constant over a wide range of systemic blood pressure levels by means of myogenic, neurogenic, or metabolic mechanisms. Moreover, much recent evidence suggests that this blood flow rate and metabolism are related to the pathophysiological mechanisms underlying various diseases.

In this chapter, we briefly review cerebral and spinal blood flow and their autoregulation together with our recent findings.

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2.2 Cerebral Autoregulation

Kety & Schmidt established N_2O methods of measuring total cerebral blood flow [1]. By using this method, they and other researchers elucidated the phenomenon of cerebral autoregulation, referring to the ability of the brain vascular bed to maintain cerebral perfusion despite changes in blood pressure [2, 3]. Basically, cerebral blood flow remains constant even if blood pressure changes to approximately 50 % of the normal range under various conditions, including tilting, spinal anesthesia, or sympathetic nerve block (Fig. 2.1). Moreover, cerebral blood autoregulation is maintained even under hyperperfusion induced by treatment with vasopressin or noradrenaline [4, 5]. However, this autoregulation can be affected by diverse pathological conditions such as an excessive change in O_2/CO_2 or intracranial hypertension [6, 7].

2.3 Metabolic, Neurologic, and Myogenic Control of Cerebral Autoregulation

Many researchers have attempted to clarify the mechanism underlying automatic regulation of cerebral blood flow. It has been suggested that it is controlled by metabolic, myogenic, or neurologic control mechanisms.

From the point of view of metabolic control, $PaCO_2$ is regarded as an important modulator, and many data have demonstrated that high concentrations of it can dilate cerebral blood vessels, resulting in increased cerebral blood flow [8, 9]. This upregulation of $PaCO_2$-induced cerebral blood flow was thought to be derived not

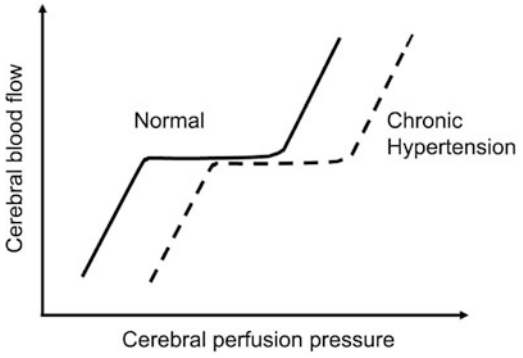

Fig. 2.1 *Cerebral autoregulation*
Cerebral autoregulation stabilizes blood flow to the brain during variations in cerebral perfusion pressure, protecting the brain against the risks of low or high blood pressure. Chronic hypertension can shift these autoregulation limits toward higher blood pressure levels. This adaptation protects the brain against hypertension but may also render it more vulnerable to hypoperfusion during episodes of hypotension

only from acidic extracellular fluid [H+] but also various kinds of bioactive substances such as endothelium-derived relaxing factor, nitric oxide, prostaglandin, and endothelin [10–13].

In 1902, Bayliss reported the phenomenon of "stretch response," in which the artery can contract against high arterial pressure [14]. It was suggested that this myogenic response also contributes to cerebral autoregulation by keeping perfusion pressure constant under change in systemic blood pressure [15].

On the other hand, basically, perivascular neurologic systems, including sympathetic nervous activity, are believed not to attenuate cerebral autoregulation, at least not under normal conditions. This is because resection of perivascular nerve fibers such as the sphenopalatine ganglia does not attenuate the cerebral autoregulation system [16]. However, the possibility that perivascular neurologic systems are involved in cerebral autoregulation under pathophysiological conditions cannot be ruled out.

2.4 Spinal Blood Flow and Its Regulation

Spinal blood flow is 40–60 % that of the brain, but tissue oxygen levels are almost the same (35–39 mmHg) [17]. As with cerebral blood, spinal blood flow is automatically regulated with change in systemic blood pressure, and CO_2 tension has a large impact on the control of spinal blood flow. The volume of spinal blood flow rises and falls in parallel with arterial CO_2 tension. Some evidence has suggested that, unlike with cerebral blood flow, the neurologic system is involved in the autoregulation of spinal blood flow. Young et al. reported that there was no autoregulation of spinal cerebral blood flow in cats with sympathectomies and that spinal cerebral blood flow changed in response to changes in systemic blood pressure [18]. However, another research group found that lower lumbar sympathectomy exerted only a moderate effect on spinal blood flow in rats [19]. Further research is needed, however, to fully clarify the neurologic system's role in spinal autoregulation.

2.5 Spinal Blood Flow and Glucose Metabolism in Neurological Disease

There is a close relationship between blood flow and glucose metabolism under physiological conditions [20]. However, several research papers have reported reductions in blood flow and glucose metabolism in the cerebral cortex or spinal cord under the pathological conditions characteristic of various neurological diseases such as Alzheimer's disease (AD) [21] and amyotrophic lateral sclerosis

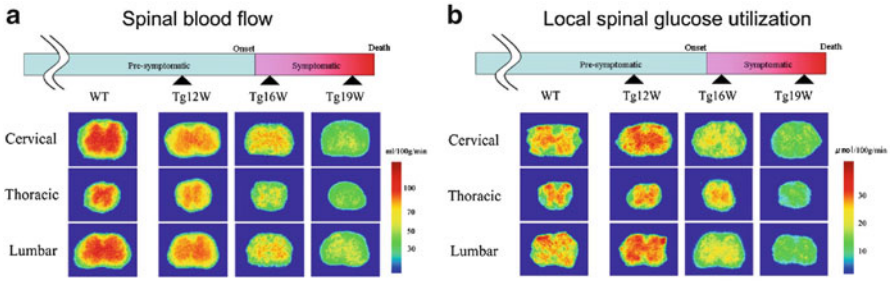

Fig. 2.2 *Spinal blood flow-glucose metabolism uncoupling in ALS model mice (Modified from Miyazaki et al. 2012)*
Autoradiograms of spinal blood flow (*left side*) and local spinal glucose utilization (*right side*) in the cervical, thoracic, and lumber cord of wild-type and G93A-SOD1 transgenic mice
Compared with wild type, spinal blood flow in ALS model mice showed a progressive decrease in the anterior gray matter from the presymptomatic stage. On the other hand, local spinal glucose utilization showed a transient increase at the presymptomatic stage and then tended to decrease at a later stage

(ALS) [22]. In an AD animal model employing transgenic mice overproducing Aβ and TGF-β1, both neurovascular and neurometabolic coupling to whisker stimulation were implicated [21]. Our group recently investigated flow-metabolism coupling with spinal circulation and glucose metabolism in ALS transgenic mice. We used transgenic mice with the G93A human SOD1 mutation and measured spinal blood flow and local spinal glucose utilization by using standard autoradiographic methods with ^{14}C-iodoantipyrine or ^{14}C-2-deoxyglucose. We found a transient increase in the local spinal glucose utilization/spinal blood flow ratio at the presymptomatic stage of disease, suggesting that this flow-metabolism uncoupling was closely involved in disease development and that it might also offer a potential surrogate marker for evaluation of disease progression (Fig. 2.2). In the near future, it should be confirmed whether this flow-metabolism uncoupling can be observed in the spinal cord of ALS patients.

2.6 Concluding Remarks

This article briefly highlights cerebral and spinal blood flow and their autoregulation, together with our recent clinical and experimental findings. Cerebral and spinal blood flow and their regulation may be related not only to vascular but also neurodegenerative diseases such as AD and ALS. This indicates the urgency of studying cerebral and spinal blood flow and metabolism in patients with neurodegenerative conditions in order to elucidate the pathophysiology of each disease.

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Chapter 3
The Neuroendocrine System and Its Regulation

Yasuhiro Nishiyama and Ken-ichiro Katsura

Abstract The neuroendocrine system is composed of the hypothalamus and pituitary gland; the nervous system controls the release of hormones from the pituitary gland. The secretory activity of the endocrine glands was formerly thought to be outside the direct control of the nervous system. Since the 1950s, the brain has been recognized as the center of the system controlling and regulating the physiological processes of the human body, and, currently, the neuroendocrine–immune network is proposed to mediate a bidirectional interaction between the neuroendocrine and immune systems. This network is responsible for maintaining homeostasis and orchestrating the essential responses to inflammation or injury through a tightly regulated network of neuropeptides, hormones, cytokines, and chemokines. Further investigation into neuroendocrine–immune crosstalk could shed light on the pathogenesis of diverse diseases, such as inflammatory and central nervous system diseases.

Keywords Neuroendocrinology • Neuroendocrine system • Hypothalamus • Pituitary gland • Neuroendocrine–immune network

3.1 Introduction

The neuroendocrine system is composed of the hypothalamus and pituitary gland; the nervous system controls the release of hormones from the pituitary gland. The secretory activity of the endocrine glands was formerly thought to be outside the direct control of the nervous system. Since the 1950s, the brain has been recognized as the center of the system controlling and regulating the physiological processes of the human body, and, currently, the neuroendocrine–immune network is proposed to mediate a bidirectional interaction between the neuroendocrine and immune

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systems. This network is responsible for maintaining homeostasis and orchestrating the essential responses to inflammation or injury through a tightly regulated network of neuropeptides, hormones, cytokines, and chemokines.

3.2 Background

Neuroendocrinology is the study of the interactions between the nervous and endocrine systems, which regulate the physiological processes of the human body. Historically, the control of biological functions was thought to be independently controlled by the nervous and endocrine systems. The neuroendocrine system is composed of the hypothalamus and pituitary gland, with the nervous system controlling the release of hormones from the pituitary gland.

3.3 History of Neuroendocrinology

The concept of neurosecretion was first proposed by Ernst Scharrer and Wolfgang Bargmann in the 1950s [1, 2]. Scharrer and his wife, Berta, observed that certain neurons in the hypothalamus of vertebrates, as well as in invertebrates without a hypothalamus, secreted cytoplasmic granules that they thought to be hormones. Bargmann demonstrated the histology of the neurohypophysis and the nerve tracts that extended from the paraventricular and supraoptic nuclei to the neural lobe of the pituitary by using Gomori's chrome alum hematoxylin–phloxine stain. Before their proposals, many endocrinologists generally ignored the observation that certain specialized nerve cells could secrete hormones, resulting in the belief that the nervous and endocrine systems were independent. Intensive studies on neurosecretory cells revealed that there are very close links between these two systems, which mainly control systemic hormonal functions. Geoffrey Harris, who is considered the "father" of neuroendocrinology, conducted extensive work on the hypothalamic control of pituitary function and demonstrated that the mammalian anterior pituitary gland is regulated by factors secreted into the hypothalamohypophysial portal circulation by hypothalamic neurons [3]. Since then, the brain has been recognized as the center of the system controlling and regulating the physiological processes of the human body.

3.4 Anatomy of the Neuroendocrine System

3.4.1 Hypothalamus

The hypothalamus, which is located anteroinferior to the thalamus and superior to the pituitary gland, is called the "master nerve control center" and encapsulates the ventral portion of the third ventricle. The anterior boundary is the anterior commissure and lamina terminalis, the mammillary bodies comprise the posterior boundary, and the superior boundary is the hypothalamic sulcus, which is the rostral continuation of the sulcus limitans. The hypothalamus is divided into four major groups of nuclei according to their location in the hypothalamic zones and regions. The anterior thalamic nuclei consist of the supraoptic and paraventricular nuclei, which are responsible for regulating blood pressure and fluid balance via the secretion of certain hormones, and the suprachiasmatic nucleus, which is involved in circadian timing. The medial thalamic nuclei consist of the ventromedial and arcuate nuclei, which are involved in the regulation of feeding behavior and body weight. The lateral nucleus includes the dorsomedial nucleus, which is involved in the control of food intake and water drinking behaviors. The posterior nucleus is the mammillary nucleus, which is involved in the control of emotional expression and the autonomic nervous system [4].

3.4.2 Pituitary Gland

The pituitary gland, weighing approximately 0.6 g in human adults, is called the "master gland" and is located within a recess in the median part of the middle cranial fossa of the sphenoid bone. This gland comprises two major components, the anterior lobe (adenohypophysis) and the posterior lobe (neurohypophysis). The anterior boundary is the optic chiasm, the posterior boundary is the dorsum sellae, which is continuous with the clivus, and the superior boundary is the hypothalamus and the floor of the third ventricle (Fig. 3.1). Other important boundaries of the pituitary gland include the cavernous sinus, laterally, which contains the internal carotid artery surrounded by sympathetic fibers, and cranial nerves III, IV, V (ophthalmic and maxillary branches), and VI. The optic chiasm is located anterosuperior to the gland and is separated from it by the cerebrospinal fluid-filled suprasellar cistern. The dural roof of the pituitary, the diaphragma sellae, covers the optic chiasm. The pituitary gland is connected to the hypothalamus through the pituitary stalk and controls homeostatic and endocrine functions.

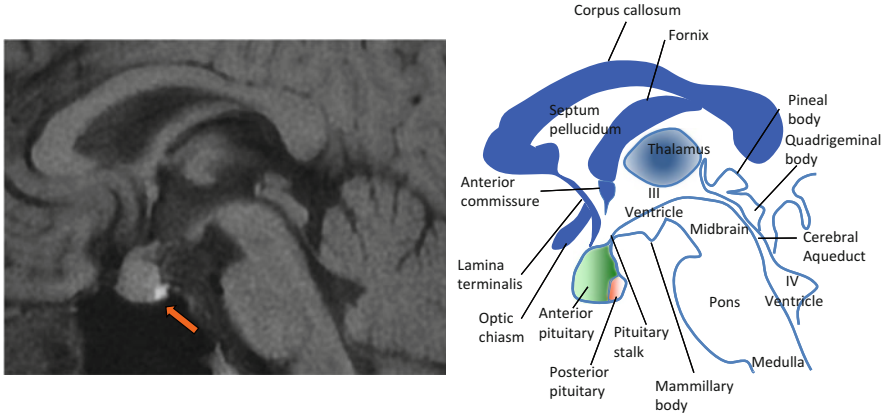

Fig. 3.1 Magnetic resonance image (MRI) (Lt) and corresponding schematic illustration (Rt) of the human hypothalamus and pituitary gland seen in the sagittal orientation. Note: The high intensity of the posterior pituitary (the so-called bright spot) in the MRI (shown by *arrow*), which is attributed to the normal representation of the functional storage of vasopressin in the posterior pituitary lobe

3.4.3 Hypothalamus and Its Connection to the Pituitary Gland

The blood supply of the pituitary stalk comes from the superior hypophyseal artery, whereas the blood supply to the neurohypophysis comes from the inferior hypophyseal artery. The cell bodies of hypothalamic secretory neurons are localized in areas protected by the blood–brain barrier (BBB), whereas their axon terminals are localized in the median eminence, which lacks a BBB. This implies a complex barrier system, allowing neurons of the central nervous system to secrete hormones into the bloodstream via the hypophyseal portal system without making the BBB leaky. The release of hypothalamic hormones promotes the secretion of anterior pituitary hormones that, in turn, regulate tissue function.

3.5 Hypothalamic Control of Pituitary Hormone

3.5.1 Anterior Pituitary

The anterior pituitary, an endocrine gland controlled by the hypothalamus, produces and secretes hormones. The anterior lobe contains glandular cells that secrete hormones directly into the bloodstream. This lobe is controlled by the hypothalamus through the vascular portal system. Hypothalamic hormones that are produced by the supraoptic, paraventricular, and arcuate nuclei of the hypothalamus control anterior pituitary hormone secretions. Neurosecretory cells send their axons into the

tuberoinfundibular tract and terminate on the capillary bed of the superior hypophyseal artery and flow together into the hypophyseal portal veins. These veins drop through the infundibular stalk and form a second capillary plexus, finally connecting with the secretory cells of the anterior pituitary. The anterior pituitary secretes its hormones into the capillary net, which drains through the cavernous sinus and internal jugular vein into the systemic circulation to transport those hormones to their peripheral target tissues. The anterior pituitary is responsible for the production of six hormones, which are regulated by the hypothalamus.

(a) Growth hormone

Growth hormone (GH) is under the dual regulation of two peptides, growth hormone-releasing hormone (GHRH) and somatostatin (growth hormone release inhibiting factor). Release of GH is determined by the balance of GHRH and somatostatin, which is controlled by stimulators (slow-wave sleep, exercise, nutrition) and inhibitors (hyperglycemia and free fatty acids). Growth hormone is necessary for cells to grow in size, an increase in protein synthesis, promotion of lipolysis, reduction of liver uptake of glucose, stimulation of the immune system, and more. With advancing age, there is a decline in GH secretion, which results in a reduction in insulin-like growth factor-1 (IGF-1) production in the liver, chondrocytes, kidney, muscle, and other tissues. The longer positive feedback loop, involving IGF-1 regulation at the hypothalamus, stimulates the secretion of growth hormone by the pituitary; a shorter negative feedback loop, demonstrated to involve direct IGF-1 action on the pituitary, leads to downregulation of GH secretion. Similar feedback loop systems exist for other major endocrine hormones. Dopamine agonist and alpha-2 adrenergic agonist are pharmacological stimulants of GH secretion, whereas beta-adrenergic agonists increase somatostatin release, inhibiting GH secretion.

(b) Thyroid-stimulating hormone

Thyroid-stimulating hormone (TSH) release is controlled by thyrotropin-releasing hormone (TRH), which has a stimulant effect, and somatostatin and dopamine, which have inhibitory effects on its release. Thyroid-stimulating hormone is necessary to stimulate the production of thyroid hormone, iodine absorption by the thyroid gland, and thyroxine and triiodothyronine (T3) synthesis and release from the thyroid gland. Thyroxine and T3 inhibit TSH production and release at the level of the pituitary (direct long loop) and inhibit the release of TRH at the level of the hypothalamus (indirect long loop).

(c) Adrenocorticotropic hormone

Adrenocorticotropic hormone (ACTH) is secreted from corticotrophs in response to bodily stress and circadian rhythm by corticotropin-releasing hormone (CRH) released by the hypothalamus. Circulating ACTH stimulates cortisol production in the adrenal glands. The secreted cortisol causes negative feedback on the hypothalamus and pituitary to inhibit further CRH/ACTH release. Stimulation of

corticosteroid and androgen synthesis and release from adrenocortical cells requires ACTH.

(d) Prolactin

Prolactin release is inhibited by dopamine and stimulated by TRH and vasoactive intestinal polypeptide. In contrast to other pituitary hormones, the hypothalamus strongly suppresses prolactin secretion from the pituitary. Prolactin is necessary for lactation, stimulation of milk synthesis, and its release from the mammary glands and is a mediator of sexual gratification.

(e) Luteinizing hormone and follicle-stimulating hormone

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) control the gonads in males and females. In females, LH and FSH stimulate the ovaries to produce steroids, producing estradiol during the follicular phase and progesterone during the luteal phase. In addition, LH and FSH surge at midcycle, triggering ovulation; LH turns the follicle into the corpus luteum by triggering ovulation. In males, LH stimulates testosterone production from Leydig cells. Follicle-stimulating hormone stimulates Sertoli cells to produce inhibin, which acts in a negative feedback fashion to regulate FSH secretion and enhance the production of androgen-binding protein by Sertoli cells.

3.5.2 Posterior Pituitary

The posterior pituitary is called the neurohypophysis, which is a collection of axonal projections from the hypothalamus through the infundibulum and into the posterior pituitary. This simple arrangement is completely different from that of the system in the anterior pituitary. The posterior pituitary hormones are transported down the axons, from the magnocellular neurons in the supraoptic and paraventricular nuclei through the infundibulum to the neurohypophysis, where they are secreted into the blood circulation. The posterior pituitary is responsible for the production of two hormones, oxytocin and vasopressin.

(a) Oxytocin

During lactation, oxytocin stimulates the myoepithelial cells of the mammary glands and causes milk letdown into the duct system. At parturition, oxytocin stimulates and enhances the contraction of the uterine myometrium for labor induction. An infant suckling at the breast and the stretching of the lower uterus and cervix by the pressure induced by the presence of the fetus are relayed by spinal nerves to the hypothalamus to cause the release of oxytocin.

(b) Vasopressin

Vasopressin is known as an antidiuretic hormone, and is necessary for an increase in water permeability in the distal convoluted tubule and collecting ducts

of kidney nephrons. This increase in water permeability promotes water reabsorption and increased blood volume. Vasopressin secretion is controlled by osmotic and nonosmotic stimulation by pathways that are anatomically separated. In osmotic stimulation, osmoreceptors are present in the anterior thalamic region, which lies outside the BBB. There is a positive relationship between plasma osmolality and circulating vasopressin concentrations, with vasopressin secretion being suppressed at levels below 280 mOSm/kg. In nonosmotic stimulation, both high-pressure (aortic and carotid) and low-pressure (left atrial) receptors function through parasympathetic pathways to provide for vasopressin release. Such pathways are activated in response to acute systemic hemodynamic changes, decreases in blood pressure, and a reduction in left atrial pressure.

3.6 Neuroendocrine–Immune Network

The concept of the neuroendocrine–immune network has been proposed as a bidirectional interaction between the neuroendocrine and immune systems. This network is responsible for maintaining homeostasis and for orchestrating the essential responses to inflammation or injury through a closely regulated network of neuropeptides, hormones, cytokines, and chemokines.

That the immune system modulates brain activity, including body temperature, sleep, and feeding behavior, is well established [5]. For instance, interleukin 1 (IL-1) alerts the hypothalamus that there is "danger" in the periphery. This cytokine activates a febrile response through neurons in the preoptic area of the anterior hypothalamus. Considerable evidence suggests that IL-1 passes through the BBB and induces cyclooxygenase-2 and microsomal prostaglandin E synthase-1 activity. Interleukin-1β and prostaglandin E2, as proinflammatory stimuli, are secreted into the brain parenchyma and stimulate a temperature increase induced through the activity of preoptic neurons in the hypothalamus [6–8].

In addition, patients who experience acute ischemic injury to the central nervous system (CNS) present with moderate to severe hyperglycemia, and hyperglycemia following CNS injury is an independent risk factor for poor outcomes [9, 10]. Therefore, investigations into the basic mechanisms for both the induction of hyperglycemia and the consequences of it for ischemic outcomes are essential. Advanced glycation end products (AGE) and their receptors (RAGE) regulate inflammation and the dysfunction of glucose metabolism in response to CNS injury. Activation of RAGE induces inflammatory responses via the immune cells in the CNS, and consequent glucose dysregulation, reactive oxidant species production, and neuronal damage might cause tissue damage or poorer functional outcomes [11]. Therefore, the AGE–RAGE axis could be a therapeutic target for metabolic diseases and ischemia.

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Chapter 4
Molecular Mechanisms of Brain Ischemia and Its Protection

Hiroyuki Uchino, Miyuki Chijiiwa, Yukihiko Ogihara, and Eskil Elmer

Abstract Ischemia is defined as a reduction in blood flow to a level that is sufficient to alter normal cellular function. Brain tissue is highly sensitive to ischemia, such that even brief ischemic periods in neurons can initiate a complex sequence of events that may ultimately culminate in cell death. Stroke and cardiac arrest induce the cessation of cerebral blood flow, which can result in brain damage. The primary intervention to salvage the brain under such a pathological condition is to restore the cerebral blood flow to the ischemic region. However, paradoxically, restoration of blood flow can cause additional damage and exacerbate the neurocognitive deficits in patients who suffered a brain ischemic event, which is a phenomenon referred to as "reperfusion injury." Transient brain ischemia following a stroke, cardiac arrest, hypoxia, head trauma, cerebral tumor, cerebrovascular disorder, and intracranial infection results from the complex interplay of multiple pathways including excitotoxicity, acidotoxicity, ionic imbalance, peri-infarct depolarization, oxidative and nitrative stress, inflammation, and apoptosis. Many lines of evidence have shown that mitochondria suffer severe damage in response to ischemic injury. Mitochondrial dysfunction based on the mitochondrial permeability transition (MPT) after reperfusion, particularly involving the calcineurin/immunophilin signal transduction pathway, appears to play a pivotal role in the induction of neuronal cell death. Here, we discuss the underlying pathophysiology of brain damage, which is a devastating pathological condition, and highlight the central signal transduction pathway involved in brain damage, which reveals potential targets for therapeutic intervention.

Keywords Ischemic brain damage • Mitochondrial dysfunction • Reperfusion injury • Excitotoxicity • Mitochondrial permeability transition (MPT) • Calcineurin/immunophilin

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4.1 Introduction

Many studies have examined the mechanisms involved in ischemic brain injury. However, no effective pharmacological treatment directed at tissues of the central nervous system (CNS) has been established to prevent the pathological conditions that occur as a consequence. Therefore, all aspects of the basic mechanisms responsible for brain damage require urgent elucidation. Recently, our research has aimed toward understanding the involvement of and the importance of calcium and the calcineurin/immunophilin signal transduction pathway in brain damage. We previously demonstrated that immunosuppressants interacting with the calcineurin/immunophilin signal transduction pathway show potent neuroprotective effects in several animal models of ischemic brain damage, and these effects are considered to be separate from their action on immunocompetent cells [1–6].

In clinical anesthesiology, the pathological conditions that involve neuronal degeneration can be broadly divided into several categories as follows: (1) global ischemia due to an extended period of cardiac arrest [7, 8]; (2) cerebral infarction (focal ischemia) that occurs after the occlusion of cerebral arteries [9]; (3) direct injuries due to head trauma and cerebral compression associated with hematoma or cerebral edema [10]; (4) increased intracranial pressure (ICP) and secondary hypoxic brain damage due to cerebrovascular spasm [11, 12]; (5) encephalitis or meningitis caused by viruses, bacteria, parasites, fungi, and spirochetes [13–15]; and (6) seizures caused by head trauma, cerebral tumors, cerebrovascular disorders, intracranial infections, and abnormal metabolism [16, 17]. These conditions are likely to share many aspects of the pathological mechanisms resulting in brain damage and neurological impairment. Although the most crucial mechanisms responsible for the induction of brain damage remain unclear, it has been suggested that mitochondrial dysfunction is significantly involved. The elucidation of the basic pathophysiology for each of these pathological conditions that involve neuronal degeneration is of great importance for the development of effective neuroprotective pharmaceutical agents.

In this chapter, we outline the role of increased intracellular calcium, reactive oxygen species (ROS), and inflammation in ischemic neuronal cell death, with special emphasis on the calcineurin/immunophilin signal transduction pathway and the mitochondrial permeability transition (MPT), which is a pathological state of the inner mitochondrial membrane leading to bioenergetic failure [18–21].

4.2 Induction of Ischemic Neuronal Cell Death: The Glutamate-Ca^{2+} Theory

Ischemia is defined as a reduction in blood flow to a level that is sufficient to alter normal cellular function. Brain tissue is highly sensitive to ischemia, such that even brief ischemic periods in neurons can initiate a complex sequence of events that may ultimately culminate in cell death. Different brain regions have varying thresholds for ischemic cell damage, with the white matter being more resilient than the gray matter [1]. Discontinuation of aerobic metabolism due to cerebral ischemia provokes the immediate loss of energy substrates and promotes anaerobic glycolysis with the accumulation of intracellular lactic acid and H^+, leading to intracerebral acidosis. Under conditions of hyperglycemia, intracerebral acidosis is exaggerated. Furthermore, there is a loss of energy-dependent ion homeostasis primarily caused by the inhibition of the plasma membrane ATP-dependent Na^+/K^+ exchanger, resulting in an increase in extracellular K^+ as well as intracellular Na^+, leading to cellular depolarization. The ion gradients that are normally established across the plasma membrane have many functions, for example, they are used to remove excess intracellular Ca^{2+} as well as used for the reuptake of extracellular glutamate. These functions are abolished during ischemia. Moreover, Ca^{2+} influx via voltage-dependent Ca^{2+} channels can contribute to the release of glutamate from presynaptic terminals to the extracellular space [22]. The excessive release of glutamate further provokes an increase in intracellular Ca^{2+} and Na^+ levels by the binding of glutamate to its postsynaptic receptors (*i.e.,* N-methyl D-aspartate [NMDA] receptors and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid [AMPA] receptors). This increase in intracellular Ca^{2+} and Na^+ levels activates the signal transduction pathways mediated by the activation of Ca^{2+}-dependent enzymes including nitric oxide synthase (NOS), phospholipase A2 (PLA2), and calmodulin kinase, which then trigger the following intracellular events: degradation of lipid membrane components, an increase in the levels of free fatty acids, alteration of gene expression, alteration of the phosphorylation and dephosphorylation state of proteins, degradation of proteins of the cytoskeleton, and enzymatic and mitochondrial production of free radicals such as ROS (*e.g.,* superoxide, hydroxyl radicals, and H_2O_2) or reactive nitrogen species (RNS) (Fig. 4.1). In addition, the increased intracellular Ca^{2+} levels will trigger mitochondrial dysfunction (described separately below and in Fig. 4.2). This results in the deterioration of neuronal cell membranes and organelles, induction of downstream cascades involving increased Ca^{2+} cycling and Ca^{2+} overload (calcium dysregulation), activation of suicide programs, disturbance of axonal transport, activation of macrophages by the expression of adhesion factors, and platelet aggregation associated with microvascular dysfunction, which will eventually lead to unavoidable cell death (Fig. 4.1).

This glutamate-Ca^{2+} theory of excitotoxic neuronal cell death is widely accepted [23–25]. According to this theory, the most important aspect of the pathogenesis of cerebral ischemia is the restriction of substrates and oxygen to the mitochondrial

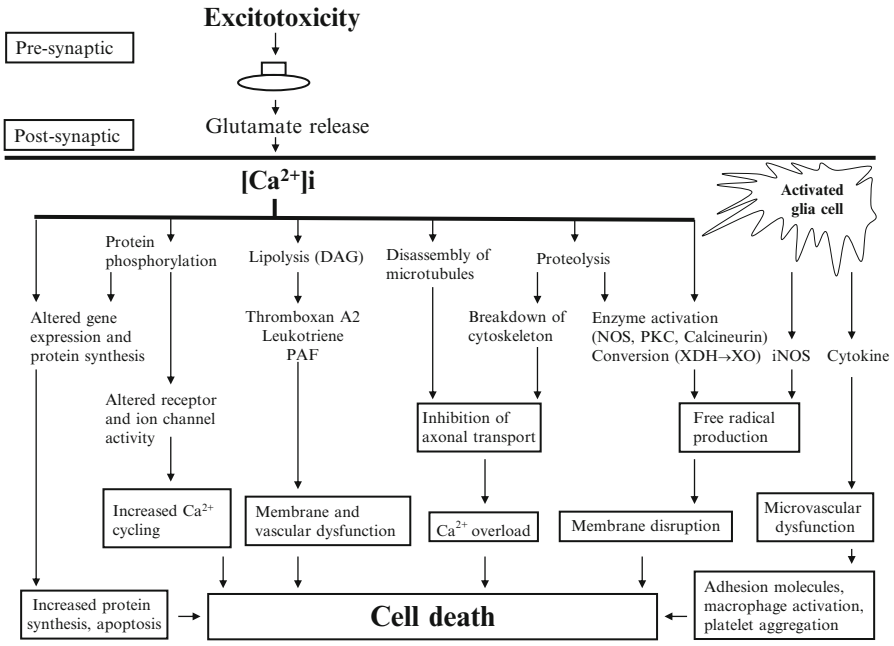

Fig. 4.1 *The cell death cascade induced after cerebral ischemia*
Ischemia induces the loss of ATP-dependent ion homeostasis and leads to an increase in intracellular Na^+ and extracellular K^+. Eventually, the cells undergo depolarization. As a result, excessive Ca^{2+} influx due to the activation of VSCC (voltage sensitive calcium channel), NMDA, and AMPA receptors activates numerous signal transduction cascades. This eventually induces the mitochondrial permeability transition (MPT), leading to mitochondrial dysfunction

respiratory system and the induction of cellular ATP crisis. It is the loss of cellular energy and its repercussions (as described above) that trigger acute or delayed neuronal cell death. However, recent analyses of the role played by heart and liver mitochondria in reperfusion injury [26, 27] strongly indicate that direct calcium-triggered mitochondrial dysfunction and neuronal cell death associated with the induction of the MPT may be involved in reperfusion injury under situations of decreased cellular energy levels (lowered levels of ATP) and increased oxidative stress (Fig. 4.2). During the last 10 years, we have investigated and characterized the MPT in isolated mitochondria from the CNS as well as examined the role of inhibitors of the MPT in in vivo models of brain disease. The MPT is an exciting new putative therapeutic target for intervention in ischemia reperfusion injury [3, 8, 9, 28–35].

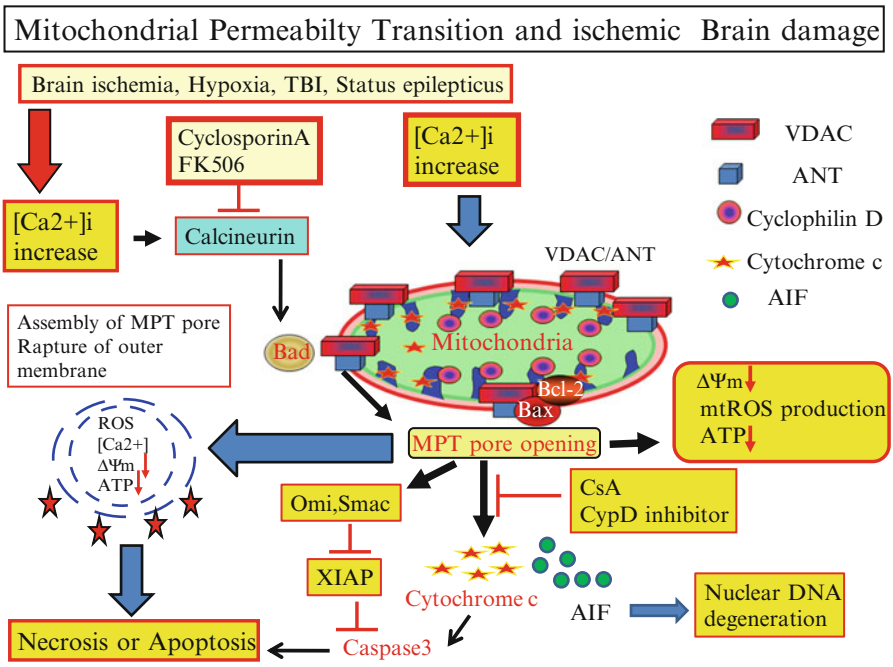

Fig. 4.2 *Importance of calcineurin/immunophilin signal transduction neuronal cell death via the MPT*

Various forms of stress, such as brain ischemia, hypoxia, traumatic brain injury, status epilepticus, and encephalitis induce mitochondrial dysfunction and the MPT that lead to apoptosis or necrosis. Calcineurin and immunophilin (CypD) are the key factors that induce the apoptotic pathway, and the immunosuppressants CsA and FK506 exert their neuroprotection by the inhibition of calcineurin and CypD activity

4.3 Reperfusion Injury

The restoration of cerebral blood flow, which is known as "reperfusion," elicits multiple cellular and physiologic events. Reperfusion reverses the disruption of cellular functions that was induced by ischemia. In adults, ischemic insults to the brain typically result from stroke (caused by either thrombotic occlusion or rupture of a blood vessel) [36] or cardiac arrest [37], whereas in infants cerebral ischemia can be initiated by complications during delivery, resulting in neonatal hypoxic-ischemic encephalopathy [38]. Spontaneous reperfusion or reperfusion created by an intervention can cause additional and substantial brain damage, which is referred to as "reperfusion injury." Reperfusion induces pathological events such as lipid peroxidation due to the elevation of ROS, inflammation, and calcium overload (calcium dysregulation) that leads to MPT associated with mitochondrial dysfunction [26, 27, 39, 40] (further discussed below).

4.4 Reactive Oxygen Species (ROS)

It is well known that reperfusion following brain ischemia induces the production of a large amount of ROS ubiquitously throughout a cell. There are a number of possible cellular sources of these free radicals, including xanthine oxidase, cyclooxygenase, lipoxygenase, cytochrome p450, endothelial nitric oxide synthase, and NADPH oxidase. Mitochondria also produce ROS in the form of a superoxide anion (O^{2-}), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH^-) which have been suggested to play important roles in the regulation of signal transduction and cellular metabolism [41]. Alterations of phosphorylating (state 3) and basal (state 4) respiration and respiratory control indicate a normalization of the electron transport system after reperfusion. However, secondary mitochondrial dysfunction is a prominent consequence of transient cerebral ischemia [42] resulting in a reduction of mitochondrial ATP synthesis. The other major target of ROS is lipids, and the peroxidative action of ROS promotes the inactivation of key metabolic enzymes that regulate glucose metabolism. ROS are inactivated by endogenous mitochondrial and cytoplasmic scavenging systems. However, ischemic reperfusion can sometimes overwhelm these scavenging systems, resulting in the production of ROS originating primarily from mitochondrial complex I and III of the electron transport chain, causing oxidative damage to the mitochondria and consequently the cell [43]. Other highly reactive free radicals are produced by protein nitrosylation due to the reaction of NO and superoxide anions, which can also lead to the dysregulation of cellular homeostasis.

4.5 Disturbance of Mitochondrial Ca^{2+} Homeostasis in Neurons

Ca^{2+} is the main second messenger that helps neurons to connect their depolarization status with synaptic activity, which is the most crucial activity of neurons. Mitochondria contain two membranes, an outer membrane permeable to solutes and an inner membrane impermeable to solutes that harbors the respiratory chain complexes. During ischemia, neuronal Ca^{2+} channels and transporters as well as glutamate receptors are overactivated, and the increased activity of plasma membrane Ca^{2+} channels can then trigger the entry of Ca^{2+} into the cytosol, leading to Ca^{2+} overload. Mitochondria powerfully sequester Ca^{2+} to prevent the elevation of cytosolic Ca^{2+}, but prolonged depolarization and Ca^{2+} influx lead to mitochondrial Ca^{2+} overload. Mitochondrial Ca^{2+} overload is induced by three mechanisms: (1) increased mitochondrial Ca^{2+} uptake following the release of Ca^{2+} from the endoplasmic reticulum and Ca^{2+} influx from the extracellular space, (2) reduced Ca^{2+} extrusion through the mitochondrial Na^+/Ca^{2+} exchanger, and (3) changes in the capacity of mitochondrial Ca^{2+} buffering [44]. Moderate increases in mitochondrial Ca^{2+} concentration are necessary and sufficient to adjust ATP production to

cell demand, but mitochondrial Ca^{2+} overload leads to the MPT, which causes the disruption of mitochondrial membrane integrity, irreversible oxidative damage, and the loss of ATP production, finally resulting in cell death. On the other hand, preventing or adjusting cellular conditions to decrease the sensitivity of mitochondria to undergo the MPT will protect the energized state of the mitochondria. This may be achieved by altering the redox state, decreasing energy demand, or supplying the cells with pharmacological inhibitors of the MPT, such as cyclophilin inhibitors [45] (see also below).

4.6 Inflammation

Brain ischemia induces an inflammatory reaction that leads to mitochondrial damage [46]. This phenomenon occurs very rapidly and is more robust during reperfusion. The inflammatory reaction of the blood vessels occurs immediately after vessel occlusion and induces the activation of platelets and endothelial cells. The expression of adhesion molecules including selectins, intercellular adhesion molecules, and vascular cell adhesion molecules is induced by the adhesion of neutrophils initially and then later monocytes to the endothelium. Activated leukocytes contribute to blood vessel occlusion, which disturbs vascular patency and releases proinflammatory cytokines, proteases, and ROS that induce vascular damage at the endothelial surface, leading to thrombus formation, vasospasm, and breakdown of the blood-brain barrier, further promoting the infiltration of leukocytes into the brain. Activation of microglia, which are the resident tissue macrophages, occurs within minutes of the onset of ischemia. After neuronal cell death, danger-associated molecular pattern molecules activate the pattern recognition receptors, including the Toll-like receptors expressed on microglia, and contribute to the inflammatory response in brain ischemia. Microglia also produce ROS that can cause mutations in mitochondrial DNA and damage the enzymes of the respiratory chain, leading to dysfunction of oxidative phosphorylation and increased ROS production [47]. The early inflammatory response therefore appears to induce the secondary failure of bioenergetic function.

4.7 Molecular Basis of the Mitochondrial Permeability Transition

It is still unclear whether the elevation of mitochondrial matrix Ca^{2+} levels during ischemia is causally related to the neuronal cell death that occurs after cerebral ischemia. The MPT was traditionally considered to be mediated by the formation of an MPT pore, which is a dynamic complex of several proteins. This protein complex was proposed to be located at the contact sites between the inner and

outer mitochondrial membranes, which are sites important for metabolic regulation as well as interaction with the cytosol, intermembrane space, and the matrix compartments [48, 49]. The current general hypothesis is that the MPT is formed by the voltage-dependent anion channel (VDAC or porin) of the outer membrane, the adenine nucleotide translocase (ANT) of the inner membrane, and cyclophilin D (CypD) located in the matrix compartment [49]. However, a recent gene deletion study has questioned the role of VDAC as an essential component and regulator of the MPT [50].

The increased permeability of the inner mitochondrial membrane can also possibly be induced by the concerted action of other proteins such as the uncoupling proteins and the Tom/Tim transport system, as well as by the aggregation of misfolded membrane proteins. However, the proposed core components of the MPT pore, in particular ANT and CypD, are likely to be the proteins involved in the MPT phenomenon during calcium overload under pathophysiological conditions.

Hansson et al. reported that adult viable human brain and liver mitochondria possess an active CypD-sensitive MPT and CypD inhibition plays an important role for neuroprotection [51–53].

In summary, the obligate molecular components of the MPT have not yet been resolved. Initially, there was the hypothesis that the MPT requires a complex consisting of the inner membrane protein ANT, the outer membrane component VDAC/porin, and the matrix modulator CypD. However, emerging data have suggested that some of these initial components are not obligatory for the Ca^{2+}-induced increase in permeability of the inner mitochondrial membrane and can be replaced with other known proteins present in mitochondria or other proteins yet to be identified.

4.8 Role of the MPT in Neurodegeneration

Mitochondrial function is dependent on the internal homeostasis of the cell and is dependent more particularly on the capability of mitochondria to maintain a state of selective membrane permeability. The loss of ATP; an increase in the levels of calcium, phosphate, and free fatty acids; and the generation of free radicals are key factors in inducing the MPT (Fig. 4.2). The proton gradient and the mitochondrial membrane potential ($\Delta\Psi m$) are rapidly lost as the hydrogen ions extruded from the mitochondria by the electron transport chain rapidly fall back through the MPT pores, uncoupling oxidation of metabolic substrates and respiration from the phosphorylation of ADP. The consequences of the MPT are dramatic when the inner membrane rapidly becomes permeable to solutes of up to 1,500 Da (Fig. 4.2). Importantly, this transition, if prolonged, can affect respiration in different ways according to the substrate being oxidized. Induction of the MPT in mitochondria energized with complex I-linked substrates is followed by complete respiratory inhibition due to the loss of pyridine nucleotides [54, 55]. Induction of the MPT in

mitochondria energized with complex II-linked substrates is followed by uncoupling.

The mitochondrial matrix is dense in proteins, and the induction of MPT pores will result in an osmotic influx of water into the matrix, causing the inner membrane to unfold and expand, resulting in mitochondrial swelling, as well as causing the outer membrane to rupture, inducing the release of proapoptotic proteins such as cytochrome c (CytC), apoptosis-inducing factor (AIF), Omi, and Smac (Fig. 4.2).

Prolonged and extensive MPT will lead to the termination of ATP production and necrotic cell death, if the energy balance cannot be compensated by anaerobic metabolism.

4.9 Calcineurin and Cell Death

Calcineurin was first discovered by Wang et al. in 1976 as an inhibitor of calmodulin (CaM)-dependent cyclic phosphodiesterase [56]. Calcineurin is a serine/threonine phosphatase regulated by Ca^{2+}/CaM and is highly enriched in neural tissue, comprising more than 1 % of the total protein content in brain tissue [57], which indicates its importance as a regulator of protein phosphorylation, and thereby cellular function, in the CNS. Calcineurin is abundantly distributed in the hippocampus, striatum, and cerebral cortex. Subcellularly, it is primarily found bound to the cell membrane or the cytoskeletal elements and is enriched in postsynaptic densities. Calcineurin is best known as being a target for the widely used immunosuppressive molecules cyclosporin-A (CsA) and tacrolimus (FK506) [58]. In this process, the proteins that bind to CsA and FK506, which are the so-called immunophilins (cyclophilins and FK-binding proteins, respectively), play an important role in the inhibition of calcineurin and the subsequent immunosuppressive effect. Both CsA and FK506 form complexes with specific immunophilins to cause steric hindrance of the calcineurin catalytic site, which inhibits its activity. Under physiological conditions, the effects of calcineurin are greatly multifaceted, for example, it can dephosphorylate NMDA receptors, IP3 receptors, and ryanodine receptors, which are all relevant to the regulation of intracellular Ca^{2+} levels. Furthermore, Morioka et al. [59] reported that calcineurin can play a role as a Ca^{2+}-buffering protein, and another report suggested that it exercises neuroprotective effects by promoting the expression of the antioxidant superoxide dismutase (SOD) via NFκB after cerebral ischemia. Shibasaki et al. demonstrated the interaction between members of the antiapoptotic Bcl-2 protein family and calcineurin activity, indicating an important role for calcineurin in the regulation of apoptosis [60]. They furthermore demonstrated that calcineurin specifically participates in a Ca^{2+}-inducible mechanism for apoptosis induction by regulating BAD (a proapoptotic Bcl-2 protein family member) phosphorylation [61] (see Fig. 4.2).

4.10 Pharmacological Targets in the Development of Neuroprotective Agents

Pharmacological inhibition or genetic downregulation of calcineurin activity is clearly neuroprotective [61], and the anti-ischemic effect of calcineurin-inhibiting immunosuppressive agents started to attract attention when Sharkey et al. first reported the protective effect of FK506 in a rat model of focal ischemia in 1994 [62]. The following year, Uchino et al. demonstrated the protective effect of CsA in forebrain ischemia [1]. Since these initial findings, a large amount of experimental evidence has supported the protective role of calcineurin inhibition in the pathogenesis of brain damage in a wide range of disease models (reviewed in [1, 63]). However, the effects of CsA and FK506 are not restricted to the inhibition of calcineurin. For CsA, this is evident as the non-calcineurin-inhibiting (non-immunosuppressive) cyclosporins, such as DEBIO-025 ($MeAla^3EtVal^4$ CsA) or NIM811 ($MeIle^4$ CsA), retain their potent effects on mitochondrial function in vitro [34, 64] and are neuroprotective in vivo [65–67]. Inhibition of the mitochondrial CypD, which is a proposed component of the MPT pore described above, results in decreased sensitivity to the calcium-induced MPT (similar to mutant mice with a genetic deletion of CypD [50, 51]). FK506 does not exert any effects on mitochondrial CypD or the MPT phenomenon. The calcineurin and CypD pathways converge at the immunosuppressant CsA (which inhibits both pathways), and cyclosporins and other pharmacological agents modulating the activity of either (or both) calcineurin or CypD may finally provide the first class of effective neuroprotective agents for clinical use. Mitochondrial protection may be categorized into three different pharmacological approaches: (1) inhibition of the MPT, in which the mechanisms of actions of the various therapeutic agents are often complex and interconnected; (2) reduction of oxidative stress, Ca^{2+} overload, and inflammation; and (3) improvement of mitochondrial metabolic functions.

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Chapter 5
Molecular Mechanism of Ischemic Damage to the Spinal Cord and Its Protection

Mishiya Matsumoto and Atsuo Yamashita

Abstract One of the most fearful complications after thoracoabdominal aortic aneurysm surgery is spinal cord ischemia. Ischemic spinal cord damage is considered to occur through essentially the same mechanism as ischemic brain damage. While brain ischemia research generally focuses on vulnerable neurons such as those in the hippocampus, that on spinal cord ischemia usually focuses on motor neurons. Furthermore, ischemic damage to the long nerve fibers that comprise the conduction path in the spinal cord is also recognized as an important problem.

Delayed spinal cord damage may occur after surgery for thoracoabdominal aortic aneurysm. It is unknown as to whether delayed spinal cord damage in humans occurs through the same mechanism as it does in animal models. In rabbit models, the onset of delayed spinal cord damage is accompanied by considerable ischemia-related change in the gray matter of the spinal cord. In contrast, delayed spinal cord damage following surgery for thoracoabdominal aortic aneurysm is often resolved by improving spinal cord perfusion. This must be taken into account when extrapolating the results of animal studies to humans.

Free radicals appear to play an important role in both the pathogenesis of ischemia-reperfusion damage and the acquisition of ischemic tolerance. A large amount of free radicals causes cellular damage, while an appropriate amount plays an important role in signal transduction. This implies that treatment strategies to completely eliminate free radicals, even during ischemia-reperfusion, are not necessarily successful. Fine control of free radicals appears to be important for spinal cord protection.

Keywords Spinal cord ischemia • Spinal cord protection • Thoracoabdominal aortic aneurysm • Delayed motor neuronal death • Ischemic tolerance

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5.1 Introduction

Most cases of spinal cord ischemia occur during surgery for thoracoabdominal aortic aneurysm. Common causes of spinal cord ischemia in this context include aortic cross clamping during aortic reconstruction and subsequent temporary insufficient blood supply to the spinal cord, inadequate revascularization of the spinal cord, and decreased blood flow to the spinal cord due to intravascular stent placement. Ischemic spinal cord damage is considered to occur through essentially the same mechanism as ischemic brain damage. While brain ischemia research generally focuses on vulnerable neurons such as those in the hippocampus, that on spinal cord ischemia usually focuses on motor neurons. Furthermore, ischemic damage to the long nerve fibers that comprise the conduction path in the spinal cord is also recognized as an important problem.

5.1.1 Specifics of Spinal Cord Blood Flow

The spinal cord is supplied by one anterior and two posterior spinal arteries which course along it. The anterior and posterior spinal arteries, respectively, supply the ventral two thirds and dorsal one third of the spinal cord in cross section. Both arteries branch cranially from the bilateral vertebral arteries. In the thoracic and lumbar spinal regions, the anterior and posterior radicular arteries branch from the intercostal or lumbar artery to join the anterior and posterior spinal arteries, respectively. The anterior and posterior spinal arteries are not recognized simply as branches of the vertebral artery but rather as being formed by the joining of the ascending and descending branches of the radicular artery, a branch of the intercostal or lumbar artery. Consequently, blood does not always flow in the cranial to caudal direction in these arteries; in some parts, it flows in the caudal to cranial direction.

5.1.2 Selective Vulnerability of the Spinal Cord

During spinal cord ischemia, the most vulnerable parts of the gray matter are Rexed layers III to VII, while the least vulnerable are layers I, II, and X [1]. The major reason for this is that Rexed layers III to VII are located between the areas perfused by the anterior and posterior spinal arteries, respectively. Animal studies have shown that the less vulnerable parts of the spinal cord are rich in nitric oxide synthase-containing cells [2], suggesting that the vasodilatory effect of nitric oxide plays an important role in the maintenance of blood flow in the gray matter in the presence of decreased spinal cord blood flow. This is supported by the fact that nitric oxide synthesis inhibitors exacerbate ischemic spinal cord damage

[3]. Selective damage to layers III to VII caused by a rather mild ischemic stimulus results in the manifestation of spastic paralysis and hyperesthesia, most likely due to damage to the inhibitory interneurons distributed in these layers [4]. The application of a stronger ischemic stimulus can cause damage to layers VIII and IX, in which motor neurons of the anterior horn of the spinal cord are distributed, resulting in the manifestation of flaccid paralysis.

It has generally been accepted that the gray matter is more vulnerable to ischemia than the white matter. However, a study using a rat model of spinal cord ischemia suggested that the white matter is more vulnerable and that damaged white matter may be largely responsible for the development of spastic paralysis [5]. On the other hand, rabbit studies have shown that the gray matter is more vulnerable and that a good correlation exists between the severity of motor neuron damage and that of motor dysfunction [6, 7], suggesting the need for further investigation on this issue.

5.2 Mechanisms of Death of Motor Neurons

In animal models of transient spinal cord ischemia, introduction of prolonged ischemia results in irreversible paraplegia. In contrast, introduction of relatively short-term ischemia results in transient paraplegia followed by almost complete restoration of motor function within a few hours and a subsequent delay in motor dysfunction affecting especially the hind limbs within 1–2 days [8]. This delayed hind limb motor dysfunction is considered to be due to the delayed death of motor neurons. It is unknown whether this delayed death of motor neurons occurs through the same mechanism as that of delayed neuronal death observed in the hippocampus after short-term cerebral ischemia. Given a potential therapeutic time window for delayed motor neuronal death, the elucidation of its mechanism may lead to the development of new strategies for spinal cord protection.

5.2.1 Mechanisms of Delayed Motor Neuronal Death

One study using a rabbit model of transient spinal cord ischemia suggested that disruption of the blood-spinal cord barrier occurs several hours after ischemia-reperfusion and that resulting edema may be responsible for delayed motor dysfunction [8]. Damage and fragmentation of DNA, expression of Fas antigen, and activation of caspase 3 and Akt (serine-threonine kinase) have also been observed in these models, suggesting the involvement of apoptosis in the mechanism of delayed motor neuronal death [9]. It has been hypothesized that, in the presence of mild ischemic stimulus, two conflicting cascades of survival and death signals are activated and that whether the cell lives or dies is determined slowly according to the power balance between them, with cell death mediated by the apoptotic

machinery. This hypothesis is also supported by the results of a recent study using caspase 3-knockout mice [10]. The degree of involvement of apoptosis in delayed motor neuronal death is still controversial, with some studies showing the absence of a protective effect of caspase inhibitors [11] and others identifying no evidence of the involvement of apoptosis in delayed motor neuronal death through either detailed morphological examination or DNA fragmentation analysis [12].

5.2.2 Involvement of Glial Cells

Growing attention has been given to the involvement of astrocytes and microglia in the development of hind limb motor dysfunction after transient spinal cord ischemia. Activation of astrocytes occurs rapidly 12–24 h after ischemia-reperfusion, during which delayed motor neuronal death also occurs [13]. It has been proposed that in the brain, activated astrocytes excessively produce S-100β protein, which activates inducible nitric oxide synthase in astrocytes, leading to neuronal death [14]. Although nitric oxide may play an important role in the maintenance of blood flow in the presence of decreased spinal cord blood flow after ischemia-reperfusion [2], nitric oxide reacts with superoxide to produce peroxynitrite anions, a more potent tissue-damaging agent. Although it remains unknown as to whether activated astrocytes are friends or foes of motor neurons, evidence has suggested their involvement in delayed motor neuronal death to some extent. In a clinical setting, an increased cerebrospinal fluid level of S-100β protein has also been observed in patients with spinal cord ischemia [15].

Biphasic activation of microglia also occurs after ischemic reperfusion [13, 16]. The first peak appears to be caused by the stimulus of ischemic reperfusion and the second peak appears to reflect their reaction to damaged tissues as tissue scavengers [13]. Animal studies have shown increased levels of inflammatory cytokines such as interleukin-1β (IL-1β) and IL-6 after ischemia-reperfusion [16]. Moreover, treatment of pre-ischemic animals with minocycline, an agent that inhibits microglial activation, has been shown to prevent ischemic spinal cord damage [17].

5.3 Damage to the White Matter

Unlike the brain, the spinal cord contains long nerve fibers such as those comprising the lateral corticospinal and spinothalamic tracts, and these nerve fibers may also be damaged by ischemia. Nerve fibers of central neuronal cells are substantially more vulnerable to ischemia than those of peripheral neuronal cells [18]. For example, peripheral nerve fibers exhibit no change in resting membrane potential or action

potential, even after exposure to 30 min ischemia, whereas central nerve fibers are depolarized immediately after exposure to ischemia and generate almost no action potential after a few minutes. Ischemia-related damage to central nerve fibers is believed to be ultimately mediated by the activation of various enzymes following an increase in calcium ion concentration in the nerve fiber, although the mechanism by which calcium ion concentration increases differs between nerve fibers and the neuronal cell body. In nerve fibers, depolarization is followed immediately by the continuous influx of sodium ions through sodium channels. Such an increase in the intracellular concentration of sodium ions and depolarization are believed to promote the intracellular influx of calcium ions through the sodium ion-calcium ion exchange system. The myelin sheath of nerve fibers is formed by oligodendrocytes inside the spinal cord and by Schwann cells outside it. It has been shown that oligodendrocytes can be damaged by glutamate via activation of AMPA receptors [19].

In rabbit models, damage to the gray matter became evident 1–2 days after ischemia-reperfusion, whereas damage to the white matter was not evident for the first 2 days after reperfusion and manifested in severer form 4 or 14 days later [20]. The reason for this delayed manifestation in white matter damage remains unknown.

5.4 Spinal Cord Protection

5.4.1 Hypothermia

There is no doubt that hypothermia is protective to the central nervous system. In a rabbit model of transient spinal cord ischemia, a body temperature decrease of only 3–4 °C had a clear protective effect on the spinal cord [7]. This protective effect appears to be mediated by the inhibition of the increase in glutamate concentration in the presence of ischemia, as well as by metabolic inhibition by hypothermia [21]. Epidural cooling has been proposed as a method to reduce the spinal cord temperature while preventing an excessive decrease in whole-body temperature. In animal experiments, epidural infusion of saline cooled to 5 °C had a dramatic protective effect on the spinal cord [22]. This technique has also been applied to patients in some institutions and produced favorable outcomes [23]. When using this technique, extra care must be taken to prevent an increase in cerebrospinal fluid pressure. Cerebrospinal fluid drainage is required in cases of an excessive increase in pressure. The appropriateness of this technique must be determined carefully, taking its invasiveness into account.

5.4.2 Ischemic Tolerance

Along with hypothermia, ischemic tolerance has also been shown to have a consistent cerebroprotective effect in animal models. A number of studies have suggested the acquisition of ischemic tolerance by the spinal cord [24, 25], whereas others have shown negative results [26]. Ischemic tolerance is defined as being acquired following ischemic preconditioning; ischemic tolerance acquired by other mechanisms such as hyperbaric oxygen therapy is referred to as cross-tolerance. Ischemic tolerance can be further divided into acute and delayed tolerance, based on the interval between preconditioning and fatal insult. Acute and delayed ischemic tolerance occur within a few hours and between 1 and 7 days after nonfatal insult, respectively. In general, a higher protective effect is exerted by ischemic tolerance than by cross-tolerance and by delayed ischemic tolerance than by acute ischemic tolerance. The role of free radicals produced during preconditioning has been suggested to be important in the mechanism of ischemic tolerance acquisition [27].

Attention has been paid to the potential clinical application of cross-tolerance and remote preconditioning. As an example of cross-tolerance, a protective effect of hyperbaric oxygen therapy on the spinal cord has been reported in an animal study using rabbits [28]. As an example of remote preconditioning, a strong protective effect was observed in a rabbit model where both legs were subjected to 2 cycles of 10 min ischemia and 10 min reperfusion, followed by application of a fatal ischemic stimulus after 30 min [29]. Although these techniques seem to be promising for clinical application, further animal studies are needed to verify the reproducibility of the results.

5.4.3 Glycemic Control

It is well known that hyperglycemia enhances brain damage caused by ischemia; the same applies to the spinal cord. In animals, a difference in blood glucose level of only 40 mg/dL has been shown to influence the outcome of spinal cord injury [30]. Active use of insulin is therefore recommended for hyperglycemic patients. However, the use of insulin itself at clinical doses has been shown to have no protective effect on the spinal cord [31].

5.4.4 Spinal Cord Protection by Drugs

Although many drugs have been shown to exert a protective effect on the spinal cord in animals, none of them have been applied in humans [32]. The major concern regarding the use of drugs for spinal cord protection is the occurrence of adverse

drug reactions. However, if the protective effect of those drugs already in clinical use or proven to be safe in humans is demonstrated in animals, such drugs may be promising for clinical application. Drugs and therapies that are attracting growing attention include erythropoietin [33], minocycline [17], and hydrogen inhalation [34].

Taken together, in all animal experimental data obtained to date, no anesthetic agent appears to have a strong spinal cord protective effect. Although a large amount of morphine administered to the rat spinal subarachnoid space following spinal cord ischemia-reperfusion has been suggested to exacerbate spinal cord damage [35], it seems unlikely that the use of narcotics at clinical doses exacerbates spinal cord damage [36].

5.5 Conclusion

Delayed spinal cord damage may occur after surgery for thoracoabdominal aortic aneurysm. It is unknown as to whether delayed spinal cord damage in humans occurs through the same mechanism as it does in animal models. In rabbit models, the onset of delayed spinal cord damage is accompanied by considerable ischemia-related change in the gray matter of the spinal cord [13]. In contrast, delayed spinal cord damage following surgery for thoracoabdominal aortic aneurysm is often resolved by improving spinal cord perfusion. This must be taken into account when extrapolating the results of animal studies to humans.

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Chapter 6
Mitochondrial Physiology and Cerebrospinal Protection

Morika Suzuki, Hiroki Kato, and Naomi Hachiya

Abstract Mitochondria maintain their numbers by the fusion and fission of preexisting mitochondria. Continuous mitochondrial fusion mixes the compartments, whereas fission segregates morphologically and functionally damaged mitochondria. This changing of their shape allows mitochondria to control the life and death processes of cells, such as apoptosis, the maintenance of cellular homeostasis, and ultimately the processes that occur in neurological disorders and metabolic diseases. GTPase family proteins and their regulators modulate the fusion/fission events, and a type of autophagy known as mitophagy removes damaged mitochondria. Although the molecular mechanistic effects of anesthetics on mitochondria are not yet clear, an enhanced understanding of this knowledge will be useful for the establishment of therapeutic approaches.

Keywords Mitochondrial dynamics • GTPase • Mitophagy • MAM • mPTP

6.1 Introduction

Mitochondria are double-membrane-bound organelles in eukaryotic cells that are essential for various cellular processes. Their primary function is to supply metabolic energy to cells in the form of ATP, which is generated by oxidative phosphorylation. Mitochondria are also required for essential metabolic processes including the assembly of iron-sulfur clusters [1], which are indispensable cofactors for many mitochondrial and extramitochondrial enzymes.

Most mitochondrial proteins are encoded by nuclear genes; therefore, the proteins are posttranslationally imported as precursors from the cytosol into the mitochondria [2]. However, mitochondria also possess a small amount of their own DNA (mtDNA), which encodes for mitochondrial ribosomal RNAs, transfer

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RNAs, and some proteins required for respiration. Mitochondria are also involved in many catabolic/anabolic processes, including the citric acid cycle, the β-oxidation of fatty acids, and the biosynthesis of heme, certain phospholipids, and other metabolites.

A constant change of mitochondrial morphology known as a mitochondrial dynamics is essential for maintaining healthy mitochondria. Mitochondrial fusion/fission is indispensable not only to sustain respiratory activity but also to control cellular processes such as embryonic development, neuronal plasticity, apoptosis, and calcium signaling. Recently, mitochondrial dynamics has received much attention because of its involvement in pathophysiologic mechanisms of neuronal diseases.

In the following section, we review the current knowledge about the molecular mechanisms regulating mitochondrial physiology and discuss the effects of anesthetics on mitochondria.

6.2 Physiological Role of Mitochondrial Dynamics

Mitochondrial fusion and fission depend on four GTPases: Mfn1, Mfn2, Opa1, and Drp1. Mitofusins (Mfn1 and Mfn2) are localized and anchored to the outer membrane of the mitochondria (OMM) with a large N-terminal GTPase domain and a C-terminal coiled-coil domain exposed to the cytosol. Mitofusins play crucial roles in the fusion of mitochondrial OMM via their GTPase activity. Mutations in Mfn2 gene cause a classic axonal peripheral sensorimotor neuropathy Charcot-Marie-Tooth disease type 2A (CMT2A) [3–5]. The knockout of Mfn1 gene results in small fragmented mitochondria that are broadly spread throughout the cell, whereas the knockout of Mfn2 gene leads to large fragmented mitochondria concentrated near the nucleus [6].

For the inner mitochondrial membrane (IMM) fusion, Opa1 (a gene product of optic atrophy type I) is required [7–9]. There are eight Opa1 splice variants [8, 10, 11], and the L-forms are anchored to the IMM with their GTPase domains exposed to intermembrane space (IMS) in the mitochondria. Subsequently, the L-forms of Opa1 are processed to produce the S-forms, either in the IMS by the AAA protease (i-AAA protease) or in the matrix by m-AAA protease, depending on the location of the processing sites [12–14]. Under normal conditions, both the L-forms and S-forms of Opa1 are essential for efficient mitochondrial fusion [15, 16]. Disruption of the mitochondrial membrane potential by protonophore carbonyl cyanide m-chlorophenyl hydrazone (CCCP) induces significant fragmentation of mitochondria concomitant with the rapid conversion of Opa1 from the L- to the S-form. Cellular stress, such as the loss of mtDNA, ATP deficiency, or apoptosis, causes similar processing of Opa1. This “induced” Opa1 processing is thought to mediate by Oma1 (for overlapping activity with m-AAA protease), a protease with multiple membrane-spanning segments and a zinc-binding motif [17, 18]. Opa1 has also been reported to be involved in the maintenance of crista structure; the knockdown

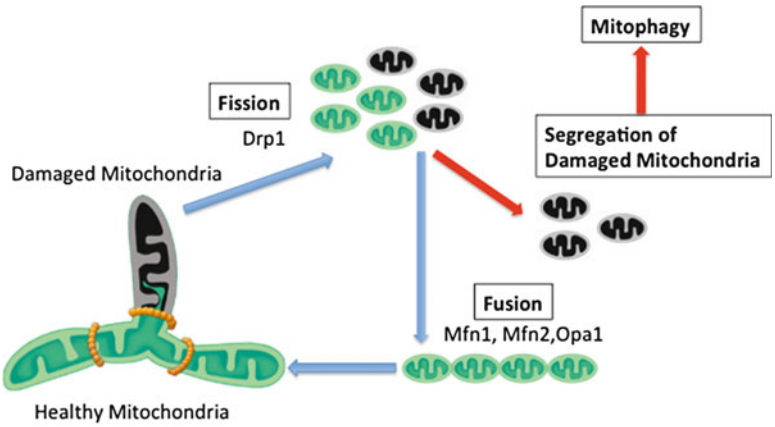

Fig. 6.1 *Mitochondrial dynamics*
Mitochondria maintain their morphology by continuous fusion and fission cycles

of Opa1 initiates a breakdown of the cristae concomitant with cytochrome c release and induction of apoptosis [13, 19, 20].

For the fission of mitochondria, dynamin-related protein1 (Drp1) translocates to the OMM from the cytosol in order to form the contractile ring, which ultimately splits the mitochondria into two fragments (Fig. 6.1). It seems that Drp1-dependent mitochondrial fragmentation occurs early in the apoptotic pathway, prior to or simultaneously with outer membrane permeabilization and before the effector caspase activation [21, 22]. The small ubiquitin-like modifier (SUMO) protein also affects Drp1 activity; overexpression of SUMO1 stabilizes Drp1 in a Bax-/Bak-dependent manner on the mitochondrial membrane and induces mitochondrial fission, suggesting that SUMOylation is a step in the regulation of Drp1 during early apoptosis progression [23].

Abnormal mitochondrial dynamics frequently cause neuronal synaptic loss and cell death in some human neurological diseases and also have been found to be related to pathological conditions associated with oxidative stress. In addition, the lack of mitochondrial fusion leads to a defect in oxidative phosphorylation, because the cell cannot exchange the contents of damaged mitochondria for that of healthy mitochondria. Thus, they are unable to repair or maintain the mtDNA-encoded proteins required for electron transport, resulting in respiration defects [24].

6.3 Mitochondrial Quality Control

Mitochondrial fission requires for the maintenance of healthy state of the organelles. After the mitochondrial fission, damaged mitochondria are eliminated by autophagy, also referred to as mitophagy (Fig. 6.1) [25, 26]. Mitochondrial removal occurs due to decreased membrane potential of the IMM and reduced Opa1 levels.

Two gene products mutated in familial Parkinson's disease, namely, PTEN-induced mitochondrial protein kinase 1 (PINK1) and the cytoplasmic ubiquitin E3 ligase Parkin involved in the molecular mechanisms of mitophagy [27–29]. In healthy mitochondria, the protein level of PINK1 is constitutively suppressed, and the protease presenilin-associated rhomboid-like protein PARL causes degradation of PINK1. When mitochondria lose their inner membrane potential and become uncoupled, PINK1 accumulates on the OMM and subsequently labels the damaged mitochondria. As a consequence, PINK1 recruits the E3 ligase Parkin from the cytosol; once there, Parkin ubiquitinates protein machinery involved in mitochondrial dynamics, such as Mfn1 and Mfn2, and degrades them with proteasome by the action of AAA^+ ATPase p97, thereby preventing fusion and promoting mitophagy [30–32].

6.4 Mitochondrial Ca^{2+} Homeostasis and Ischemic Reperfusion Injury

Maintenance and regulation of the IMM permeability are crucial to sustain ATP produced by oxidative phosphorylation of mitochondria. An increase in IMM permeability is defined as the mitochondrial permeability transition pore (mPTP), a term first introduced by Haworth and Hunter in the 1970s [33]. They defined mPTP as a state in which ions and solutes with molecular masses of up to about 1.5 kDa enter mitochondria, leading to matrix swelling. Involvement of the mPTP in cell death was hypothesized 27 years ago [34]; early support of this was obtained in hepatocytes subjected to oxidative stress and the accumulation of reactive oxygen species (ROS) concomitant with Ca^{2+}overload and concentration in the matrix [35, 36], anoxia [37], or treatment with ATP [38] in cardiomyocytes [39] and isolated hearts [40] exposed to ischemia followed by reperfusion. Presently, it is a well-known fact that the opening of the mPTP uncouples mitochondria and is involved in determining the pathways that are activated for apoptosis and necrosis. mPTP can be inhibited by submicromolar concentrations of cyclosporin A (CsA) [41] by binding to cyclophilin D (CypD) in the mitochondrial matrix. CypD belongs to the cyclophilin protein family known as peptidyl-prolyl cis-trans isomerases (PPIases) that catalyze the cis-trans isomerization of peptidyl-prolyl bonds and exhibit chaperone activity for protein folding. There are seven major cyclophilin isoforms in various subcellular compartments, the cytoplasm (CypD, CypNK, Cyp40), endoplasmic reticulum (ER) (CypB, CyP-C), nucleus (CypE), and mitochondria (CypD) [42]. Uchino and coworkers demonstrated that mitochondria in the spinal cord exhibit lower calcium retention capacity without any difference in the susceptibility to CypD [43]. The molecular mechanisms of this phenomenon are still unknown, but this finding provides a clue toward understanding the physiological mechanisms involved in tissue-specific differences in mitochondrial Ca^{2+} homeostasis and mPTP.

The CypD is specifically associated with mPTP opening that is involved in the cell death during ischemia-reperfusion in the brain and heart. In ischemia, the cells are unable to sustain a negative cell membrane potential leading to the opening of voltage-gated Ca^{2+} channels followed by the release of excitatory amino acids to the extracellular space. This event leads to a massive entry of Ca^{2+} into the cells and results in an influx of cytosolic free Ca^{2+} into the mitochondrial matrix by Ca^{2+} channels and exchangers located on the IMM.

Interestingly, the ER also is involved in this event; exposure to toxic levels of excitatory neurotransmitters that enter the cell causes the release of Ca^{2+} from the ER via both ryanodine receptors and inositol triphosphate receptors (IP3Rs). This released Ca^{2+} enters the mitochondria, and accelerated Ca^{2+} overload of mitochondria leads to the activation of apoptosis. These contact sites through which the ER communicates with the mitochondria are denoted as the mitochondria-associated ER membrane (MAM) [44]; other Ca^{2+}-binding ER chaperones such as calnexin, calreticulin, and ERp44 localize in the MAM [45–47]. Mfn2 is also enriched in the MAM interacting with Mfn1 as well as itself on the mitochondria to form interorganellar bridges that allow communication via Ca^{2+} signaling [48, 49].

Recently, Giorgio et al. described that mPTP is identical to the F_0F_1ATP synthase dimer that exhibits the same properties as the mitochondrial megachannel (MMC) [50], which is inhibited by CsA [51] and possesses all the key regulatory features of mPTP [52]. Alavian et al. used culture cell experiments to describe that the c-subunit ring of F_0F_1ATP synthase is a candidate for the mPTP [53].

6.5 Mitochondria and Anesthetics

It has been reported that several anesthetics interact with mitochondria. Although there is convincing evidence that anesthetics affect mitochondrial structure, oxidative phosphorylation, and ATP generation, the underlying mechanism on how anesthetics affect mitochondria has not been elucidated [54, 55]. Remarkably, volatile anesthetic drugs have been recently shown to enhance the generation of free radicals, especially in cardiac cells, possibly due to mild uncoupling of the mitochondrial electron transport chain. Propofol has a structure similar to phenol-based derivatives such as the endogenous antioxidant vitamin E, and it has scavenging activity against reactive oxygen spices (ROS) and nitric oxide. Propofol has been shown to be protective in several organs, including the brain, liver, and heart in experimental models of injury suggesting that propofol-induced cardioprotection may partly result from a direct effect on myocardial calcium influx or from inhibition of mPTP [56, 57]. This effect may not be independent of the radical scavenging effect; however, free radicals are believed to modulate mPTP [58]. Although propofol protects cells from ischemia-reperfusion injury when administered before the initiation of ischemia [59], its administration alone may be ineffective [60]. Recently, Yue et al. reported that propofol maintains neuronal

mtDNA and, thus, protects neuronal cells from the cerebral damage due to ischemia-reperfusion injury in rat [61].

6.6 Conclusion and Perspectives

A growing body of evidence indicates that mitochondria are likely one of the targets of anesthetics and thought to have an important role in the anesthetic-induced neuronal cell death. However, the underlying molecular mechanisms of such phenomenon have not been elucidated. Mitochondria continuously and dynamically change their morphology via the four GTPase-dependent fusion and fission. Such mitochondrial dynamics affect various biological processes, including bioenergetics, cellular metabolism, mitochondrial maintenance, synaptic integrity, and neuronal cell death. Oxidative stress and breakdown of Ca^{2+} homeostasis lead to mPTP formation, which is identified as F_0F_1ATP synthetase. Although the molecular targets of anesthetics on/in mitochondria are still unknown, the identification and understanding of these targets and mechanisms are important toward the establishment of appropriate therapeutic approaches in the future.

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Chapter 7
Stem Cells: How We Could Restore the Brain Function After Ischemic Damage

Zaal Kokaia and Vladimer Darasalia

Abstract Ischemic stroke is caused by occlusion of a cerebral artery, which gives rise to focal ischemia with irreversible injury in a core region and partially reversible damage in the surrounding penumbra zone. Stroke leads to neural death and consequently neurological impairments. Therapeutic intervention of stroke comprises thrombolysis and thrombectomy by chemical or surgical means, respectively. If done in time, these treatments may improve stroke outcome. However, many stroke patients cannot get sufficient degree of such treatment due to incompatibility or delay with admission to the clinic and suffer chronic neurological impairments. This has raised the need to develop effective treatments to improve poststroke recovery. Induced brain plasticity and cell replacement using neural stem cells are two promising strategies for therapy for stroke. This review will discuss the potential of such therapy as well as the factors that need to be taken into account for successful development of new therapy. Neural stem cells are multipotent with the capacity to self-renew and generate mature cells of the nervous system. They can be obtained from embryonic, fetal, or adult central nervous system, as well as through genetic reprogramming of somatic cells. Neural stem cell transplantation has proved to be effective in rodent studies. However, to translate these results into the clinical application, the variety of intrinsic and external factors must be carefully evaluated. This includes accurate stroke outcome predictions, choice of neural stem cell sources and evaluation of the risk of malignant transformation, selection of cell implantation paradigms and criteria for suitable patients.

Keywords Stroke • Stem cells • Transplantation • Neurogenesis • Regeneration

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7.1 Introduction

Stroke is the leading cause of disability in adults. Fifteen million people suffer stroke worldwide each year. Of these, five million die and another five million are permanently disabled. Ischemic stroke is the most common form of stroke. It usually results from the thrombotic occlusion of the major blood vessel in the brain and leads to neural death. The location and the size of the damaged brain region and consequent neurological impairments are contingent upon the anatomical location of the occluded blood vessel and the duration of occlusion.

7.2 Current Treatments of Ischemic Stroke

Established methods of acute therapeutic intervention comprise thrombolysis and thrombectomy [1, 2]. The end goal of both treatments is the removal of thrombotic clot from the occluded blood vessel using either chemical or surgical methods, respectively. The effectiveness of both strategies depends on how quickly patients are hospitalized from the onset of symptoms [3, 4]. Because of such dependency on timely intervention and rapid neuronal death, many stroke patients suffer chronic neurological impairments, and the physical therapy alone is insufficient for good recovery [5–7].

7.3 Future Treatment of Stroke-Induced Neurological Deficits

The recovery from stroke-induced neurological impairments in long term can be achieved by two means: modulation of plasticity and replacement of stroke-affected or killed cells [8–10].

7.3.1 Brain Plasticity

Plasticity entails the remodeling or rearrangement of synaptic connections between remaining brain cells in order to reconstitute damaged neural circuits and consequently restore the neurological function. The capacity of the brain to do so largely depends on the size of the damage, the complexity of damaged circuits, and patient's age. In most cases, e.g., with small focal cortical stroke, the brain plasticity together with the physical therapy is quite effective for restoring impaired functions [11, 12]. However, larger stroke may lead to death of many neurons and substantial damage to complex brain circuits. This will limit the capacity and effectiveness of

synaptic rearrangement due to reduced physical availability of neurons for establishing new connections [12, 13].

7.3.2 Stem Cells

Experimental animal studies have demonstrated that systemic or intracerebral delivery of stem cells may become a new therapeutic strategy in stroke. Transplantation of stem cells of various origins and stages of development has been shown to lead to improvement in experimental models of stroke through several mechanisms including neuronal replacement, modulation of inflammation, neuroprotection, and stimulation of angiogenesis [10].

Many clinical trials with stem cell delivery in stroke patients are in progress with the goal of functional improvements through mechanisms other than neuronal replacement. These approaches may provide therapeutic benefit, but the ultimate long-term goal for stem cell research in stroke should probably be to generate specific neurons for replacement in order to reconstruct injured neural circuitry. Therefore, in the present chapter, we will consider the prospects of development of cell replacement strategies in stroke patients based on transplantation of neural stem/progenitor cells (NSPCs).

7.3.2.1 Neural Stem/Progenitor Cells

The discovery of neural stem cells and their ability to differentiate into neurons and integrate into the existing brain circuits has become one of the bases for the development of cell replacement strategies for stroke patients. Effective replacement of even a small portion of lost neurons through transplantation would increase the effectiveness of brain plasticity by providing the extra opportunities to establish new synaptic connections [14, 15].

Neural stem cells are multipotent with the capacity to self-renew and generate mature cells that comprise the nervous system. In the culture system as well as in the neurogenic zones of the adult brain, neural stem cells are always present together with their progeny and often it is impossible to separate them. Therefore, in most of the cases, we are dealing with not pure neural stem cells, but NSPCs. Over the past decade, the NSPCs have been extensively studied for their capacity to mitigate stroke-induced neurological impairments. The main advantage of NSPCs over pluripotent embryonic stem cells (ESCs) is their “commitment” toward neuronal phenotype. Such “commitment” toward a particular phenotype reduces the risks of malignant growth after transplantation, and the probability of malignant growth seemingly has negative correlation with the state of stem cell differentiation toward maturity [16].

7.3.2.2 Sources of Neural Stem Cells

Neural stem cells can be obtained from fetal or adult central nervous system (CNS) or can be derived from ESCs and induced pluripotent stem cells (iPSCs).

In addition to the ethical controversy, the fetal NSPCs are limited by their availability. These cells are usually obtained from aborted, dead human fetuses, and if used without in vitro expansion, it is difficult to predict when and how many will be available at any given time. This complicates the possibility to plan clinical application with primary tissue. Additionally, the material from one fetus is unlikely to be sufficient for achieving desired clinical outcome in patients with stroke. Therefore, several preparations will be needed, which in turn will further complicate planning of clinical application.

Adult NSPCs can be isolated from neurogenic niches of adult CNS – subventricular zone (SVZ) or subgranular zone of hippocampal dentate gyrus [17]. In this case, the source availability is also the main limiting factor, which is further complicated by the difficulty to isolate and successfully maintain these cells in vitro [18–20]. Moreover, it is unclear what would constitute the appropriate donor. It is highly inconceivable that it will be possible to use patient's own NSPCs, and most likely additional sources will be required. The latter also complicates the potential ethical and tissue compatibility issues.

Based on availability, expansion capacity, and practicalities for future clinical application, ESCs and iPSCs are the most likely sources of NSPCs for stroke therapy. Both of these types of stem cell are pluripotent and have the capacity to be expanded and maintained in vitro for an extended period of time.

Embryonic stem cells are derived from the inner cell mass of a blastocyst. The common source is the leftover blastocysts from in vitro fertilization procedures. Isolation of ESCs from the blastocyst results in destruction of fertilized embryo, which raises ethical issues. Based on ethical concerns, many countries have banned the fertilization of human eggs for the sole purpose of obtaining ESCs [21].

Induced pluripotent stem cells are artificially derived from adult somatic cells most commonly from skin cells [22, 23]. After isolation, the somatic cells are manipulated to express specific gene characteristic to stem cells. Induced pluripotent stem cells are similar to ESCs in many aspects; they can form embryonic bodies and be differentiated in various cell types. The main advantage of iPSCs for clinical application is the possibility to use patient's own cells as the source [24, 25]. This in turn eliminates the donor/recipient compatibility issues. Additionally, iPSCs have also been generated without using viral vectors [26], which reduces the need for introduction of foreign genetic material into the cells' genome and therefore potentially reduces the risk for functional or malignant genetic alterations.

For both cell types, ESCs and iPSCs, the main drawback is the higher risk of malignant transformation due to their pluripotency. However, the risk for such transformation can be substantially limited if pluripotent cells are fated toward multipotent, tissue-specific stem cells, e.g., NSPCs [16].

7.3.3 *Stem Cell-Based Therapy for Stroke: How to Make It Work?*

Regardless of the stem cell source, the effectiveness of cell replacement therapy for stroke will most likely depend on the number of factors unrelated to the origin of stem cells. The tissue damage after stroke can be classified under two categories – ischemic core and the penumbra [27, 28]. The core area is irreversibly damaged, while the penumbra region can be salvaged by the timely intervention and is most responsive to pharmacological intervention [29, 30]. Stroke induces severe inflammation [31] and reactive gliosis [32], which contribute to progression of penumbra (reversible damage) into the core (irreversible damage) and ultimately form a glial scar that can potentially hinder regeneration [33].

When considering NSPC transplantation as a therapy for stroke, there are three factors, which must be taken into consideration: timing of transplantation, placement of the graft in relation to the damage, and the number of grafted NSPCs.

7.3.3.1 Timing of Transplantation

The inflammation after stroke is a dynamic process, which plays an important role in the formation of microenvironment of stroke-damaged tissue. The activity of immune cells might have important impact on the properties of grafted NSPCs [34]. Most likely, in acute poststroke phase, which constitutes from few hours to few days, the inflammatory process exacerbates the ischemic damage similar to spinal cord injury [35]. At later time points, this process is gradually replaced by reparatory and regenerative actions of activated microglia and infiltrated monocyte-derived macrophages [36, 37]. Therefore, NSPC transplantation within few days of stroke would pose a serious challenge to graft survival. Moreover, permanent stroke-induced neurological impairments cannot be accurately predicted at this early stage, since many stroke patients recover spontaneously or through physical therapy within 2–6 months [38, 39]. Consequently, the need of cell replacement therapy cannot be determined at such early stage. However, if further development of stroke evaluation and outcome-predicting methods in the future can project the expected outcome with higher level of accuracy, the timing of therapy prescription could be moved ever closer to the onset of stroke. It must be noted though that regardless of how fast the outcome is predicted, if patients' own iPSCs are used, the time to obtain sufficient amount of NSPCs suitable for transplantation will be considerable. Therefore, the most practical approach for the clinical use of cell replacement therapy is first to determine the need of such therapy and obtain sufficient information for analyses and prediction of the outcome, estimate the magnitude of needed therapy (amount of lost cells to be replaced), and then prepare the NSPCs accordingly. Considering these factors, the likely candidate for transplantation therapy would be a patient in a subacute or chronic phase of stroke, after few weeks or even months after ischemic attack. Preclinical cell therapy studies for

stroke may give us the accurate answer regarding the optimal implantation time for different cell sources [40], but during the clinical application, the decisive factor will still be the time required for outcome prediction and preparation of cells for transplantation.

7.3.3.2 Placement of the Graft

Another important factor for successful cell replacement therapy for stroke is the placement of the graft, which will determine not only its survival but also the potential to integrate within the host brain and reconstruct damaged neuronal circuits. Considering that graft survival will depend on nutrient availability and milder inflammatory state, the ischemic core is an unlikely candidate for successful intracerebral transplantation therapy. The intact part of the brain adjacent to the insult site would also be an unlikely choice, as the transplantation procedure will eventually cause some damage to the tissue, which in turn will induce inflammation and exacerbate the damage. The ischemic penumbra, on the other hand, is characterized by revascularization and high plasticity [41, 42]. The surviving neurons and glia are actively involved in synaptic remodeling and tissue repair [43, 44]. Additionally, a number of growth factors and cytokines are upregulated within the penumbra region that could potentially aid the graft survival and integration [45, 46].

7.3.3.3 Optimal Number of Grafted Neural Stem Cells

The number of grafted NSPCs will also play an important role in determining the efficacy of the cell replacement therapy [47]. A significant proportion of grafted NSPCs will be likely damaged and killed during the procedure, and it is important to reliably estimate the final number for surviving cells. The number of implanted cells should be calculated based on the nutritional capacity of implantation region. High number of grafted cells may result in a deficit of available nutrients and oxygen for the graft survival. This may lead to severe cell loss within the graft and induce strong immune reaction that will further reduce the chances of successful outcome. On the other hand, if a small amount of NSPCs is grafted, the resulted cell replacement may not be sufficient to have a meaningful impact on neurological recovery. Continued initial proliferation of grafted cells should be also taken into consideration [47].

To date, the development of cell transplantation strategies using iPSCs is still in its initial stage, where most efforts are made toward “proof of concept” approaches to validate the potential of these cells as a source for cell replacement therapy. However, in order to bring them closer to clinical application, the transplantation paradigms (timing, number, implantation site and the creation of permissive microenvironment for cell survival, differentiation, and integration) need to be first developed and optimized specifically for these cells.

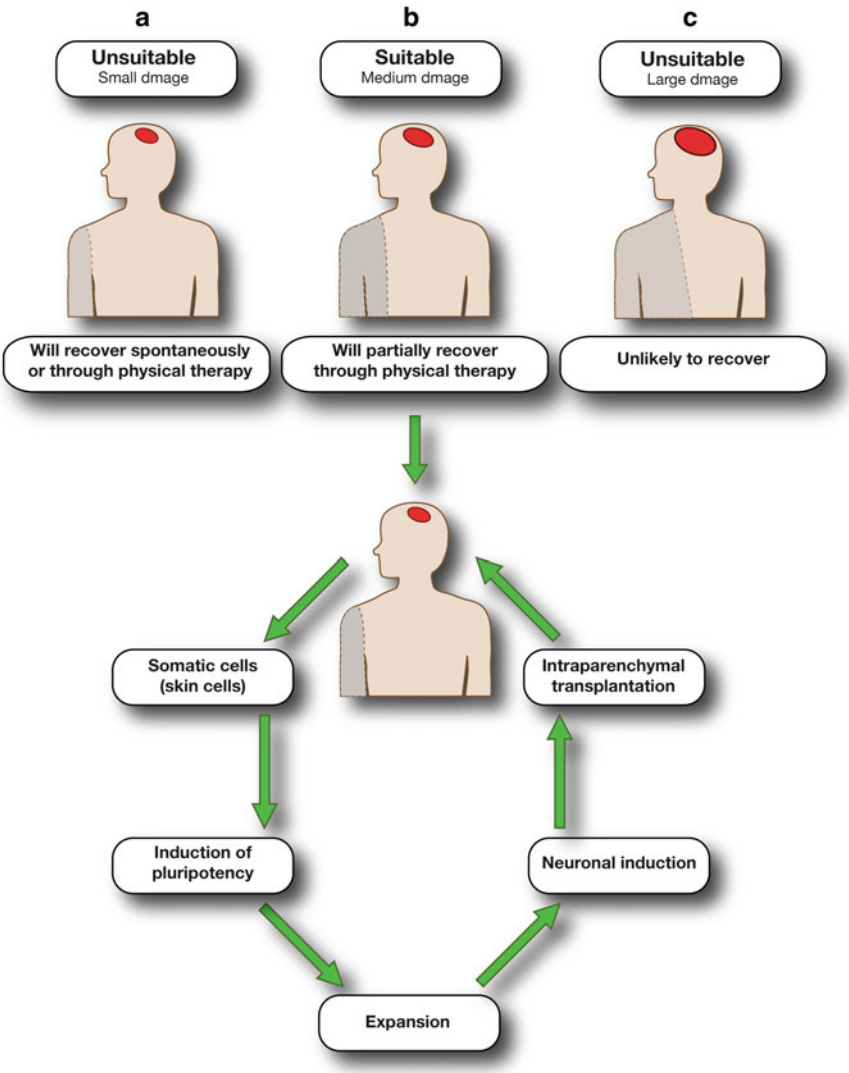

Fig. 7.1 *Induced pluripotent stem (iPS) cells for the treatment of stroke:* The initial step for successful cell replacement therapy is careful patient selection. Three types of patients are presented on the illustration. (**a**) A patient with a small damage, who will likely recover spontaneously or through physical therapy; no additional intervention is required. (**b**) A patient with a medium-sized damage, who will recover to some degree, but still exhibit significant neurological impairments. This patient will likely benefit the most from the cell replacement therapy. (**c**) A patient with a large brain damage and with severe neurological impairment and high risk of mortality or stroke recurrence. This patient will unlikely benefit from cell replacement therapy due to extensive damage to many neural circuits. After the most suitable patient is selected, the somatic cells (skin cells) are extracted and the pluripotency induced, which is followed by in vitro expansion to generate sufficient number of stem cells. The iPS cells are then pre-differentiated to NSC phenotype (neural induction) and grafted into the stroke-damaged brain

7.3.3.4 Patient Selection

Correct patient selection could be the single most important factor in obtaining the desirable outcome from cell replacement therapy. Patients should be selected based on the location and the size of ischemic damage, the level of neurological impairments, age, overall health status, and an accurate prediction of the magnitude of neurological impairments. Such selection should be based on prior preclinical and clinical studies. This should allow predicting the potential outcome within the reasonable margin of certainty for individual cases.

7.4 Conclusions

All factors discussed above must be thoroughly investigated in preclinical studies before cell replacement therapy for stroke is applied to the clinic. The concept of NSPC therapy for stroke is illustrated in Fig. 7.1. The NSPC-based approach to stroke therapy has generated great enthusiasm within the scientific and medical circles. However, the ultimate success of such therapy is dependent on the choices of NSPC source, thorough assessment and evaluation of key factors (timing, graft placement, NSPC amount), and the choice of suitable patients.

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Part III
General Consideration: Neuropharmacology for Neuroanesthesia

Chapter 8
Volatile Anesthetics and Neuroprotection

Yasunori Mishima and Kazuo Ushijima

Abstract Since 1963, many studies have demonstrated the protective and preconditioning effects of volatile anesthetics on cerebral ischemia, and it has also been suggested that they can delay neuronal cell death, especially in the developing brain. Various molecular mechanisms involving the numerous pathways of the neuronal cell death cascade have been reported to be involved in these neuroprotective effects. Although volatile anesthetics allow neurological function to be maintained after mild insult, neuronal cell death cannot be completely prevented in the convalescent stage in moderate-to-severe cases. The neuroprotective effects of volatile anesthetics are expected to contribute to improving treatment strategies by delaying neuronal cell death and extending the therapeutic window.

Keywords Volatile anesthetics • Neuroprotection • Preconditioning

8.1 Introduction

Since the neuroprotective effects of cyclopropane were first reported [1], many studies have suggested that other volatile anesthetics also have neuroprotective effects. At the time of the abovementioned study, the suppression of cerebral metabolism was considered to be the main factor responsible for these effects, while now it is believed that other protective factors are involved [2, 3]. In addition to the neuroprotective effects of volatile anesthetics, their preconditioning and postconditioning effects during ischemia have also been clarified.

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8.2 Neuroprotective Impact During Ischemia

Research on the neuroprotective effects of volatile anesthetics has mainly involved animal experiments examining excitotoxicity using 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid (AMPA) and N-methyl-D-aspartate (NMDA), ischemia, or oxygen–glucose deprivation. Most experiments have demonstrated that volatile anesthetics have protective effects against short-term ischemia. However, they also delay neuronal cell death during long-term ischemia. Therefore, it is considered that volatile anesthetic-mediated neuroprotection can be sustained if the ischemic insult is mild, although volatile anesthetics do not exhibit long-term protective effects in cases involving moderate-to-severe insults [4]. In addition, sex and the dose of volatile anesthetic have also been reported to affect prognosis. More studies have examined the effects of isoflurane than have investigated the effects of sevoflurane or desflurane; however, nearly identical effects have been reported for all of these anesthetics. While only a small number of clinical studies have been performed, decreased cerebral blood flow leading to encephalographic changes is significantly less common in patients anesthetized with isoflurane than with halothane [5]. Furthermore, desflurane produces greater oxygen saturation in ischemic regions than thiopental [6].

8.3 Preconditioning Effects

All current methods of achieving ischemic tolerance are invasive and difficult to apply in a clinical setting. Therefore, the preconditioning effects of volatile anesthetics have attracted attention due to their relative safety. Preconditioning with volatile anesthetics has been reported to be effective against both focal and global brain ischemia, as well as in spinal ischemia models [7–11]. While mitochondrial adenosine triphosphate (ATP)-dependent potassium (mitoK_{ATP}) channels were initially considered to be responsible for the preconditioning effects of volatile anesthetics, it is now considered that these effects are mainly mediated by mitochondrial permeability transition pores (mPTPs). Most studies that have verified the preconditioning effects of volatile anesthetics have involved isoflurane [7, 8, 12–14], although sevoflurane [15–19] and desflurane [20–23] have been demonstrated to have similar effects.

8.4 Postconditioning Effects

Some studies have shown that volatile anesthetic postconditioning reduces the extent of ischemia-induced neuronal injuries [24, 25]. Mitochondrial structures, such as mitoK_{ATP} channels and mPTPs, and functions are likely to be involved in

the neuroprotective mechanisms of volatile anesthetics. However, at present no studies have obtained conclusive evidence confirming the postconditioning effects of volatile anesthetics.

8.5 Neuroprotective Mechanisms

The suppression of cerebral metabolism was initially considered to be the main mechanism responsible for the neuroprotective effects of volatile anesthetics. However, once it was determined that volatile anesthetics activate gamma-aminobutyric acid (GABA) receptors and the two-pore domain potassium channel TREK-1, but suppress glutamate receptors and voltage-dependent K^+, Na^+, and Ca^{2+} channels, mainstream opinion began to support the idea that the general anesthesia and neuroprotective effects of volatile anesthetics were caused by interactions between these receptors/channels (Fig. 8.1).

8.5.1 Mechanisms of Neuroprotection and Preconditioning

8.5.1.1 Modulation of Cerebral Metabolic Rate

Volatile anesthetics reduce energy consumption in response to ischemia-induced reductions in the supply of energy, leading to a markedly reduced cerebral metabolic rate (CMR) and protection of the brain [26]. Animal experiments have shown that isoflurane and sevoflurane maintain high levels of ATP and phosphocreatine and reduce lactic acid accumulation during ischemia [27]. Furthermore, volatile anesthetics induce strong concentration-dependent suppression of electroencephalographic (EEG) activity, which leads to a decrease in the CMR. However, once the concentration at which EEG activity plateaus has been exceeded, the CMR does not decrease further, even if the anesthetic concentration is increased [28]. In addition, the range of the CMR is considered to be fixed, regardless of the type of anesthetic used. Finally, the relationships between the decrease in the CMR and the prevention of histological damage or improvements in neurological function remain unclear.

8.5.1.2 Inhibition of Glutamate Release

The preconditioning and neuroprotection induced by volatile anesthetics are considered to involve the modulation of glutamate excitotoxicity [4, 29]. By suppressing the temporary depolarization that accompanies ischemia, volatile anesthetics exert protective effects during ischemia by inhibiting glutamate release, which prevents excessive calcium influx into neurons [17, 30–32]. However, it is

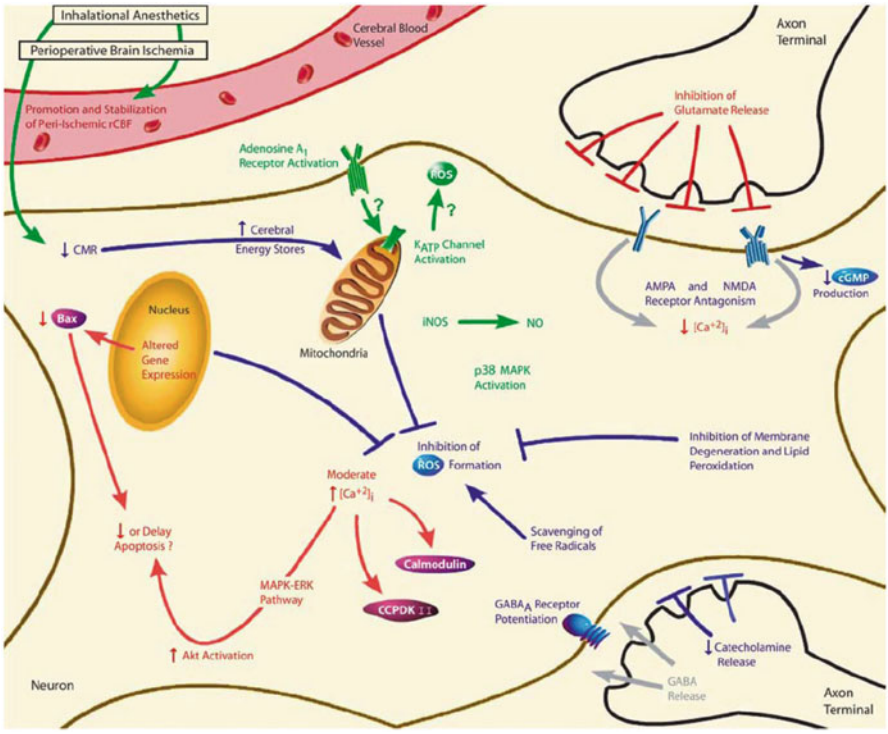

Fig. 8.1 Neuroprotective effects of volatile anesthetics are indicated by *blue lines* and preconditioning effects by *green lines*. Mechanisms that might account for neuroprotective or preconditioning effects of volatile anesthetics are indicated by *red lines*. Several of these mechanisms have been implicated in both preconditioning and pretreatment effects of volatile agents on ischemic brain injuries (Reprinted with permission from Journal of Cerebral Blood Flow & Metabolism)

unlikely that the inhibition of glutamate release alone improves the prognosis of brain ischemia [33].

8.5.1.3 Antagonization of NMDA and AMPA Receptors

The activation of postsynaptic receptors such as those for NMDA and AMPA can induce neuronal cell damage. Volatile anesthetics, particularly isoflurane, exhibit neuroprotective effects by suppressing these receptors [34–40].

8.5.1.4 Effects on Intracellular Calcium and Calcium-Dependent Processes

The administration of volatile anesthetics before, during, and after ischemia suppresses NMDA receptor-mediated Ca^{2+} influx and reduces ischemia-induced cell death [41–43]. It also prevents intracellular Ca^{2+} overloading in ischemic/hypoxic neurons and maintains the $[Ca^{2+}]_i$ within a survivable range [44]. These effects on $[Ca^{2+}]_i$ also suppress the opening of mPTPs and activate the antiapoptotic factor Akt and mitogen-activated protein kinase–extracellular regulated kinase pathway, thereby inhibiting apoptosis.

8.5.1.5 Antioxidant Mechanisms

Suppression of the accumulation of ischemia-induced extracellular glutamate together with excessive overloading with Ca^{2+} downregulates the production of free radicals and peroxidation of lipids that accompanies reperfusion and induces free radical scavenging [15, 45, 46]. Strong evidence indicates that isoflurane increases the production of heme oxygenase-1, which plays a central role in the endogenous antioxidative mechanism; thus, the antioxidant effects of volatile anesthetics appear promising [47]. Moreover, volatile anesthetics may also reduce oxidative stress-induced cell injury through other, more indirect mechanisms [48].

8.5.2 Mechanisms of Neuroprotection

8.5.2.1 GABA Receptors

One previous study demonstrated that the neuroprotective effects of isoflurane were blocked by administration of a $GABA_A$ receptor antagonist [49]. As the neuroprotection afforded by isoflurane cannot be reversed by $GABA_B$ receptor antagonists [49, 50], it appears that isoflurane has affinity for $GABA_A$ and that $GABA_A$ activation plays an important role in neuroprotection.

8.5.2.2 Two-Pore-Domain Potassium Channels

Among two-pore-domain potassium (K_2P) channels, TREK-1 is crucial because it is activated by polyunsaturated fatty acids (PUFAs), lysophospholipids (LPLs), and volatile anesthetics such as isoflurane, sevoflurane, desflurane, and xenon. TREK-1 is expressed in both pre- and postsynaptic neurons. The activation of TREK-1 in response to volatile anesthetics, PUFAs, or LPLs leads to the closure of voltage-dependent calcium channels. The resultant decrease in the $[Ca^{2+}]_i$ suppresses the release of glutamate. At the postsynaptic level, TREK-1-induced hyperpolarization

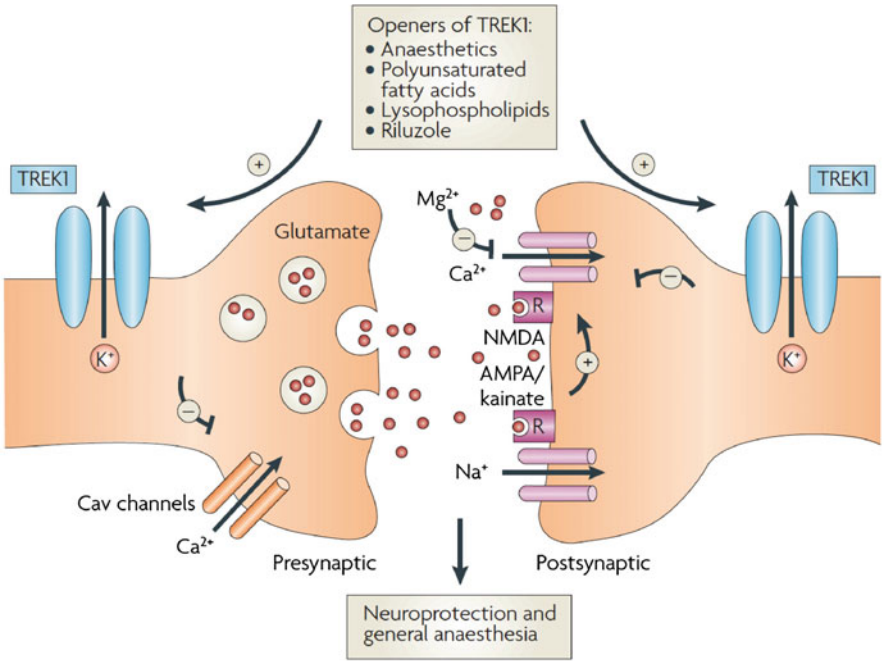

Fig. 8.2 TREK-1 is expressed in both pre- and postsynaptic neurons. Activation of TREK-1 decreases intracellular calcium levels and suppresses glutamate release. At postsynaptic level, TREK-1 induces hyperpolarization, which eventually reduces neurotransmission and glutamate toxicity (Reprinted with permission from Nature Reviews Neuroscience)

increases the voltage-dependent magnesium blockade of NMDA receptors and reduces neurotransmission and glutamate toxicity [51].

TREK-1 activation inhibits the neurological impairment caused by ischemia or epilepsy [52–54], and these neuroprotective effects disappear in TREK-1 null mice [53], suggesting that the neuroprotective effects of volatile anesthetics might also be mediated by TREK-1 (Fig. 8.2).

8.5.2.3 Catecholamine Release

Both cerebral and circulating catecholamines such as dopamine have been implicated in the exacerbation of ischemic brain injuries [55, 56], and some studies have reported that volatile anesthetics contribute to neuroprotection by suppressing catecholamine release [57–60].

8.5.3 Mechanisms of Preconditioning Effects

8.5.3.1 Nitric Oxide Production

Volatile anesthetics increase the production of inducible nitric oxide synthase (iNOS), which plays an important role in preconditioning [7, 61, 62]. iNOS-induced NO production also increases the expression of the antiapoptotic protein Bcl-2. Pretreatment with volatile anesthetics promotes prolonged iNOS-dependent neuroprotection, suggesting that iNOS is involved in the preconditioning effects of these drugs.

8.5.3.2 Adenosine A1 Receptor

The activation of adenosine A1 receptors is involved in the preconditioning mechanism of isoflurane [13]. It has been suggested that ischemic tolerance is acquired through the activation of K_{ATP} channels in the ischemic myocardium [63], but this has not been demonstrated in the ischemic brain.

8.5.4 Mitochondrial Functions

It has been suggested that mitoK_{ATP} and mPTPs play important roles in ischemic preconditioning, and mitoK_{ATP} blockers have been found to attenuate the preconditioning effects of isoflurane and sevoflurane in brain ischemia. The opening of mPTPs by calcium induces mitochondrial apoptosis. However, preconditioning with volatile anesthetics suppresses the opening of mPTPs.

8.6 Future Possibilities and Issues Associated with Neuroprotection by Volatile Anesthetics

The extent of the neuroprotective effects of volatile anesthetics has not been clarified in a clinical setting. Although the neuroprotective effects of volatile anesthetics have been confirmed in many animal studies, it is considered that these effects are generally not long-lasting [64]. However, as the neuroprotective effects of volatile anesthetics on cerebral ischemia can be prolonged by employing a combination of isoflurane and caspase inhibition [65], it might be possible to use volatile anesthetics to delay cell apoptosis. Thus, volatile anesthetics offer direct neuroprotective effects and could be used to improve current treatment strategies by extending the therapeutic window.

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Chapter 9
Intravenous Anesthetics and Neuroprotection

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Abstract Some intravenous anesthetics have been vigorously investigated as logical candidates for neuroprotectants. Generally, such anesthetics can suppress excitotoxicity and depolarization during ischemia and the early period of reperfusion, effects which contribute to the neuroprotective efficacy of these drugs. Neuronal death, however, is believed to be an ongoing process which continues for a long time after any initial ischemic injury has occurred. Recently, the neuroprotective efficacy of anesthetics has been called into doubt due to this process coupled with the complexity of postischemic events. In this chapter, the neuroprotective properties of intravenous anesthetics are reviewed, focusing on barbiturates, benzodiazepines, dexmedetomidine, and propofol.

Keywords Barbiturates • Benzodiazepines • Dexmedetomidine • Propofol

9.1 Introduction

Cerebral ischemia can occur in a variety of situations, and the complications can be devastating. Therefore, the protection and salvage of cerebral neuronal function is a priority once cerebral ischemic insult has occurred. Cerebral ischemia is a condition in which there is insufficient blood flow to the brain to meet metabolic demand. Anesthetics generally have the ability to suppress the cerebral metabolic rate, facilitating preservation of the tissue energy balance during transient ischemia. This suggests that anesthetics might reduce ischemic injury, which is partially true. Indeed, most anesthetics not only suppress the cerebral metabolic rate but also antagonize glutamate-mediated excitotoxicity, which plays a major role in the initiation of neuronal injury, and enhance inhibitory synaptic transmission, which is mediated by the potentiation of gamma-aminobutyric acid (GABA)-ergic

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activity. Some anesthetics have been vigorously investigated as logical candidates for neuroprotectants due to their favorable properties in this respect. Most of them appear to be neuroprotective in experimentally induced cerebral ischemia if present during ischemic insult. Most patients, however, do not receive medical care until hours after the ischemic insult has occurred, making the clinical application of such agents difficult. Another concern with anesthetic-induced neuroprotection is the apparent lack of a long-term effect [1]. Much recent investigation has shown that postischemic neuronal death is a dynamic process, in which neurons continue to die over a long period of time after the initial ischemic injury has occurred [2, 3]. A number of mechanisms contribute to postischemic neuronal injury. During ischemia and the early period of reperfusion, glutamate-mediated excitotoxicity and ischemic neuronal depolarization lead to rapid neuronal death. Anesthetics can suppress excitotoxicity and ischemic depolarization, resulting in neuroprotection [4–7]. In the later stages of postischemic recovery, however, the development of inflammation within the brain together with neuronal apoptosis leads to delayed neuronal death [8–10]. In general, it is believed that neuronal death is an ongoing process which continues over a long period of time after the initial ischemic injury has occurred, whether that injury is global or focal in nature. In recent decades, the neuroprotective efficacy of anesthetics has been called into doubt due to this ongoing process and the complexity of postischemic events. This raises the question as to whether the concept of anesthetic-induced neuroprotection has become unattractive or old fashioned. However, we believe that it would be too hasty to reach a definitive verdict yet. At the very least, the neuroprotective efficacy of anesthetics reported so far affords us a therapeutic window in which to tackle the problem of cerebral ischemia. In this chapter, the neuroprotective properties of such anesthetics are reviewed, focusing on barbiturates, benzodiazepines, dexmedetomidine, and propofol.

9.2 Barbiturates

In numerous experimental models of focal cerebral ischemia, barbiturates administered before, during, or even after ischemic insult have exhibited significant neuroprotective efficacy [11–13]. Meanwhile, in the early 1970s, the presence of barbiturates during ischemic insult was reported to exert neuroprotective activity in global cerebral ischemia [14]. Moreover, a study using a monkey model of global cerebral ischemia revealed that the administration of large doses of thiopental after ischemia protected the brain [15]. These studies were followed by a series of others reporting contradictive results for this class of agents, however [16–18]. This discrepancy in the results may have been because no postischemic management, including temperature control, was carried out in the earlier studies, resulting in the effect of the drugs being overestimated. In order to resolve this issue, a multicenter, randomized, clinical trial was launched to determine the neuroprotective efficacy of thiopental in comatose survivors of cardiac arrest [19]. This study showed no

beneficial effect of thiopental loading between 10 and 50 min after resuscitation on 1-year neurological outcome compared with in patients receiving standard therapy. Two clinical trials have tested the effect of thiopental in preventing stroke during coronary artery bypass grafting using cardiopulmonary bypass [20, 21]: one reported no beneficial effect, with adverse effects (prolonged extubation and hypotension), while the other noted that thiopental reduced stroke events. This is the only clinical trial suggesting that barbiturates exert a neuroprotective effect. Moreover, the neuroprotective efficacy of barbiturates has only been evaluated after a short recovery period, and their long-term effect in this regard remains to be determined.

9.3 Benzodiazepines

Benzodiazepines have been reported to offer unique neuroprotective effects against cerebral ischemia. Extracellular GABA shows an immediate, short-term increase following ischemia as a self-defense mechanism. Therefore, benzodiazepine-mediated GABA stimulation during this period has no further neuronal protective effect, as the inhibitory neurotransmission system is already saturated with internally accumulated GABA following global cerebral ischemia [22]. On the other hand, it has been reported that administration of benzodiazepines, and especially diazepam, after this period has a profound neuroprotective effect [23–28]. The mechanisms contributing to benzodiazepine-mediated neuroprotection are unclear. In a focal model, postischemic administration of benzodiazepine resulted in a significantly smaller lesion volume than in the controls, except in those who had received diazepam before induction of the lesion [29]. In humans, the early GABAergic activation (EGASIS) trial, a large, multicenter, randomized, clinical trial to evaluate the effect of diazepam as an early neuroprotective drug in acute stroke, showed no apparent neuroprotective efficacy for this drug in acute ischemic stroke patients [30]. It was noted, however, that "diazepam treatment in acute ischemic stroke deserves further attention considering the theoretical underpinnings and experimental evidence." The chronic administration of benzodiazepines can induce tolerance under such conditions in a clinical setting. In animal experiments, it has been reported that oral administration of flurazepam for 4 weeks induced tolerance [31]. Recently, it was reported that chronic administration of benzodiazepine induced tolerance to the drug, which could potentially worsen ischemic neuronal injury and abolish the neuroprotective efficacy of postischemic diazepam [32]. The study population in the EGASIS trial might have included patients with benzodiazepine tolerance. Regarding this issue, it was commented that the neuroprotective effect of postischemic diazepam might have been restored by using higher doses in benzodiazepine-tolerant animals. This suggests that a review of the patient's history in this respect would allow the dose to be adjusted accordingly. This is an important issue which requires clarification, as candidates in whom postischemic intervention would be effective are limited. Like other anesthetics, benzodiazepines appear to

provide limited long-term neuroprotection [28, 33]. However, they still offer promise, as they allow the therapeutic time window after stroke to be expanded by delaying neuronal death.

9.4 Dexmedetomidine

Dexmedetomidine, a highly selective α_2-adrenoreceptor agonist with sedative, analgesic, and sympatholytic properties, is known to provide neuroprotection under ischemic conditions. Cerebral ischemia is clearly associated with an increase in circulating and extracellular brain catecholamine concentrations. Administration of dexmedetomidine in various animal models of ischemia, whether global or focal, inhibited this increase in sympathetic tone, improving neurologic outcome [34–36]. This is probably because the suppression of enhanced catecholamine concentrations exerts a neuroprotective effect by balancing the ratio of cerebral oxygen demand to supply, reducing excitotoxicity. One contradictive report, however, showed that increased circulating catecholamine concentrations during cerebral ischemia were suppressed by dexmedetomidine. On the other hand, dexmedetomidine does not suppress elevation in brain noradrenaline or glutamate concentrations associated with cerebral ischemia [37, 38]. This suggests that the neuroprotective effects of dexmedetomidine are related to mechanisms other than the inhibition of presynaptic noradrenaline or glutamate release in the brain. Recently, it was reported that dexmedetomidine altered the expression of apoptosis or cell survival regulating factors after cerebral ischemia [39, 40]. The neuroprotective effect of dexmedetomidine appears to be limited with postischemic administration. One study, however, has provided some interesting results: high-dose, but not small dose, administration of dexmedetomidine after global cerebral ischemia reduced neuronal damage only in the dentate gyrus of the hippocampus, and these results were reversed with pre-ischemic administration; in short, a pre-ischemic high dose did not reduce neuronal damage [34]. With pre-ischemic administration, it was reported that dexmedetomidine did not affect the neuronal outcome when the ischemic insult was severe [41]. Another interesting report focusing on α_2-adrenergic properties and ischemic condition warned that high-dose dexmedetomidine might be associated with cerebral hypoperfusion and the exacerbation of ischemic brain injury, possibly through α_2-induced cerebral vasoconstriction [42]. Taken together, these studies suggest that in order to obtain a neuroprotective effect, the dose of dexmedetomidine needs to be adjusted according to the severity of ischemia or timing of administration. One clinical trial has assessed the neuroprotective efficacy of dexmedetomidine during coronary artery bypass grafting surgery [43]. This study used serum S-100B protein, neuron-specific enolase, and lactate measurements as surrogate outcomes. None of these parameters was affected by dexmedetomidine treatment. However, the observational period was only 24 h, and the sample size was very small ($n = 24$). Therefore,

it seems that no conclusion can yet be drawn with regard to the neuroprotective efficacy of dexmedetomidine in humans.

9.5 Propofol

Propofol has been reported to have free radical-scavenging properties, as well as work as a cerebral metabolic depressant by inhibiting synaptic activity [44]. Recent studies have revealed that propofol can markedly attenuate apoptotic and autophagic processes via the altered expression of apoptosis- and autophagy-related proteins [45–47]. With these properties, propofol has generally proven itself to be neuroprotective in models of focal and global ischemia [44–53]. It was reported that pretreatment with propofol, but not during ischemia, resulted in no protection against focal ischemic insult [54]; however, propofol administration started immediately and even 1 h after an ischemic insult significantly reduced infarct size compared with control rats [50, 52, 53]. Meanwhile, propofol should be administered during ischemia if neuroprotection is to be obtained against global cerebral ischemia [44–47, 49, 51]. As in studies researching the neuroprotective properties of inhalational anesthetics, the sustainability of the protective effects of propofol on the brain have also been investigated. Initially, it was reported that postischemic propofol infusion decreased infarction volume 3 days, but not 3 weeks, after insult in an endothelin-induced focal ischemia model [51]. Another group using a middle cerebral artery occlusion model reported that postischemic propofol administration induced long-term neuroprotection after focal ischemia [52]. In regard to global ischemic models, it was reported that propofol showed sustained neuroprotection for up to 28 days after ischemia by reducing eosinophilic and apoptotic injury in a model of hemispheric ischemia combined with hemorrhagic hypotension [47]. One clinical trial has assessed the neuroprotective efficacy of propofol during valve surgery [55]. Neurologic and neuropsychologic tests were performed on postoperative days 1–70. Propofol was adjusted to achieve electroencephalographic burst suppression during surgery. No reduction in the incidence or severity of neurologic or neuropsychologic dysfunction was observed, however.

9.6 Conclusion

Most intravenous anesthetics are attractive and logical candidates as neuroprotective measures during ischemia, directly altering the tissue energy balance and thus reducing the cerebral metabolic rate. The events occurring after ischemia, however, are ongoing and induce other complex processes, including excitotoxicity, inflammation, and apoptosis. Some anesthetics may be effective in inhibiting unfavorable cascades following ischemia, but not all. Anesthetics are not magical drugs; they can increase the therapeutic window, however, allowing

Table 9.1 Summary of neuroprotective effects of intravenous anesthetics in experimental studies

	Pre-administration focal ischemia	Post-administration focal ischemia	Pre-administration global ischemia	Post-administration global ischemia	Long-term effect
Barbiturates	Effective	Effective	Ineffective	Ineffective	Not determined
Benzodiazepines	Ineffective	Effective	Ineffective	Effective	Not determined
Dexmedetomidine	Effective	Ineffective	Effective	Limited	Not determined
Propofol	Effective	Effective	Effective	Ineffective?	Possible

These findings are based on the results of animal, not human, studies. The focus has been on whether administration was pre- or postischemic, whether the problem was focal or global, and long-term efficacy
Pre-administration focal ischemia: drugs were administered before focal ischemic event
Post-administration focal ischemia: drugs were administered after focal ischemic event
Pre-administration global ischemia: drugs were administered before global ischemic event
Post-administration global ischemia: drugs were administered after global ischemic event
Long-term effect: long-term neuroprotective efficacy of each drug

application of other interventions against ongoing events, as pointed out previously. Therefore, it may be too early to form a definitive judgment on anesthetics in this respect. They still have the potential to play a major role in neuroprotection. A rough summary of the effectiveness of the intravenous anesthetics discussed in this chapter in terms of their neuroprotective properties is given in Table 9.1. It should be noted that these findings are based on the results of animal, not human, experiments and that the focus has been on whether administration was pre- or postischemic, whether the problem was focal or global, and long-term efficacy.

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Chapter 10
Opioids and Adjuvant Drugs

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Abstract Anesthetic agents can alter cerebral hemodynamics, which can improve or worsen intracranial conditions during surgical procedures. The effects of opioids and other adjuvant analgesics on cerebral hemodynamics are presented in this chapter.

Opioids: Although reports differ, cerebral blood flow (CBF) and cerebral metabolic rate of oxygen ($CMRO_2$) remain unaltered or are modestly increased with the administration of clinical doses of opioids, but supraclinical doses of opioids decrease both CBF and $CMRO_2$. However, the cerebrovascular response to a change in mean arterial pressure (MAP) or arterial carbon dioxide tension is unaffected by opioids. Opioids do not increase intracranial pressure (ICP) directly. These findings suggest that clinical doses of opioids can be used safely for neuroanesthesia. The impact of opioids on an ischemic cerebrospinal injury is also discussed.

Adjuvant analgesics: A substantial dose of lidocaine may decrease $CMRO_2$. Indomethacin, but not other cyclooxygenase inhibitors, decreases CBF and ICP without decreasing MAP.

Keywords Cerebral hemodynamics • Cerebral blood flow • Opioids • Lidocaine • Nonsteroidal anti-inflammatory drugs

10.1 Introduction

Anesthetic agents can alter cerebral hemodynamics such as cerebral blood flow (CBF), cerebral metabolic rate of oxygen ($CMRO_2$), physiological cerebrovascular response to change in mean arterial pressure (cerebral autoregulation), cerebrovascular carbon dioxide (CO_2) reactivity, and intracranial pressure (ICP). These alterations may worsen intracranial conditions during a surgical procedure. However, some conditions may be improved by taking advantage of the effects of

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anesthetic agents. In this chapter, we describe the effects of opioids and other adjuvant analgesics on cerebral hemodynamics.

10.2 Opioids

The effects of opioids on cerebral hemodynamics can be altered by choices in study design such as opioid doses (i.e., supraclinical versus clinical), background anesthetic agents, baseline brain conditions (i.e., healthy volunteers versus patients with brain pathology), species, animal models, and techniques used to measure arterial CO_2 tension (i.e., blood-gas analyses versus end tidal measurements). In consideration of these factors, we reviewed studies of opioids conducted mainly in humans, focusing particularly on dose (clinical, low-to-moderate dose; supraclinical, high dose).

10.2.1 Morphine

Few studies have investigated the effects of morphine on cerebral hemodynamics in humans, and only one study has reported the effects without background anesthetics. Moyer et al. [1] evaluated the effects of intravenous morphine (60 mg) on cerebral hemodynamics and oxygen metabolism in healthy, awake human volunteers. They reported that CBF was not altered by morphine, although $CMRO_2$ was markedly reduced. Reduced $CMRO_2$ usually induces a decrease in CBF. However, in this study, ventilation was not kept constant; therefore, morphine-induced respiratory depression resulted in an increase in arterial CO_2 tension ($PaCO_2$). High $PaCO_2$ may have dilated the cerebral vasculature and consequently increased CBF to normal levels. Jobes et al. [2] reported that either 1 or 3 mg/kg intravenous morphine produced no alteration in CBF or $CMRO_2$ in healthy volunteers anesthetized with 70 % nitrous oxide (N_2O) and ventilated to maintain a constant $PaCO_2$ at 40 mm Hg. Given that N_2O increases CBF and $CMRO_2$, the morphine must have reduced CBF and $CMRO_2$. These available human data indicate that substantial doses of morphine reduce both CBF and $CMRO_2$.

Morphine-N_2O anesthesia did not affect cerebral autoregulation in normal human subjects when $PaCO_2$ was kept constant at 40 mm Hg [3]. To our knowledge, there are no reports investigating the effects of morphine on cerebrovascular CO_2 reactivity or ICP in humans.

10.2.2 Fentanyl

Most human studies using low-to-moderate dose (1.5–25 μg/kg) intravenous fentanyl have shown a slight increase or no change in CBF [4–7]. Hanel et al. [4] investigated the effects of 25 μg/kg fentanyl on CBF without background anesthetics in patients undergoing elective coronary artery bypass graft by using transcranial Doppler ultrasonography. They concluded that CBF did not change with this dose of fentanyl, as long as MAP and $PaCO_2$ were constant. In contrast, Trindle et al. [6] reported that 16 μg/kg fentanyl increased CBF by approximately 25 %. This increase in CBF may have been related to a decrease in MAP observed in the fentanyl group. Firestone et al. [7] reported the effect of 1.5 μg/kg fentanyl on regional CBF by using positron emission tomography (PET). Fentanyl significantly increased regional CBF consistent with neuronal activation in the anterior cingulate and prefrontal cortices, as well as in caudate nuclei. These areas are involved in pain-related processing.

Carlsson et al. [8] examined the effects of high-dose (25–400 μg/kg) intravenous fentanyl on CBF and $CMRO_2$ in rats and concluded that high-dose fentanyl decreased both CBF and $CMRO_2$ in a dose-dependent manner. In humans, low-dose (2 μg/kg) fentanyl produced minimal electroencephalographic changes, whereas higher doses (50–70 μg/kg) resulted in high-voltage slow waves (delta waves), suggesting a state consistent with the decrease in $CMRO_2$ produced by high-dose fentanyl [9].

Collectively, clinical-dose fentanyl provides either a modest increase or no alteration in CBF, whereas supraclinical-dose fentanyl reduces both CBF and $CMRO_2$.

One study in dogs suggested that fentanyl had no effect on cerebral autoregulation [10]. This remains to be investigated in humans, however. Fentanyl did not affect cerebrovascular CO_2 reactivity in humans [11]. In addition, fentanyl did not increase ICP, as long as MAP remained constant [12–15].

10.2.3 Alfentanil

Few studies have investigated the effects of alfentanil on cerebral hemodynamics in humans. Mayberg et al. [16] evaluated the effects of low-to-moderate dose (25 or 50 μg/kg) alfentanil on CBF during isoflurane-N_2O anesthesia in patients undergoing craniotomy and found that alfentanil did not change CBF. It was also reported that 10 to 50 μg/kg alfentanil did not alter $CMRO_2$ in humans [16, 17]. Cerebrovascular CO_2 reactivity was not affected by clinical doses of alfentanil [17]. In one study on dogs, even high-dose (320 μg/kg) alfentanil did not alter CBF or $CMRO_2$, and both cerebral autoregulation and cerebrovascular CO_2 reactivity remained intact [18]. No increase in ICP was observed by the administration of alfentanil

in patients undergoing supratentorial craniotomy during either isoflurane-N_2O [19] or propofol-fentanyl anesthesia [17], as long as MAP was constant.

10.2.4 Sufentanil

Some investigators have reported that low-to-moderate dose (0.5–3 μg/kg) intravenous sufentanil did not change CBF [4, 20]. However, Trindle et al. [6] reported that approximately 1.7 μg/kg sufentanil increased CBF by 25 % in patients undergoing non-intracranial neurosurgery without background anesthetics. Hanel et al. [4] reported that high-dose (6 μg/kg) sufentanil was associated with a 27 to 30 % decrease in CBF. In dogs, high-dose (20 μg/kg) sufentanil also resulted in a decrease in CBF along with a 35 to 40 % decrease in $CMRO_2$ [21].

There are no human studies investigating the effects of sufentanil on $CMRO_2$, cerebral autoregulation, or cerebrovascular CO_2 reactivity. Clinical doses (0.3–3 μg/kg) of sufentanil did not increase ICP when MAP was kept constant [22, 23], even when the patient presented with intracranial hypertension following severe brain trauma [24].

10.2.5 Remifentanil

With low-to-moderate doses (0.05–0.25 μg/kg/min) of continuous remifentanil infusion, CBF was either unaltered or modestly increased, similar to with other opioids [25–29]. Wagner et al. [27] evaluated the effects of low- (0.05 μg/kg/min) or moderate-dose (0.15 μg/kg/min) remifentanil on regional CBF by using PET. Low-dose remifentanil significantly increased relative regional CBF in the lateral prefrontal and inferior parietal cortices and supplementary motor area. In contrast, relative decreases in regional CBF were observed in the basal mediofrontal cortex, cerebellum, superior temporal lobe, and mid-brain gray matter. Moderate-dose remifentanil further increased regional CBF in the mediofrontal and anterior cingulate cortices, occipital lobe transition, and caudal periventricular gray matter. These remifentanil-induced relative regional CBF increases occurred in areas involved in pain processing. Lorenz et al. [28, 29] reported similar effects on regional CBF by using magnetic resonance imaging. They implied that these findings were consistent with cerebral excitement and/or disinhibition caused by low-to-moderate dose remifentanil, which would be suppressed by high-dose remifentanil [29].

High-dose (2–4 μg/kg/min) remifentanil decreased CBF without impairing cerebrovascular CO_2 reactivity [30]. Paris et al. [31] compared the effects of two different high-dose remifentanil regimes (2 μg/kg i.v. followed by 1 μg/kg/min continuous i.v. versus 5 μg/kg i.v. followed by 3 μg/kg/min continuous i.v.) on CBF in isocapnic cardiac patients without background anesthetics. They reported that the

higher-dose remifentanil regime decreased CBF, which may have been due to a reduction in $CMRO_2$.

Remifentanil did not alter cerebral autoregulation [32]. Cerebrovascular CO_2 reactivity remained intact during 0.35 μg/kg/min remifentanil infusion combined with N_2O anesthesia in patients undergoing craniotomy [33]. High-dose remifentanil did not alter cerebrovascular CO_2 reactivity in healthy volunteers [30]. No increase was observed in ICP by remifentanil, even when patients had head trauma [25].

Remifentanil hydrochloride is a nonspecific, esterase-metabolized opioid; the context-sensitive half-life of remifentanil is very short, regardless of renal or hepatic function [34, 35]. This ultra-short action property of remifentanil enables us to evaluate neurological findings soon after neurosurgery. Considering these properties, remifentanil appears to be a good first-line opioid for neuroanesthesia.

10.2.6 Summary of Opioids

Although not all reports agree, the general effects of opioids on cerebral hemodynamics are as follows (Table 10.1):

1. With low-to-moderate (i.e., clinical) dose opioid administration, CBF and $CMRO_2$ are either unaltered or modestly increased.
2. High (i.e., supraclinical) doses of opioids result in a decrease in both CBF and $CMRO_2$.
3. Neither cerebral autoregulation nor cerebrovascular $PaCO_2$ reactivity are affected by opioids.
4. Opioids do not increase ICP, as long as MAP remains constant.

These findings suggest that clinical doses of opioids do not seriously alter cerebral hemodynamics; hence, opioids can be safely used for neuroanesthesia.

10.3 Do Opioids Exacerbate Ischemic Cerebrospinal Injury?

Some investigators have suggested that administration of opioids induces motor dysfunction after cerebral or spinal ischemia [39–42]. Baskin and Hosobuchi [39] reported that intravenous administration of morphine exacerbated hemiparesis in patients with cerebral ischemia, and this hemiparesis was completely reversed by naloxone. A similar phenomenon was induced by fentanyl administration in rats: fentanyl exacerbated incomplete forebrain ischemia [40]. Kakinohana et al. [42] reported that neuraxial morphine may trigger transient motor dysfunction after a short period of spinal cord ischemia in humans and rats. They also reported that this

Table 10.1 Effects of opioids and adjuvant drugs on cerebral hemodynamics

	CBF	$CMRO_2$	Cerebral autoregulation	Cerebrovascular CO_2 reactivity	ICP
Morphine (60 mg, 1–3 μg/kg)	↓ or →	↓ or →	→	–	–
Fentanyl					
Low-to-moderate dose (1.5–25 μg/kg)	→ or ↑	–	–	→	→
High dose (>25 μg/kg)	↓*(~50 %* [8]*)*	↓*(~35 %* [8]*)*	→	–	–
Alfentanil					
Low-to-moderate dose (10–50 μg/kg)	→	→	→	→	→
High-dose (320 μg/kg)	→	→	→	→	–
Sufentanil					
Low-to-moderate dose (0.5–3 μg/kg)	→ or ↑	–	–	–	→
High dose (>6 μg/kg)	↓(27–30 % [4])	↓*(35–40 %* [21]*)*	–	–	–
Remifentanil					
Low-to-moderate dose (0.05–0.5 μg/kg/min)	→ or ↑	–	→	→	→
High dose (2–4 μg/kg/min)	↓(31 % [31])	↓	–	→	–
Lidocaine (3–15 mg/kg)	→	↓*(10–27 %* [36]*)*	–	–	→
Indomethacin (0.1–0.3 mg/kg/h, 0.83 mg/kg)	↓(26–35 % [37])	→	–	↓ or →	↓(77 % [38])

Values in italics are derived from animal studies
CBF cerebral blood flow, *$CMRO_2$* cerebral metabolic rate of oxygen, *ICP* intracranial pressure, → no change, ↑ increase, ↓ decrease, – not analyzed

opioid-induced motor dysfunction was associated with mu and delta, but not kappa, opioid receptors [43]. However, other studies found that neither fentanyl nor remifentanil exacerbated ischemic spinal cord injury in rats [44] or rabbits [45].

In a clinical setting, when cerebral or spinal ischemia is suspected following the observation of an amplitude reduction in a motor-evoked potential or during a clinical assessment in the perioperative period, reducing mu-agonist opioid use and utilizing other analgesic agents and regional anesthesia techniques should be considered.

10.4 Adjuvant Drugs

Opioids are essential analgesic agents for neurosurgical anesthesia. Nevertheless, in recent years, a multimodal-analgesia concept has been developed that suggests administering a combination of opioids, regional anesthesia, local infiltration, and non-opioid analgesic drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) to provide better analgesia while limiting opioid use. The effects of lidocaine and NSAIDs (especially indomethacin) on cerebral hemodynamics are described in this section.

10.4.1 Lidocaine

In dogs, 3 mg/kg and 15 mg/kg of intravenous lidocaine reduced $CMRO_2$ by 10 % and 27 %, respectively, without alteration in CBF [36]. The reduction in $CMRO_2$ produced by a very large dose (160 mg/kg) of intravenous lidocaine was greater than that produced by high-dose pentobarbital in dogs [46]. The authors suggested that the membrane-stabilizing effect of lidocaine decreased the energy requirement for the maintenance of membrane integrity, resulting in a marked reduction in $CMRO_2$ [46]. However, excess doses of local anesthetics can cause systemic toxicity. Sakabe et al. [36] reported that lidocaine-induced seizure increased $CMRO_2$; hence, CBF increased to meet the additional cerebral oxygen demand. The scalp region is rich in blood supply and, therefore, local infiltration around the scalp can easily cause local anesthetics systemic toxicity (LAST). Thus, doses of local anesthetics should be carefully monitored, especially in patients with intracranial pathologies, to prevent LAST.

Intravenous lidocaine is an effective means to prevent the increases in ICP that can accompany a nociceptive stimulus such as a tracheal intubation [47] or application of a pin-type head holder [48] without a decrease in MAP.

10.4.2 NSAIDs

Indomethacin acts as a cerebral vasoconstrictor. Indomethacin decreases CBF without alteration in $CMRO_2$. An indomethacin dose as low as 0.1 mg/kg/h was effective in reducing CBF [37]. Either rectal application of 100 mg or oral administration of 1.5 mg/kg indomethacin also reduced CBF [37, 49]. In one study evaluating the effects of perioperative indomethacin on ICP, CBF, and $CMRO_2$ in patients undergoing craniotomy for supratentorial tumors, Budgaard et al. [38] observed a significant decrease in ICP after intravenous administration of 50 mg indomethacin; this decrease was caused by a significant reduction in CBF. Indomethacin administration reduced ICP without decreasing MAP; hence, cerebral

perfusion pressure increased [38]. Whether indomethacin administration impairs cerebrovascular CO_2 reactivity [49, 50] or not [51] remains controversial.

The mechanism of indomethacin-induced cerebral vasoconstriction is not fully understood, although it may be directly due to cyclooxygenase inhibition. However, other cyclooxygenase inhibitors such as diclofenac, naproxen, ibuprofen, flurbiprofen, aspirin, and sulindac do not alter either CBF or ICP [37, 49, 52, 53].

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Chapter 11
Steroids, Diuretics, and Anticonvulsants

Yuki Sugiyama and Mikito Kawamata

Abstract Edema formation induced by increased vascular permeability worsens tissue damage and exacerbates residual neuronal function. To prevent such secondary damage, many drugs with the potential to reduce edema formation have been used and studied. However, many randomized controlled trials have shown that steroid therapy did not improve neurologic function; on the contrary, steroid therapy caused a higher incidence of side effects. Therefore, steroid administration is not recommended in acute neuronal injury, except for edema associated with brain tumor.

Diuretics are used widely in neurosurgery to reduce brain volume and intracranial pressure. Mannitol is effective at doses of 0.25–1 g/kg body weight. Loop diuretics are used as combination drugs with mannitol to facilitate urination.

Any cortical damage or irritation associated with brain injury, including that induced by brain surgery, has the potential to induce seizures. Diazepam and phenytoin are widely used to stop seizures. Intravenous anesthetics have anticonvulsant effects.

Keywords Methylprednisolone • Mannitol • Benzodiazepine • Propofol

11.1 Introduction

Edema formation worsens brain damage and exacerbates residual neuronal function. To prevent such secondary damage, several drugs including steroids and diuretics (mannitol and loop diuretics) have widely been used during a preoperative period for neurosurgery. In addition, any cortical damage or irritation associated with brain injury, including that induced by neurosurgery, has the potential to induce seizures. In this chapter, we will focus on benefits of usage of such drugs during the preoperative period for neuroanesthetic management. We will also discuss about adverse effects of such drugs.

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11.2 Steroids

Steroids have been used to assist in the control of cerebral edema in patients with brain disease. Steroids are thought to restore altered vascular permeability or increased blood–brain barrier permeability resulting from tissue damage [1]. However, steroid therapy has a high incidence of side effects such as infection, gastrointestinal bleeding, and hyperglycemia [2–5]. Therefore, steroid administration is not recommended in acute neuronal injury, except for edema associated with brain tumors [6, 7].

11.2.1 Brain Tumor, Metastatic Brain Tumor

The effectiveness of steroids in reducing cerebral edema associated with brain tumors is well known. Administration of steroids before elective surgery has the potential to reduce edema formation and improve neuronal function before craniotomy. Administration of steroids in patients with symptoms of increased intracranial pressure (ICP), such as consciousness disorder, headache, vomiting, and motor dysfunction, is standard care. Starting doses of dexamethasone are 4–16 mg/day [6, 7].

11.2.2 Traumatic Brain Injury

Administration of steroids in adult patients with head injuries has been abandoned as a result of controlled trials showing deleterious effects. The majority of these trials showed that steroids did not improve outcome or lower intracranial pressure in patients with severe traumatic brain injury (TBI). On the contrary, a high dose of methylprednisolone was associated with increased mortality [2]. The use of steroids is also not recommended in the treatment of severe TBI in pediatric patients [3].

11.2.3 Acute Spinal Cord Injury

The efficacy of steroids for SCI has been investigated in a number of studies, the most widely recognized of which is the National Acute Spinal Cord Injury Study (NASCIS). In the NASCIS2 trial (1990) [8], methylprednisolone was administered at an initial loading dose of 30 mg/kg within 8 h of injury, followed by administration at 5.4 mg/kg/h for 23 h. The results showed that neurological function was improved by methylprednisolone in the acute phase of SCI. However, in NASCIS3 (1997) [9], it was shown that methylprednisolone induced severe pneumonia and

sepsis. The harmful side effects of methylprednisolone administration include infection, hyperglycemia, gastrointestinal hemorrhage, and myopathy. In guidelines on the management of acute SCI published in 2013, it was concluded that there was no consistent or compelling medical evidence to justify the administration of methylprednisolone for acute SCI [5].

11.3 Diuretics

Diuretics are used widely in neurosurgery to control brain volume and intracranial pressure by reducing the intracellular and extracellular fluid compartments. Osmotic diuretics are preferentially used in perioperative situations because of their speed of action and efficacy. Loop diuretics used as combination drugs with mannitol can be effective in facilitating urination.

11.3.1 Mannitol

Mannitol is a widely used osmotic diuretic. It passes the glomerular filter, is not reabsorbed, and is excreted in an unchanged form, resulting in facilitation of urination via its osmotic effect [2–4, 10]. Mannitol is administered at a dose of 0.25–1 g/kg over a period of 15–20 min [10]. The mechanisms by which mannitol reduces ICP are thought to be as follows [2]:

- Mannitol has been shown to control ICP by reducing blood viscosity. This results from viscosity-mediated reflex vasoconstriction, which allows cerebral blood flow to be maintained, despite a reduced level of cerebral blood volume.
- Mannitol administration reduces ICP by an osmotic effect as a result of fluid movement from the brain parenchyma into the intravascular region. This effect takes 15–30 min and persists for up to 6 h.

Acute hyponatremia and hyperkalemia are side effects of intraoperative mannitol administration. Rebound swelling is another side effect of mannitol administration. Mannitol accumulates in injured brain tissue, and fluid movement occurs from the intravascular space to the brain parenchyma, resulting in exacerbation of brain edema. Mannitol administration with serum osmolarity levels >320 mOsm poses the risk of the development of acute tubular necrosis and renal failure.

11.3.2 Glycerol

Glycerol is also an osmotic diuretic. Glycerol is metabolized and enters the glycolytic pathway [10]. Glycerol is used to control increased ICP caused by severe

stroke. Administration of glycerol in severe stroke patients with ICP elevation improved 14-day survival [11]. *10 % glycerol is administered at a dose of 1–1.2 mL/kg*.

11.3.3 Loop Diuretics

Loop diuretics inhibit sodium and chloride reabsorption by acting as a Na-K-2Cl cotransporter at the loop of Henle, thus promoting urine excretion. Hypokalemia and metabolic alkalemia are side effects of loop diuretic administration [10]. Furosemide is administered intravenously at a dose of 5–20 mg.

11.4 Anticonvulsants

Seizures are caused by irritation of the cerebral cortex. Seizures rarely occur under general anesthesia; however, in awake craniotomy, seizure is one of the most serious complications. If seizures occur, surgery should be discontinued immediately, and the appropriate treatment discussed between the anesthesiologists and the neurosurgeons. Propofol is widely used for treating seizures during operative periods. Phenytoin, midazolam, and thiopental are also used. If a single injection is insufficient to stop the seizure, continuous infusion should be considered.

11.4.1 Post-neurosurgery

There are still no guidelines on post-neurosurgical prophylactic anticonvulsants.

11.4.2 Traumatic Brain Injury

Anticonvulsants decrease the incidence of early posttraumatic seizures (PTS) (within 7 days of injury). Prophylactic use of phenytoin or valproate is not recommended for preventing late PTS [2–4].

11.4.3 Subarachnoid Hemorrhage

The use of prophylactic anticonvulsants may be considered in the immediate posthemorrhagic period. Routine long-term use of anticonvulsants is not

recommended but may be considered in patients with known risk factors for delayed seizure disorder such as prior seizure, intracerebral hematoma, intractable hypertension, infarction, or aneurysm in the middle cerebral artery [12, 13]. Although recommended drugs and doses are not stated in the guidelines, phenytoin is widely used in subarachnoid hemorrhage.

11.4.4 Benzodiazepines (Diazepam, Midazolam)

Benzodiazepines increase the affinity of gamma-aminobutyric acid (GABA) for GABAa receptors by binding to this receptor complex and promoting opening of chloride ion channels, resulting in the inhibition of neuronal excitation [14]. In seizures, diazepam is administered at a dose of 10 mg and midazolam at a dose of 0.1–0.3 mg/kg [15].

11.4.5 Phenytoin

Phenytoin stabilizes the inactive state of voltage-gated sodium channels and decreases sodium influx into neurons [16]. In seizures, phenytoin is administered at a dose of 5–20 mg/kg [15]. Recently, fosphenytoin has also been used as a prodrug of phenytoin.

11.4.6 Barbiturates (Thiopental, Phenobarbital)

Barbiturates increase the effect of GABA or directly open chloride ion channels by binding to $GABA_A$ receptors [14]. In seizures, phenobarbital is administered at a dose of 15–20 mg/kg. The dose of thiopental in seizures is the same as that in general anesthesia [15].

11.4.7 Propofol

The mechanism of action of propofol is still unclear; however, propofol is considered to be a GABA agonist and to suppress seizures via GABA-mediated inhibition [17]. The dose of propofol in seizures is the same as that in general anesthesia [15].

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Chapter 12
Neuroprotective Drugs

Michihiro Murozono

Abstract Cerebral nerve injury is a critical condition and one often encountered in the management of patients in the clinical field. Pathological conditions such as cerebral ischemia, head trauma, and hypoxia can result in marked impairment of cerebral function, even if the patient's life is saved. We have been studying the mechanisms underlying pathologically induced neuronal cell death with the aim of developing new therapeutic methods of minimizing neuronal damage after insult. Many advances have been made in intensive care technologies aimed at salvaging neuronal cells on the brink of death and recovering brain function as our understanding of the mechanisms underlying this phenomenon has deepened. A breakthrough has yet to be achieved, however, in the development of effective therapies.

Many potential treatments for brain injury have been identified in experimental studies, and a number of neuroprotective drugs have undergone preclinical development. None of this, however, has translated into clinical success. There are many reasons for these contradictory results, including the different types of brain injury and therapeutic window involved. Here, we outline the current status of neuroprotective agents, both preclinically and clinically, and also identify problems associated with translating neuroprotection from bench to bedside.

Keywords Neuroprotection • Brain • Ischemia • Pharmacotherapy

12.1 Introduction

Pathological conditions leading to brain injury are often encountered in the clinical field. Many advances have been made in intensive care technologies aimed at salvaging neuronal cells on the brink of death and recovering brain function as our understanding of the mechanisms underlying this phenomenon has deepened. However, no breakthrough has been achieved in the development of effective therapies. Many potential treatments for brain injury have been identified in experimental studies, and a number of neuroprotective drugs have undergone preclinical

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development. None of this, however, has translated into clinical success. There are many reasons for these contradictory results, such as variation in the type of injury and therapeutic window involved. In this chapter, we will review the current status of neuroprotective agents, both preclinically and clinically, and the problems associated with translating neuroprotection from bench to bedside.

12.2 Neuroprotection by Pharmacotherapy

To date, many neuroprotective agents have been developed based on the cascade of biochemical events leading to cell death (Figs. 12.1 and 12.2 [1]). We report below the current clinical status of drugs that have been developed as neuroprotective agents (Table 12.1 [1]).

Diuretics (Mannitol, Furosemide) Mannitol administration results in the reduction of brain edema, reduction of blood viscosity, improvement in local circulation, and increased free radical removal [2]. Rapid administration causes a rise in central

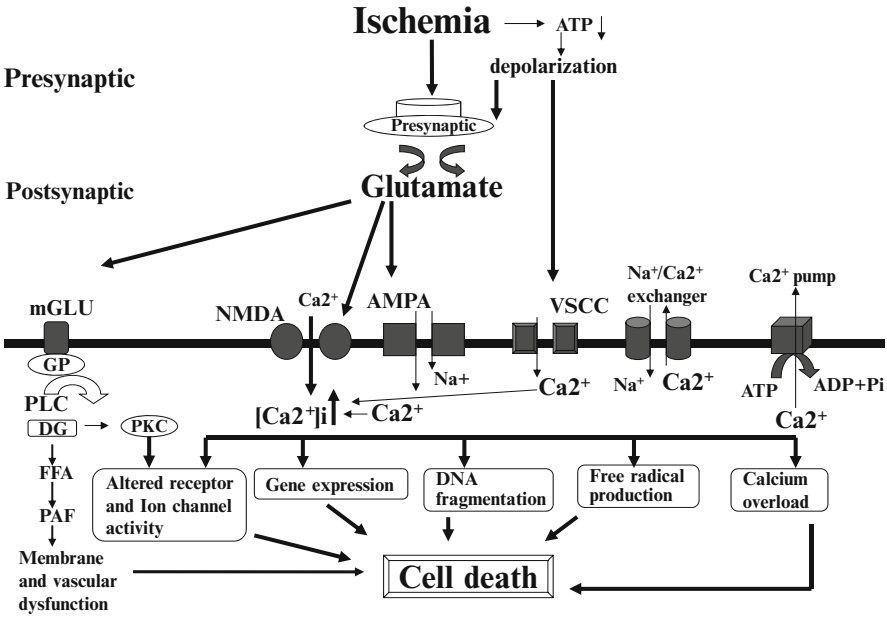

Fig. 12.1 Mechanism of ischemia-induced neuronal death (extracellular). In intracellular signaling system described by glutamate-Ca^{2+} hypothesis, ischemia induces extracellular glutamate release, resulting in the activation of metabotropic glutamate receptors and an increase in the level of intracellular Ca^{2+}. *VSCC* voltage-sensitive Ca^{2+} channel, *AMPA* amino-hydroxy-methyl-isoxalone propionic acid, *NMDA* N-methyl-D-aspartic acid, *mGlu* metabotropic glutamate, *GP* G-protein, *PLC* phospholipase C, *DG* diacylglycerol, *PKC* protein kinase C, *FFA* free fatty acid, *PAF* platelet-activating factor

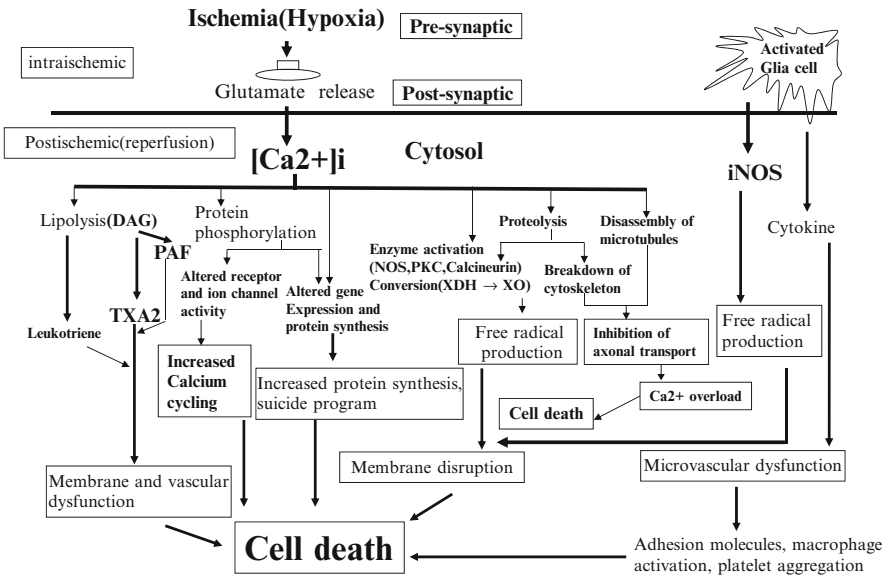

Fig. 12.2 Mechanism of ischemia-induced neuronal death (intracellular). Events such as PKC activation, gene expression, DNA fragmentation, production of free radicals, Ca^{2+} overload, and cell membrane dysfunction induce an increase in intracellular Ca^{2+} levels, leading to cell death. Mitochondria are currently attracting attention as potential contributory factor in this series of reactions. *DAG* diacylglycerol, *PAF* platelet-activating factor, *NOS* nitric oxide synthase, *PKC* protein kinase C, *iNOS* inducible nitric oxide synthase

venous pressure, and patients should be closely watched for signs of hyponatremia. The "Sendai cocktail" (a combination of 500 ml of 20 % mannitol, 300 mg vitamin E, and 50 mg dexamethasone) is also used.

Tissue Plasminogen Activator (tPA) Intravenous administration of tPA is recommended for cases less than 3 h after onset of cerebral infarction. However, there are suggestions that this time window can be extended to 4.5 h post-onset [3].

Ca^{2+} Channel Blockers Calcium channel blockers appear to exert a cerebroprotective effect via cerebrovascular expansion and the suppression of Ca^{2+} influx into nerve cells. It has been reported that nimodipine improves the neurological score in patients at risk of angiospasm after subarachnoid hemorrhage and cerebral infarction [4]. However, this result was not supported by those of a large-scale meta-analysis of 15 studies of cerebral infarction [5], in which no effect was found in nine of them.

Na+ Channel Blockers No neuroprotective effect was observed with lifarizine [6] or fosphenytoin [7], and the results of clinical studies of lubeluzole are contradictory [8].

Antioxidants and Free Radical Scavengers Tirilazad (21-aminosteroid) was not effective as a neuroprotectant, and the study was discontinued [9]. Ebselen was

Table 12.1 Neuroprotective drugs developed so far and results of clinical trials

Category, mechanism	Drug name, name of multicenter study, and its results	Category, mechanism	Drug name, name of multicenter study, and its results
Ca^{2+} channel blocker	Nimodipine: no benefit (VENUS)	Noncompetitive NMDA antagonist	Dizocilpine, discontinued dextrorphan: no benefit
Na^{+} channel blocker	Lifarizine, no benefit; lubeluzole, no benefit; fosphenytoin, discontinued	Competitive NMDA antagonist	Selfotel: discontinued
GABA agonist	Clomethiazole: no effect	AMPA/KA receptor antagonist	NBQX, discontinued; YM872, RCT
Free radical scavenger	Edaravone, clinical use; ebselen, phase III; NXY059: phase III; tirilazad, discontinued	Metabotropic receptor antagonist	Group I, II, III: RCT being planned
Growth factor	bFGF: abandoned AX200 (filgrastim, G-CSF analogue), phase II	HMG-CoA reductase inhibitor	Lovastatin: phase II; simvastatin, phase III
Growth factors, oxygen delivery	Human chorionic gonadotropin (hCG)/erythropoietin (NTx-265): phase II	Hemodiluting agent	Albumin: phase III (ALIAS)
Ganglioside	No benefit	Membrane stabilizer	Citicoline (CDP choline): phase III
$MgSO_4$	Fast MAG: ongoing (IMAGE)	Iron chelator	Deferoxamine mesylate: phase II
Opioid receptor antagonist	Nalmefene: no benefit	Metal ion chelator	DP-b99: phase III
Polyamine receptor antagonist	Eliprodil: discontinued	Antibiotic, pleiotropic protective effects	Minocycline: phase III
Glycine antagonist	ACEA1021: No benefit, Gavestinel: No benefit	Other	Piracetam: Phase III

VEVUS very early nimodipine use in stroke, *NMDA* N-methyl-D-aspartic acid, *GABA* gamma-aminobutyric acid, *AMPA* amino-hydroxy-methyl-isoxalone propionic acid, *KA* kainate, *NBQX* 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione, *RCT* randomized controlled trial, *bFGF* basic fibroblast growth factor, *ALIAS* Albumin in Acute Stroke, *Fast MAG* Field Administration of Stroke Therapy-Magnesium, *ACEA1021* 5-nitro-6,7-dichloro-1,4-dihydro-2,3-quinoxalinedione

given to 302 patients with cerebral infarction onsets of less than 48 h, resulting in significant improvements in neurological symptoms and bionomics after 12 weeks [10]; large-scale clinical research is ongoing. In addition, NXY059 showed a reduction in cerebral infarction in animal studies, and large-scale clinical testing is ongoing [11]. Edaravone was developed in Japan, and much clinical utility has been reported.

Growth Factors Basic fibroblast growth factor (bFGF) showed a protective effect for nerve cells, but the mortality rate was high in a multi-facility randomized controlled trial [12], and the third phase was discontinued. AX200 and NTx-265 are in ongoing phase II trials [13].

Magnesium Magnesium sulfate ($MgSO_4$) has recently been attracting attention. A large-scale study, the Field Administration of Stroke Therapy-Magnesium Trial (FAST-MSG), in which $MgSO_4$ is administered at the time of hospital transportation soon after the onset of cerebral infarction, is currently being performed [13].

Polyamine Receptor Antagonists Eliprodil (SL820715) was found not to be effective in a phase III study, and the trial was discontinued.

Glycine Antagonists The glycine antagonist ACEA-1021 (also known as gavestinel) has been tested, but sufficient efficacy was not found in the clinical trial [14].

Noncompetitive NMDA Receptor Antagonists Several noncompetitive NMDA receptor antagonists have been developed, but clinical trials were discontinued because of side effects such as integration dysfunction syndrome and respiratory depression. Dizocilpine (MK801) treatment resulted in cerebroprotection in animal experiments. However, a clinical trial was discontinued as it also induced neuronal vacuolization and necrosis [15]. Clinical trials of dextrorphan and aptiganel (CNA102) were also discontinued due to side effects.

Competitive NMDA Receptor Antagonists Selfotel (CGS19755) is an example of a competitive NMDA receptor antagonist. In a phase III trial, patients receiving selfotel displayed a significantly higher mortality rate due to aggravation of brain edema and cerebral infarction, and the trial was discontinued [16]. NPS1506, for which a phase I trial has been completed, does not show side effects at a curative dose, and a neuroprotective action has been confirmed [17].

Amino-hydroxy-methyl-isoxalone Propionic Acid (AMPA) Receptor Antagonists The clinical trial of NBQX, an AMPA receptor antagonist, was discontinued because of the side effect of renal dysfunction [18]. A large-scale study, the AMPA Receptor Antagonist Treatment in Ischemic Stroke (ARTIST), is currently being performed for YM872.

Metabotropic Receptor Antagonists Metabotropic receptors consist of eight subtypes, divided into three groups. Antagonists of plural modality have been developed for each group [19].

HMG-CoA Reductase Inhibitors HMG-CoA reductase inhibitors block cholesterol synthesis. In a meta-analysis of clinical trials conducted in many institutions, it was reported that statins decreased the incidence of cerebral infarction by 16–30 % [20].

Hemodiluting Agents (Albumin) Albumin produces its neuroprotective effect through several mechanisms, including amelioration of brain swelling,

enhancement of blood flow to sub-occlusive microvascular lesions, maintenance of vascular patency, and prevention of reocclusion after successful thrombolysis [21]. A large placebo-controlled randomized multicenter phase III trial of albumin therapy in acute ischemic stroke (ALIAS-Part2) is currently ongoing [22].

Iron Chelators Iron overload has been associated with increased brain injury in ischemia/reperfusion experimental stroke models and ischemic stroke patients, especially in individuals receiving thrombolytic treatment [23]. Administration of deferoxamine, an iron chelator, was neuroprotective in ischemia/reperfusion animal models [24].

Metal Ion Chelators DP-b99 is a novel membrane-activated chelator of divalent metal ions such as calcium and zinc [25]. The phase III Membrane-Activated Chelator Stroke Intervention trial is currently underway.

Tetracyclines (Minocycline) The proposed mechanisms of action of minocycline include anti-inflammatory effects, reduction of microglial activation, matrix metalloproteinase activity, nitric oxide production, and inhibition of apoptosis [26]. The phase III Neuroprotection with Minocycline Therapy for Acute Stroke Recovery Trial is ongoing.

Others No clear effectiveness was found in phase III trials of piracetam [27], citicoline [28] (membrane stabilizers), or nalmefene [29] (opioid receptor antagonist).

As described above, various neuroprotective agents have been developed. However, none of these treatments provides neuroprotection without incurring side effects. Consideration of the therapeutic window is important in treating cerebral ischemia. Furthermore, it is important to use a combination of agents at the appropriate times. These include neuroprotective agents during ischemia, and agents preventing toxicity after the reperfusion of blood flow, followed by agents strengthening tissue recovery.

12.3 Why Has There Not Been More Progress in Developing Drugs for Cerebroprotection?

An effective drug has yet to be developed for the following reasons [30]:

1. Clinically, behavior is analyzed long after ischemia has occurred, whereas in experimental models drug effects are evaluated soon after.
2. Even though the mechanisms underlying brain injury are very complicated, we attempt to treat patients with drugs developed through animal experiments and which affect only one target molecule.

3. Animal models are highly controlled and homogeneous, whereas human patients are a variable and heterogeneous population. More experiments using primate models are required.
4. The dose of a drug that can be administered without problems in an animal may cause side effects in humans. In addition, the therapeutic window is very narrow, making timely application difficult.
5. Induced ischemia in animal models has identical characteristics, whereas in humans those characteristics are highly variable.
6. The measurement of the effect of a drug and the analytical methods applied remain to be standardized.
7. The potential influence of factors such as sex or age has not received enough attention.
8. Pharmaceutical companies perform drug development over the short term but still expect them to be both clinically applicable and effective in the long term.
9. Pharmaceutical companies give priority to profit and focus on developing individual drugs rather than drug combinations.
10. Government research organizations do not appreciate the importance of the development of cerebroprotective treatments.

De novo drug development requires that we elucidate fundamental mechanisms, specify target molecules, and then begin drug development. To ensure future success, it is necessary to push drug development forward through the integration of the political and business circles with government services.

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Chapter 13
Neurotoxicity of Anesthetic Agents for Developing and Adult Brain

Rui Kato, Toshikazu Hashimoto, and Yuji Morimoto

Abstract

1. Neurotoxicity of anesthetic agents to the developing brain

The neurotoxicity of various anesthetic and sedative agents to the developing brain has been clearly established in various laboratory animals, including subhuman primates. According to recent reports, anesthetic agents which block N-methyl-D-aspartate-type glutamate receptors and/or activate gamma-aminobutyric acid-A receptors have neurotoxic properties when used during synaptogenesis. Despite numerous reports, however, the precise mechanisms underlying this neurotoxicity remain unknown. Moreover, it is believed that these results cannot be easily extrapolated into human clinical practice. The results of clinical studies on the neurotoxicity of anesthesia in pediatric patients have been conflicting, and definitive epidemiological evidence remains to be established. Therefore, it would be inappropriate to suggest that anesthesiologists change their anesthetic practice based on these studies at the present time.

2. Neurotoxicity of anesthetic agents to the adult brain

Postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) are cognitive complications occurring after surgery under anesthesia. POD is a transient disturbance of consciousness, attention, cognition, or perception or disorganized thinking and can lead to various complications. It is important to determine the preoperative and intraoperative risk factors for POD in tackling this problem. It is also crucial to recognize and manage its underlying causes in ensuring an appropriate environment for a POD-free recovery. POCD is usually defined as persistent cognitive deterioration, which is clinically diagnosed using various types of neuropsychological tests. POCD and POD are both associated with the aggravation of complications after surgery under anesthesia. Although various factors such as systemic neuroinflammation have been postulated as causes of POCD, its underlying pathogenic mechanism remains to be clearly elucidated. POCD is often observed following cardiac surgery. However, recent studies have revealed that it can occur regardless of type of surgery or anesthesia. Suggested risk

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factors for POCD include advanced age, prolonged duration of surgery, respiratory and infectious complications, and the need for a second operation.

Keywords Neurotoxicity • Neurodegeneration • Cognitive dysfunction

13.1 Introduction

The neurotoxicity of anesthetic agents to the developing brain has been clearly established in animal models. On the other hand, the results of clinical studies on the neurotoxicity of anesthesia in pediatric patients have been conflicting, and definitive evidence remains to be established. Postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) are associated with the aggravation of complications after surgery under anesthesia. Understanding the risk factors and management of POD and POCD is important for the reduction of the perioperative complication rates.

13.2 Neurotoxicity to the Developing Brain

13.2.1 Anesthetic Agents Exert Neurotoxic Effect on Neonatal Laboratory Animals

Various anesthetic and sedative agents have been demonstrated to exert a clear neurotoxic effect on laboratory animals, including subhuman primates [4, 24, 29, 31, 34, 47, 50]. According to recent reports, anesthetic agents that block N-methyl-D-aspartate-type glutamate receptors (NMDAR) [29, 61] and/or activate gamma-aminobutyric acid-A receptors ($GABA_AR$) [8, 53] trigger neurological abnormalities such as acute widespread apoptotic neurodegeneration [24, 31, 34, 50], long-term neurobehavioral impairment [24, 31, 34, 47, 51], and suppression of long-term potentiation induction in the hippocampus [18, 31, 53] (Fig. 13.1, Table 13.1). This vulnerability to the neurotoxic effect of these anesthetic agents, however, is limited to only a short time during the early postnatal period (e.g., for only the first 2 weeks in rodents) [29, 51], also known as the period of synaptogenesis [16, 44]. The severity of apoptosis and neurocognitive disturbances depend on the dosage [8] and duration of exposure to these anesthetics [50]. Repeated exposure to anesthetics, or combination use of $GABA_AR$ agonists and NMDAR antagonists such as isoflurane or midazolam with nitrous oxide, causes more serious neurodegeneration than single use of these agents [24, 31, 61]. Although numerous studies have reported such neurotoxicity, the mechanisms that underlie it remain to be elucidated.

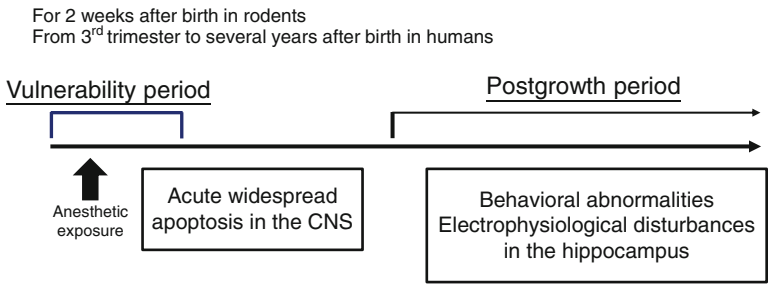

Fig. 13.1 Neurotoxicity to the developing brain

Table 13.1 Neurotoxicity of anesthetic agents to the developing brain

	Apoptosis	Behavioral abnormalities	Electrophysiological disturbances
N_2O	+	+/−	+/−
Isoflurane	+	+	+/−
Sevoflurane	+	+	+
Desflurane	+	+	N
Ketamine	+	+	N
Midazolam	+	+/−	+
Propofol	+	+	N
Thiopental	+/−	+/−	N
Pentobarbital	+	+	+
Xenon	−	N	N
Dexmedetomidine	−	−	−

+ positive, − negative, +/− positive only when combined with other agents, *N* there have been no reports

13.2.2 Neurotoxicity in Clinical Anesthesia

13.2.2.1 Can These Laboratory Data Be Extrapolated to Humans?

This cumulative evidence from animal experiments raises the very difficult question of whether anesthetic and sedative agents also trigger neuropathologic or neurobehavioral sequelae in pediatric patients. Currently, however, it is believed that caution must be exercised in extrapolating the results of animal investigations into human clinical practice, as there are so many confounding factors to be taken into consideration, including the difference in lifespan between animals and humans, the dosages of the anesthetic agents used, and the effects of environment [37, 48].

13.2.2.2 Neurotoxicity of Anesthetic Agents Is Controversial in Human Research

In humans, synaptogenesis commences in the third trimester of pregnancy and extends through several years after birth [11, 12]. Numerous infants and children undergo surgery under general anesthesia. Therefore, whether the anesthetic agents used are potentially neurotoxic is naturally of great concern to the anesthesiologist. Several clinical studies have investigated neurotoxicity in pediatric anesthesia [2, 15, 21, 27, 32, 52, 59]. One group reported that subsequent behavioral and developmental disorders were observed twice as often in children undergoing surgical repair of hernia under general anesthesia before the age of 3 years than in those in a non-surgery group [15]. It was also reported that multiple anesthesia in young children may increase the risk of learning disability compared with in children not exposed to anesthesia [21, 59]. On the other hand, Sprung et al. reported that cesarean delivery under general anesthesia did not increase the risk of learning disability compared with normal delivery [49]. Bartels et al. investigated monozygotic pairs of twins and found that those who were exposed to anesthesia before the age of 3 years had significant learning and cognitive problems compared with unexposed pairs of twins. However, in the same study, when only one of a pair of twins was exposed to anesthesia, no difference was observed in cognitive development. These results suggest comorbidity rather than anesthesia as the cause of learning and cognitive problems later in life [2].

13.2.2.3 Should Anesthetic Methods for Pediatric Patients Be Changed?

As described above, the evidence on neurocognitive dysfunction due to exposure to neonatal anesthesia is conflicting. In the majority of cases, it was impossible to conduct randomized controlled studies from an ethical point of view; furthermore, it was difficult to distinguish the effects of primary disease, clinical characteristics, and surgical procedures from the effects of anesthesia. In addition, it was difficult to standardize the anesthetic method, method of evaluation, outcome, and cultural and social background [52]. Based on these reports, in December 2012, SmartTots released a consensus statement regarding anesthesia safety in children (http://www.smarttots.org/media/smarttots-releases-consensus-statement-regarding-anesthesia-safety-in-children). This statement noted that the neurotoxicity of anesthesia remained to be clarified and that the currently used anesthetic agents and sedatives were necessary in infants and children requiring potentially painful or stressful interventions. Therefore, it would be entirely inappropriate to suggest that anesthesiologists change their anesthetic practice at the present time.

13.3 Neurotoxicity to the Adult Brain

Cognitive complications after surgery and anesthesia can be classified into two categories according to the duration of symptoms: postoperative delirium (POD) and postoperative cognitive dysfunction (POCD). The mechanisms of POD and POCD remain unknown. The neurotoxicity of anesthetic agents is suspected to be involved in the mechanisms underlying these complications, however.

13.3.1 Postoperative Delirium

13.3.1.1 Diagnosis and Prognosis

Postoperative delirium is a transient disturbance of consciousness, attention, cognition, or perception or disorganized thinking [3, 9, 30, 38] (Table 13.2). It can lead to extended periods of hospitalization, increase the incidence rate of complications, delay functional recovery, and increase mortality [17, 26, 36, 38, 58]. The incidence rate of POD varies widely, ranging from 5.1 to 52.2 % [14]. Despite the severe clinical impact of POD, however, its underlying pathophysiological mechanisms remain unknown.

13.3.1.2 Perioperative Risk Factors

It is important to determine what the preoperative and intraoperative risk factors are for POD in addressing this problem [38]. Advanced age has been reported to be the most significant factor [36]. Additional, multiple risk factors have also been investigated, and POD is now considered to be multifactorial. Dasgupta et al. conducted a systematic review of 25 articles and suggested a number of preoperative risk factors associated with POD [14] (Table 13.3). Among types of surgery, orthopedic (e.g., joint replacement and hip fracture) [25, 35] and cardiac [55] carry the highest risk. Bekker et al. reviewed perioperative factors contributing to POD [3] (Table 13.4).

13.3.1.3 Treatment and Prevention

It is also important to recognize and manage the underlying causes such as sepsis, myocardial infarction, abnormal serum glucose and electrolyte levels, dehydration, and malnutrition in treating POD. Adequate ventilation, oxygenation, and sufficient treatment of postoperative pain are important in ensuring a POD-free environment for recovery. Therapeutic measures for the management of POD are shown in Table 13.5.

Table 13.2 Symptoms of POD

Confusion
Disorientation
Cognitive deficits
Fluctuation in level of consciousness
Perceptual deficit
Disturbance of sleep-wake cycle
Hallucinations
Delusions
Anxiety
Fear
Irritability
Anger
Depression

Table 13.3 Preoperative factors associated with POD

Advanced age
Male
Preoperative cognitive impairment
Depression
Psychopathological symptoms
Use of psychotropic drugs
Poor functional status
Sensory impairment
Number of comorbidities
Institutional residence

Table 13.4 Perioperative factors associated with POD

Orthopedic (e.g., hip fracture) or cardiac surgery
Medication
Anticholinergics
Anticonvulsants
Anti-inflammatories
Inhalational anesthetics
Impaired cerebral oxygen supply
Hypotension
Hypoxemia
Anemia
Metabolic abnormalities
Electrolyte imbalance
Hypoglycemia
Hypovolemia
Endocrine disease
Infection/fever
ICU environment

Table 13.5 Prevention and treatment of POD

Prevention
Evaluation and treatment of medical problems
Detailed history of concurrent medications
Adequate cerebral oxygen supply
Avoid anticholinergic drugs
Maintain electrolyte balance
Avoid dehydration
Multicomponent geriatric intervention program
Treatment
Investigate and treat underlying cause
Adequate pain management
Pharmacological treatment
Haloperidol
Benzodiazepines for alcohol and benzodiazepine withdrawal
Supportive measures

13.3.2 Postoperative Cognitive Dysfunction

13.3.2.1 Definition and Prognosis

No standardized accepted diagnostic criteria have yet been established to define POCD [56]. It is often defined, however, as persistent cognitive deterioration, which is clinically diagnosed over a long period of time using various neuropsychological tests [5, 22, 43]. POCD and POD are both associated with aggravation of complications after surgery under anesthesia, which diminishes the quality of life, adds cost to hospitalization, and leads to poor outcomes such as high mortality [19, 23, 41, 45, 46].

13.3.2.2 Etiology

The pathogenic mechanism underlying POCD remains to be clearly elucidated. Systemic neuroinflammation, derangement of metabolism, disruption of the hemodynamics of the brain, and a supply–demand imbalance of oxygen in the central nervous system due to anesthetic exposure or surgical stress have all been postulated as possible causes [6, 10, 13, 28, 54, 57].

13.3.2.3 Perioperative Risk Factors

POCD is often observed as a complication following cardiac surgery [42]. Therefore, the use of cardiopulmonary bypass, low perfusion pressure, hypothermia, microembolisms, and unstable hemodynamics are all considered critical candidate

Table 13.6 Perioperative risk factors for POCD

Advanced age
Prolonged duration of surgery
Lower educational background
Second operation
Postoperative infection
Respiratory complications
Preoperative cognitive dysfunction
Postoperative delirium
Prior cerebrovascular event

mechanisms of POCD [1]. However, POCD is also often observed after noncardiac surgery [3, 40]. Some recent investigations have suggested that POCD might occur regardless of type of surgery [20] or anesthesia (i.e., general vs. regional) [7, 33, 60]. Other suggested risk factors included advanced age, prolonged duration of surgery, respiratory and infectious complications, and the need for a second operation [39, 40] (Table 13.6). Thus, the clinical evidence on POCD remains conflicting, and most of these earlier studies have had problems in terms of sample size and methodology such as differences in the type of surgery investigated, diversity of participants, type of neuropsychological tests used, and working definition of POCD adopted.

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Part IV
General Consideration: Monitoring in Neuroanesthesia

Chapter 14
Role of Electroencephalography for Cerebral Functions in Neuroanesthesia

Taketoshi Maehara

Abstract Electroencephalography (EEG) is the recording of electrical activity along the scalp. EEG is derived from a summation of postsynaptic potentials in the apical dendrites of the pyramidal neurons of the cerebral cortex. While modern neuroimaging techniques are capable of disclosing subtle brain lesions, EEG is still an important tool for examining measures of consciousness, the sleep cycle, the effects of hypoxia on the human brain, and epileptic activity. In this chapter, we describe basic and general information about EEG, the clinical usefulness of EEG, and characteristic EEG readings. We also briefly review how anesthetic agents affect EEG readings.

Keywords EEG • Anesthesia • ECoG • Sleep cycle • Epilepsy • Consciousness disturbance • Anesthetic agents

14.1 Introduction

Electroencephalography (EEG) is the recording of electrical activity along the scalp, first described by Hans Berger (1873–1941) in a report published in 1929 [1]. Electrical activity was recorded on photographic paper continuously over several minutes. Berger's 1929 report even described the alpha rhythm and alpha blocking response. Throughout the next decade, the 1930s, extensive studies on Berger's reports on human EEG led to fruitful results in the measurement of consciousness, the sleep cycle, the effects of hypoxia on the human brain, and epileptic activity [2]. Electroencephalography used to be the most important method for the diagnosis of cerebral disease, before the advent of computed tomography (CT) and magnetic resonance imaging (MRI). While modern neuroimaging techniques are far superior in depicting subtle brain lesions, EEG is still an important tool for examining cerebral dysfunction.

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Digital EEG, a modality that brings more useful EEG findings, is now available at most institutes. Digitally obtained EEG signals can be formatted more flexibly and measured more precisely than traditional analog EEG on paper [3]. Electroencephalography also has the potential to allow assessment of brain function, even in patients under anesthesia. Hence, basic and clinical knowledge of EEG is of great help to anesthesiologists in managing patients during surgery.

14.2 Mechanism of Electroencephalography

The electrical charges of the brain are maintained by billions of neurons, which constantly exchange ions with the extracellular environment. Ions of the same charge repel each other. The phenomenon of volume conduction occurs when large numbers of these ions are pushed out from the neuron population at the same time in a wave. Because this wave of ions reaches the electrodes of the scalp from different angles, each electrode registers a different voltage. Electroencephalography measures differences in the recorded voltages between pairs of electrodes over time.

The electrical potentials of single neurons are so small that it takes millions of neurons with similar spatial orientation acting in sync to product a readable EEG signal. Neurons with different spatial orientations cannot easily produce the volume conduction effect. Most EEG signals are thought to be produced by the pyramidal neurons of the cortex, as these neurons are well aligned and fire together. Electroencephalography signals are derived from the summation of postsynaptic potentials in the apical dendrites of the pyramidal neurons of the cerebral cortex [4].

14.3 Normal EEG

In conventional scalp EEG, electrode locations and names are specified by the International 10–20 system. The EEG voltage signal at each channel reflects a difference between voltages at two electrodes. Montages are representations of EEG channels in series used for examinations (Fig. 14.1). In a referential montage, each channel represents the difference between two reference electrodes (usually at the earlobes: A1, left ear; A2, right ear). In a bipolar montage, each channel represents the difference between two electrodes positioned next to each other. In an average reference montage, the outputs of all of the amplifiers are summed and averaged for use as a common reference [4].

An EEG is composed of frequencies and amplitudes. In the normal adult, the slow range (0.3–7 Hz) and the very fast range (>30 Hz) are little represented. Medium (8–13 Hz) and fast (14–30 Hz) are predominant. These frequencies are called delta wave (0.1–3.5 Hz), theta wave (4–7.5 Hz), alpha wave (8–13 Hz), beta wave (14–30 Hz), and gamma wave (>30 Hz) [4, 5].

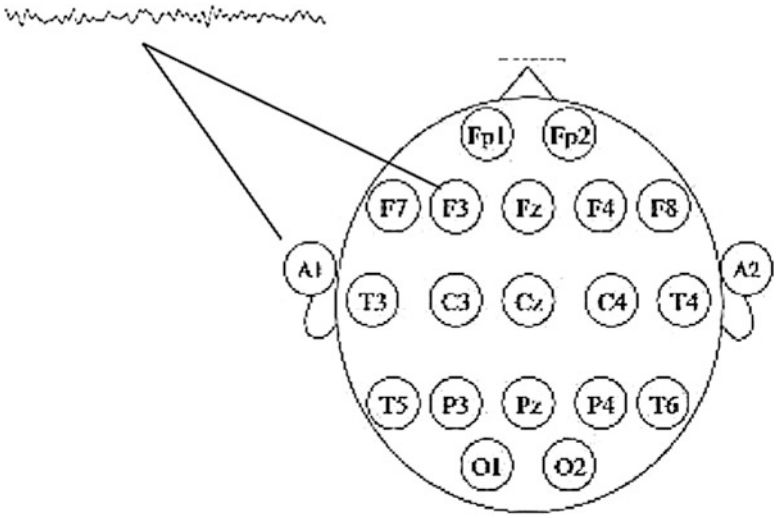

Fig. 14.1 EEG between F3 and A1 in the International 10–20 system

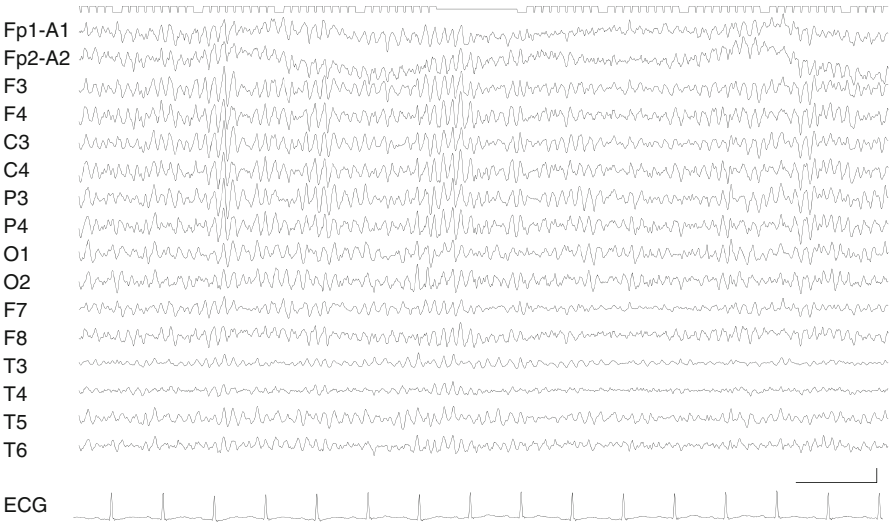

Fig. 14.2 Normal EEG of a waking adult with eyes closed (referential montage). Alpha rhythm is observed over the posterior part of the head

The EEG amplitudes are measured from peak to peak. The amplitudes of the scalp EEG usually lie in a range from 10 to 50 μV in adults. In a normal adult, alpha rhythm is observed over the posterior part of the head when the individual is awake with his or her eyes closed (Fig. 14.2).

14.4 Scalp EEG and Electrocorticography (ECoG)

EEG signals recorded on the cerebral cortex (ECoG) have much larger amplitudes and are sharply demarcated. As higher-frequency activity is attenuated to a greater extent than slower frequencies during transmission to the scalp, most rhythms tend to have a much sharper appearance in ECoG than in EEG. The ECoG contains more prominent and abundant beta potentials than EEG. The amplitudes of ECoG discharges range from 0.5 to 1.5 mV, that is, 5–10 times higher than the amplitudes of EEG [6].

14.5 Sleep Cycle

To avoid misdiagnosis, a physician should understand the characteristic EEG patterns and waves during sleep cycles before attempting to detect EEG abnormalities. Under the classification first applied after the discovery of REM sleep in 1953 [7], sleep stages were divided into non-REM sleep (slow-wave sleep) and REM sleep (paradoxical sleep of fast sleep). Under the present classification, sleep stages and their characteristic waves are designated as follows: Stage 1 (drowsiness), from alpha dropout to vertex waves; Stage 2 (light sleep), spindles, vertex waves, and K complexes (Fig. 14.3); Stage 3 (intermediate sleep), much slowing, K complexes, and some spindles; Stage 4 (deep sleep), much slowing and some K complexes; Stage REM (REM sleep), desynchronization with faster frequencies [5].

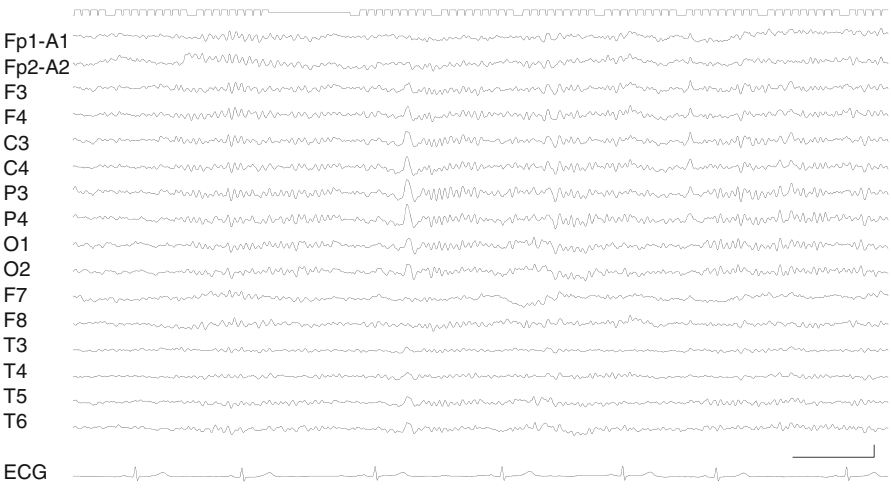

Fig. 14.3 Non-REM (Stage 2) EEG in a normal adult (referential montage). Vertex wave and spindles are observed

14.6 Clinical Use

EEG is an important tool for diagnosing various cerebral conditions such as epilepsy or consciousness disturbances such as encephalopathy, drug intoxication, or delirium. Cerebral ischemic change, severe head trauma, and increased ICP all cause neuronal damage. Decreased EEG frequency, a consequence of attenuated alpha rhythm and enhanced delta and theta waves, therefore serves as a marker of cerebral dysfunction. EEG is used as an adjunct test of brain death [4]. These applications are described in detail in other chapters of this book.

14.6.1 Diagnosis of Epilepsy

EEG is typically described in terms of basic rhythm and transient discharges. Abnormal EEG activity is broadly divided into epileptiform and non-epileptiform activity. It can also be classified as focal and diffuse abnormality. Most patients with temporal lobe epilepsy, for example, show interictal epileptic discharges during Stage 1 or 2 (Fig. 14.4). Activations, such as eye closure, photic stimulation, and hyperventilation, are also used to detect epileptic abnormality. Ictal EEG is an important technique for detecting epileptogenic areas of epileptic brains (Fig. 14.5).

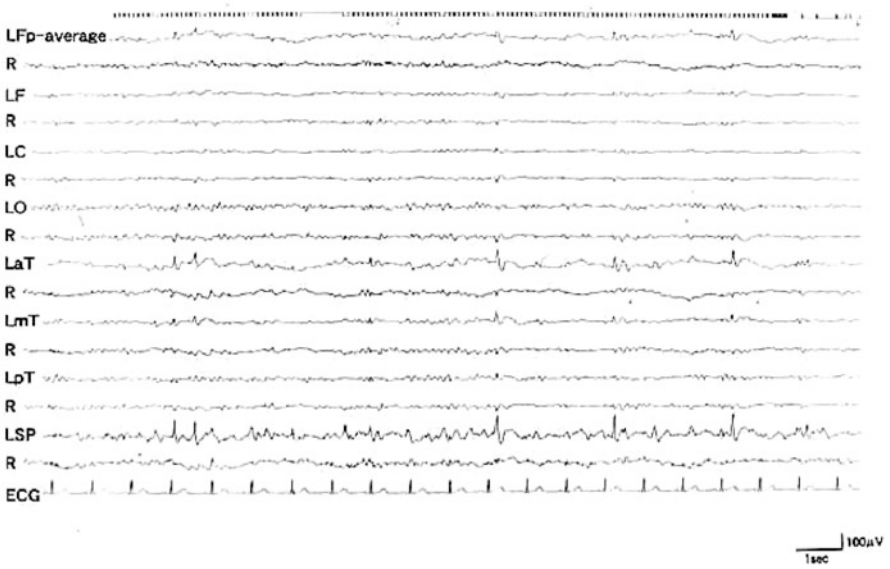

Fig. 14.4 Interictal EEG of a patient with right temporal lobe epilepsy (average reference montage). Spikes are frequently recorded in the right anterior temporal area, especially in the right sphenoidal (SP) electrode

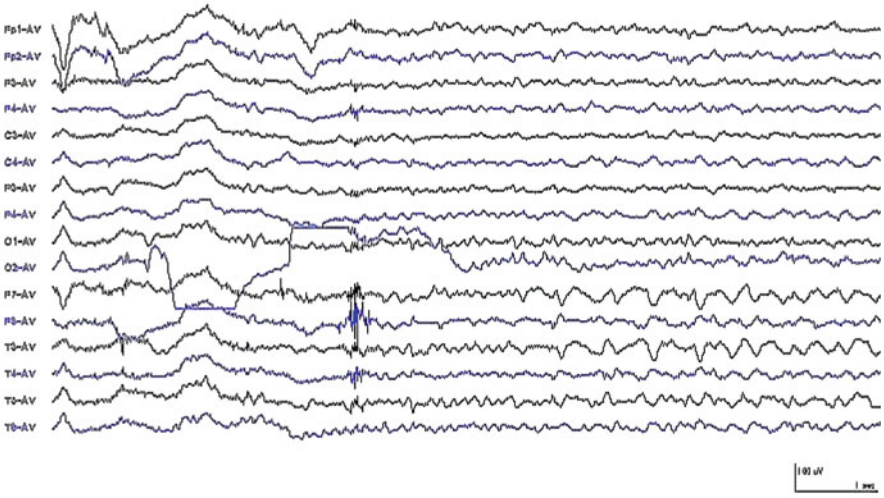

Fig. 14.5 Ictal EEG of a patient with left temporal lobe epilepsy (average reference montage). A rhythmic delta wave is observed in the left temporal area

Intraoperative ECoG is used to define and delineate epileptogenic areas during epilepsy surgery. Volatile anesthetics (desflurane, sevoflurane, halothane, enflurane, and isoflurane) have different pro- and anticonvulsant effects (described later in this chapter). Sevoflurane at 1.5 MAC is effective in enhancing the spike activity of epileptogenic areas during epilepsy surgery [8].

Status epilepticus is caused by various conditions such as encephalopathy, metabolic disease, or acute AED withdrawal during epilepsy treatment. In patients suffering from status epilepticus, rapid seizure cessation is crucial for the prevention of brain damage. Under the recent criteria, a seizure lasting more than 5 min should be regarded as status epilepticus. When intravenous phenobarbital or phenytoin is ineffective, general anesthesia is employed in intensive care units under EEG monitoring setup for burst-suppression activity [9].

14.6.2 Consciousness Disturbance

EEG is an important examination in some patients with consciousness disturbances, even in those without structural brain lesions.

Nonconvulsive status epilepticus (NCSE) is one of the major diseases treated in the neuro ICU. EEG is mandatory for the accurate diagnosis and treatment of NCSE, as it clearly shows ictal epileptic discharges (Fig. 14.6). Consciousness disturbances of various degrees can also result from hepatic encephalopathy caused by liver dysfunction, a disorder of the metabolic central nervous system. Patients with hepatic encephalopathy typically manifest massive EEG slowing, with or

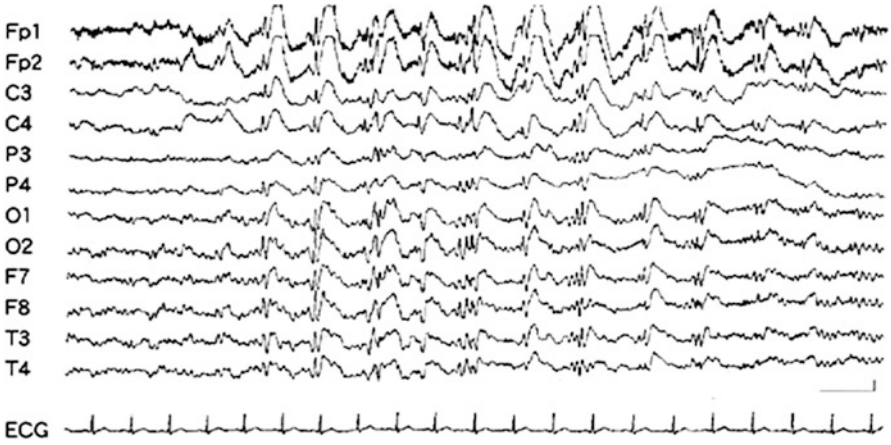

Fig. 14.6 EEG of nonconvulsive status epilepticus in a patient with metabolic disorder (referential montage). Bilateral synchronized spike and waves are continuously recorded

without triphasic waves (Fig. 14.7). Benzodiazepines, a class of agents commonly used as short- and long-term sedatives, are also used for seizure control. The beta activation following administration of benzodiazepines is similar to that seen with barbiturate. This beta activation should not be interpreted as an arousal reaction [10] (Fig. 14.8). Delirium is characterized by an acute change of mental status and consciousness. It is an especially perilous condition in elderly patients during hospital stays or after operations. Slow waves and alpha waves are both observed in EEG. Lastly, EEG is extremely useful for distinguishing delirium from NCSE or psychiatric disorders [11] (Fig. 14.9).

14.7 Effect of Anesthetic Drugs

Brain electrical activity is directly influenced by anesthetic drugs such as anesthetic gases, hypnotics, opioids, sedatives, and muscle relaxants. The effects of these drugs on CBF, CBV, and ICP may also be linked with indirect neuronal effects that alter EEG findings. Most anesthetic agents elicit changes in both the frequencies and amplitudes of EEG signals, usually in a dose-effective manner [10].

14.7.1 General EEG Changes

EEG findings change according to the depth of anesthesia. Desynchronization first appears in the excitatory phase, and then synchronization follows in the early stages of anesthesia. Further slowing and increased suppression follow in the surgical

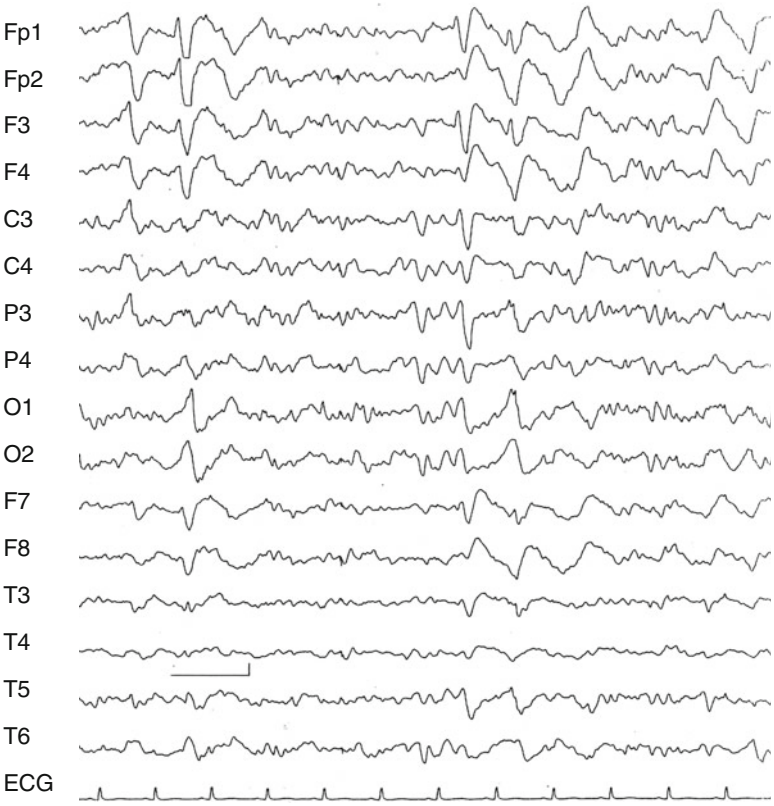

Fig. 14.7 EEG of a patient with hepatic encephalopathy (referential montage). Triphasic waves are observed in the anterior half of the brain

tolerance stage. Burst suppression manifests in an early overdose stage, and general suppression results if the dose reaches a toxic level. As to frequency changes, a loss of alpha and induction of beta component are recorded in the desynchronization state. Synchronization with higher amplitude alpha and theta component follows.

Several drugs elicit exceptional EEG activity at the initial stage. Ketamine elicits a high-amplitude theta activity superimposed with low-amplitude beta components. Propofol induces an initial increase in beta activity followed by increases of theta and delta waves after the onset of sleep. Barbiturates induce an initial increase in fast activity with spindles on EEG.

The volatile anesthetics desflurane, sevoflurane, halothane, enflurane, and isoflurane produce fast wave EEG activity at subanesthetic concentrations followed by slow components with the onset of unconsciousness. Patients given nitrous oxide (NO) may manifest a loss of alpha frequencies at NO concentrations of 30–40 %, followed by increased beta activity at concentrations around 50 % [12]. Later, at NO concentrations of 75–80 %, predominant theta components gradually appear [13].

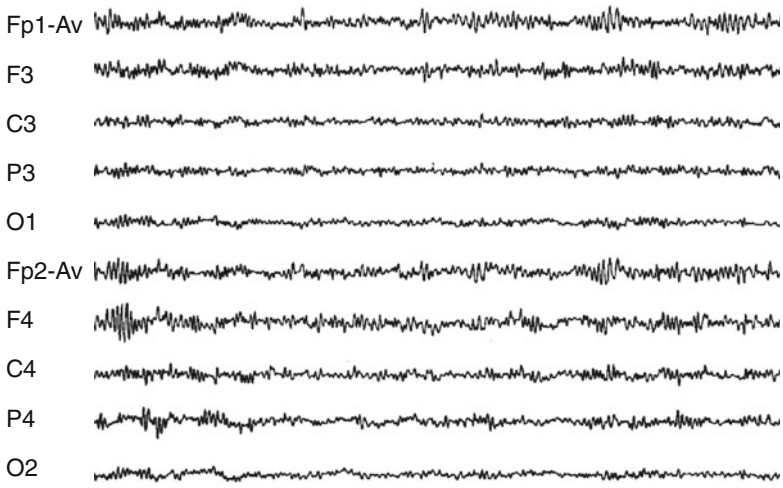

Fig. 14.8 EEG of a patient with benzodiazepine intoxication (average reference montage). Beta waves are diffusely observed

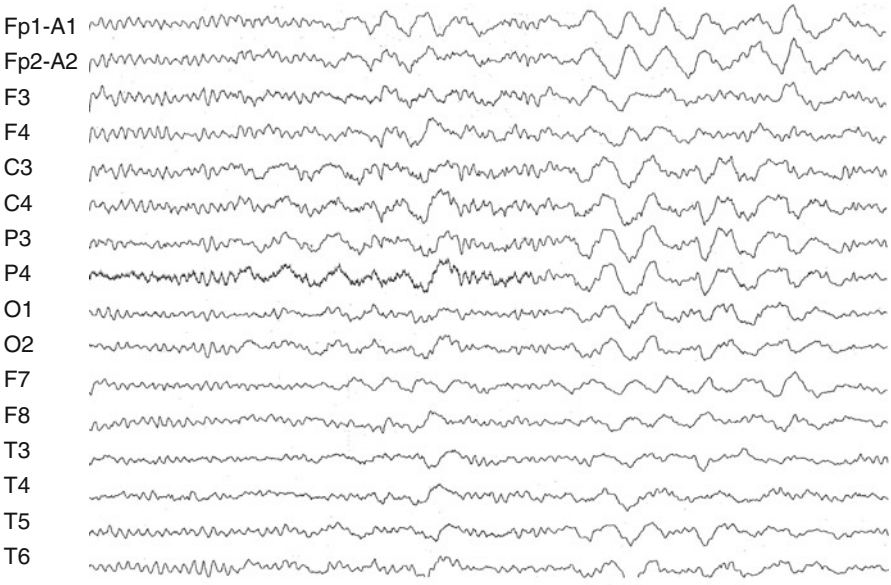

Fig. 14.9 EEG of a patient with delirium (referential montage). Both slow waves and alpha waves are observed in EEG

The EEG activity returns to baseline within 1 h following cessation of NO use. Halothane leads to a progressive slowing of EEG frequencies as the drug concentration rises [14]. At subanesthetic concentrations (<1.2 %) of isoflurane, the EEG frequency is increased, and voltage is slightly decreased.

Opioids cause a dose-dependent slowing of the EEG without initial excitation [15]. Diazepam reduces activity in the theta band and increases activity in the beta band, but the beta activation is lost in the presence of NO, opioids, or volatile anesthetics. Muscle relaxants seem to have no effect on the EEG signals.

14.7.2 Pro- and Anticonvulsive Properties

Halothane elicits no apparent enhancement of epileptiform activity [16]. Isoflurane is also thought to lack seizure-inducing effects. Propofol has anticonvulsant actions [17] and is successfully used as a continuous infusion for the treatment of refractory status epilepticus. Muscle relaxants seem to lack both pro- and anticonvulsant properties.

Unlike the agents just mentioned, there are other anesthetic drugs that may be capable of inducing seizures. Enflurane may cause generalized seizures with characteristic tonic-clonic activity and high-voltage EEG activity in humans, even at concentrations below those necessary for anesthesia [18]. Higher doses (above 4–5 mg/kg) of ketamine are known to lower the epileptic threshold. Sevoflurane has epileptogenic properties that serve well during epilepsy surgery [8].

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Chapter 15
Role and Management of Intracranial Pressure in Neuroanesthesia

Yukio Ikeda, Hiroyuki Uchino, and Ryoichi Miyashita

Abstract In neurological and neurosurgical intensive care and emergency, many pathological conditions are associated with increased intracranial pressure (ICP). The most significant factor for morbidity and mortality is increased ICP. Management of increased ICP is important, and further understanding of the physiology and pathophysiology of ICP is required. General and stepwise specific treatments should be performed to reduce increased ICP.

Keywords ICP (intracranial pressure) • CPP (cerebral perfusion pressure) • ICP monitoring • Neurocritical care

15.1 Introduction

Many pathological conditions are associated with increased intracranial pressure (ICP) in neurological and neurosurgical intensive care and emergency. The most significant factor determining morbidity and mortality in patients with these disorders is increased ICP [1–5].

15.2 Physiology of Intracranial Pressure

Intracranial pressure (ICP) is determined by the volume of three major intracranial components: the brain tissue, cerebrospinal fluid (CSF) volume, and cerebral blood volume. Brain tissue represents 80 % to 85 % of the intracranial volume: it is composed of a cellular component that includes neurons and glia and an extracellular component consisting of the interstitial fluid. CSF volume accounts for 10 %

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to 12 % of the intracranial volume; cerebral blood volume accounts for 4 % to 8 % of the intracranial volume and includes the blood in the vascular space. ICP is measurable in the intracranial subdural, epidural, subarachnoid, and intraventricular spaces. Normally, resting ICP is 0 to 15 mmHg, although straining or coughing can cause transient elevation above 15 mmHg. A sustained ICP greater than 20 mmHg is considered abnormal, with values between 20 and 40 mmHg considered moderate intracranial hypertension, and an ICP greater than 40 mmHg represents severe, usually life-threatening intracranial hypertension [1–3].

15.3 Pathophysiology of ICP

15.3.1 Monro–Kellie Hypothesis

The Monro–Kellie hypothesis is a widely accepted concept for explaining the elevation of ICP. This hypothesis states that the cranium has a fixed amount of space with the three main components. Because all the components are relatively incompressible, an increase in one of the components or introduction of an expanding mass lesion will result in a decrease in the other components so that the total volume remains fixed. If, in any of these abnormal conditions, the volumes are increased beyond compliance, an elevation of ICP occurs [1] (Fig. 15.1).

15.3.2 Intracranial Compliance

Intracranial compliance describes changes in ICP as a function of volume. Intracranial compliance or a change in volume as a function of pressure is a misnomer that is frequently used interchangeably with elastance. Increased intracranial volume is initially compensated by shifts in CSF and blood volume until this

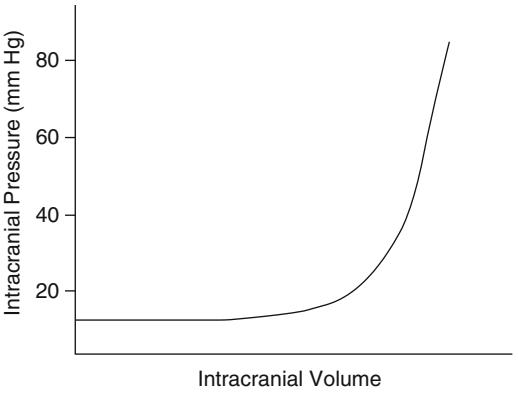

Fig. 15.1 Pressure–volume curve of intracranial elastance. Increased intracranial pressure (ICP) is initially compensated by cerebrospinal fluid and blood volume redistribution until this mechanism is overwhelmed. Subsequently, a small volume increase leads to pronounced ICP increases [5]

mechanism is overwhelmed. Subsequently, small volume increases lead to a pronounced increase in ICP and clinical deterioration [1].

15.3.3 Cerebral Perfusion Pressure (CCP)

CCP can be calculated by subtracting ICP from mean arterial blood pressure (MAP); that is, CPP = MAP−ICP. Normal cerebral perfusion pressure (CPP) is 100 mmHg; the generally accepted lower limit of CPP in a normal patient is 50 mmHg. As ICP increases, CPP decreases, which leads to cerebral ischemia. Cerebral ischemia normally results in the Cushing reflex, which increases MAP. However, this can compensate only up to a certain point, beyond which CPP will fall further, leading to severe ischemia, coma, and death if ICP is uncontrolled [1].

15.3.4 Effect of Anesthetic Agent for ICP (Table 15.1)

If the patient is to undergo surgery, anesthetic management of the "tight brain" requires meticulous strategies that include respiratory management, patient positioning, fluid management, and selection of anesthetic agents. Respiratory management includes avoidance of high peak airway pressure, PEEP (positive end-expiratory pressure), and hypoxia, the maintenance of mild hypocapnia. Patient positioning includes head up, to avoid increased central venous pressure and obstruction of the jugular vein. Fluid management includes isotonic saline administration and hyperosmotic solution. Both volatile and intravenous anesthetic agents

Table 15.1 Effects of anesthetic agents for cerebral metabolic rate of oxygen ($CMRO_2$), cerebrospinal fluid (CBF), intracranial pressure (ICP) autoregulation, and CO_2 reactivity

	$CMRO_2$	CBF	ICP	Autoregulation	CO_2 reactivity
Intravenous anesthetics					
Barbiturate	↓	↓	↓	→	→
Propofol	↓↓	↓	↓	→	→
Ketamine	→↑	→↑	→↑	→	→
Fentanyl	→↓	→↓	→↓	→	→
Remifentanyl	→↓	→↓	→↓	→	→
Dexmedetomidine	→↓	→↓	→↓	→	→
Volatile anesthetics					
Isoflurane	↓	→↑	→↑	↓	→
Sevoflurane	↓	→↑	→↑	↓	→
Desflurane	↓	→↑	→↑	↓	→
NO_2	→↑	→↑	→↑	→↓	→

can be used. Most of the volatile anesthetics and intravenous anesthetics show reduction of the cerebral metabolic rate of oxygen ($CMRO_2$) and autoregulation, and they do not affect CO_2 reactivity. The characteristics of volatile anesthetics such as isoflurane, sevoflurane, and desflurane are to increase CBF and ICP because of vasodilation; however, it is acceptable to use volatile anesthetics of less than 1 MAC because they do not affect the increase of CBF and ICP as much. Intravenous anesthetics, except ketamine, reduce $CMRO_2$ and CBF, which leads to ICP reduction. Total intravenous anesthesia accomplished by propofol is often used for the tight brain, including moderate to severe brain edema. We also should be careful to use propofol with hyperventilation as it has a synergistic action to reduce CBF that risks inducing cerebral ischemia. The effects of these propofol and volatile anesthetics on cerebral hemodynamics have been compared in many clinical trials. According to the meta-analysis on 14 studies (1,819 patients), mean ICP values were lower and CPP values higher with propofol-maintained anesthesia [6]. Available data are inadequate to compare clinically significant outcomes such as neurological morbidity or mortality. Ketamine and NO_2 have the possibility of increasing $CMRO_2$, CBF, and ICP, which may aggravate a tight brain, so we should avoid selecting these drugs for a tight brain patient. Historically, ketamine has not been used to provide sedation in patients with traumatic brain injuries (TBI) because of the risk of increasing ICP in this group of patients. However, of the studies described, some report no increase in intracranial pressure of TBI patients receiving ketamine for sedation when ventilation is controlled [7, 8]. Potential advantages of ketamine administration compared with opioids are maintenance of hemodynamics and cerebral perfusion pressure. However, the role of ketamine as a neuroprotective agent in humans remains inconclusive, and adequately powered, randomized controlled trials performed in patients undergoing surgery for TBI are necessary.

15.3.5 Abnormal ICP Waveforms

In patients with increased ICP, pathological ICP waveforms may occur. Lundberg A waves (plateau waves) are characterized by an abrupt elevation in ICP for 5 to 20 min, followed by a rapid fall in pressure to resting levels. The amplitude may reach 50 to 100 mmHg. Plateau waves are considered a high risk of further brain injury, with critically reduced perfusion as a result of a prolonged period of high ICP crisis. A high ICP crisis often occurs abruptly when either CPP or intracranial compliance is low. Lundberg B waves are shorter-duration, lower-amplitude elevations in ICP that indicate that intracranial compliance reserves are simply compromised. C waves are rhythmic variations related to the Traub–Meyer–Hering waves of systemic blood pressure and have a smaller amplitude. B and C waves have questionable clinical significance [1, 2] (Fig. 15.2).

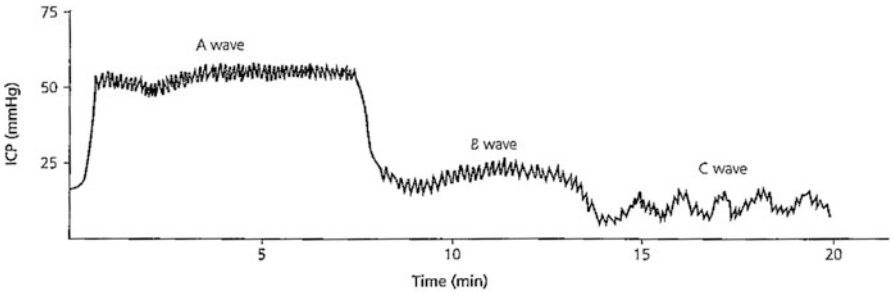

Fig. 15.2 Abnormal ICP waveforms [2]

15.4 Clinical Manifestations of Intracranial Hypertension and Herniation Syndromes

Clinical manifestations of intracranial hypertension often depend on the underlying etiology. In general, intracranial hypertension is global or bilateral rather than focal. Disturbance of consciousness such as confusion, disorientation, blurred vision, headache, nausea, vomiting, diplopia, and sixth cranial nerve palsy are typical clinical manifestations. In the late phase of intracranial hypertension, different herniation syndromes (cingulated, tentorial, central, and tonsillar) with characteristic signs can occur, which are manifested by irregular breathing patterns, decorticate rigidity, hemiplegia, and papillary inequality [1, 2] (Fig. 15.3).

15.5 ICP Monitoring

15.5.1 Indication of ICP Monitoring

Indications for ICP monitoring include a Glasgow Coma Score (GCS) of 8 or less after resuscitation combined with any of the following: abnormal computed tomography (CT) findings, a systolic blood pressure of 90 mm Hg or less, or age more than 40 years. The two most common indications for ICP monitoring are closed severe head injury and subarachnoid hemorrhage. ICP monitoring is also recommended in barbiturate therapy and hypothermia therapy. Severe coagulopathy is the only major contraindication to ICP monitoring [3, 4].

15.5.2 Method of ICP Monitoring

There are several types of ICP monitoring devices, two of which are commonly available in contemporary neurosurgical practice. The ventriculostomy catheter

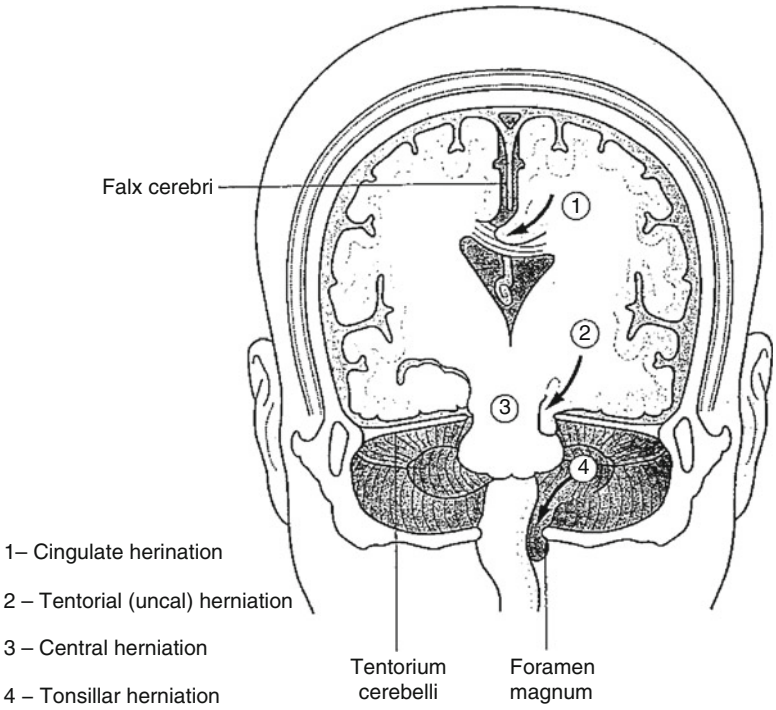

Fig. 15.3 Types of brain herniation [2]

remains the preferred method for ICP monitoring. This method provides the most reliable measurement of ICP throughout both normal and pathological ranges. The major advantage of this method is that the ventricular catheter is used both to measure the pressure and for therapeutic CSF drainage. The ventricular catheter should be tunneled under the skin and brought out through a separate stab wound, well away from the ventricular entry site, to minimize the risk of infection, which is the most serious complication of intraventricular pressure monitoring. The efficacy of prophylactic antibiotic therapy during ICP monitoring has not been determined. The second commonly available method is the fiberoptic transducer-tipped catheter system placed through a burr hole into either the parenchyma or the ventricle. This method may carry less risk of infection but does not allow therapeutic CSF drainage [1].

15.6 Treatment of Intracranial Hypertension

15.6.1 General Measures for ICP Control

High fever may potentiate brain injury and contribute to increased ICP. A high fever should be controlled with acetaminophen and cooling blankets. Seizures are also an important factor to consider during elevated ICP. For patients at risk of seizures, it is quite reasonable to administer prophylaxis with an intravenous anticonvulsant. Fluid management is also important in ICP control. Dehydration will worsen hypoxic-ischemic injury to lead to the reduction of CPP. Patients with high ICP should be kept euvolemic with isotonic saline [1, 3].

15.6.2 Head Elevation

The head should be elevated to 20–30° in patients with increased ICP to maintain optimal conditions for cerebral venous return. The effect of head elevation on ICP has been well documented, although it remains controversial as to the best head position for maintenance of optimal CPP [1, 4].

15.6.3 Hyperventilation

Hyperventilation can be a very effective therapeutic modality to rapidly reduce ICP. It is useful in acute situations and is routinely used in clinical practice. The mechanism of action of hyperventilation is to cause vasoconstriction, which reduces the cerebral blood volume and reduced ICP. However, there are two controversial aspects on the use of hyperventilation: the degree of hyperventilation and the importance of prolonged or chronic hyperventilation. Extreme hyperventilation is generally considered harmful because of the risk of exacerbation of ischemia. A recent trial of hyperventilation in patients with severe head injury concluded that hyperventilation for 5 days was deleterious. Thus, efforts should be made to avoid prolonged continuous hyperventilation [1–5].

15.6.4 Ventricular Drainage

Ventricular drainage is the simplest, most effective, and quickest method of decreasing ICP. In patients with increased ICP, this method is useful for ICP monitoring and for continuous or intermittent drainage of CSF [1–3].

15.6.5 Osmotic Diuretics and Hypertonic Saline

Mannitol, the osmotic diuretic most commonly used, is given as an intravenous bolus infusion and maximally reduces the ICP within 10 min. The reduction in ICP usually persists for 3 to 4 h. The mechanism of ICP reduction by mannitol may be related to its osmotic effect in shifting fluid from the brain tissue compartment to the intravascular compartment, as well as its ability to improve blood rheology by decreasing blood viscosity. Hypertonic saline has been increasingly used to control high ICP caused by brain swelling. Experimental and clinical studies suggest that it may be as effective as mannitol [1–5].

15.6.6 Pentobarbital

Failure of hyperventilation and mannitol to control ICP should prompt consideration of initiation of pentobarbital infusion. The mechanism of action of pentobarbital is a profound reduction of the cerebral metabolic rate. The most common complication of pentobarbital therapy is hypotension resulting from its cardiac suppression, although ileus may also occur. Hypotension caused by pentobarbital is treated with volume replacement, followed by dopamine if necessary [1, 3].

15.6.7 Hypothermia

Induced hypothermia to 32 ° to 34 °C (mild to moderate hypothermia) can effectively lower refractory ICP. Hypothermia can be achieved using various surface and endovascular cooling methods. Therapeutic hypothermia has been clinically demonstrated to control ICP, although complications may include nosocomial infection, hypotension, cardiac arrhythmias, coagulopathy, shivering, hypokalemia, hyperglycemia, and ileus. Particular caution should be taken during rewarming. Rapid rewarming may induce rebound ICP and must be performed slowly [1].

15.6.8 Other Therapies

Steroids are used to reduce increases in ICP, especially those related to vasogenic edema caused by primary or metastatic brain tumors. They are ineffective in the management of brain edema caused by head injury or cerebral infarction, although several randomized clinical trials failed to demonstrate that they improve outcomes or reduce ICP. Steroids can promote some complications, and they are not recommended for the treatment of increased ICP. Cranial decompression can

preserve brain tissue displacement and herniation and effectively improve and usually normalize ICP. Several studies have found that hemicraniectomy definitely improves survival after malignant cerebral infarction. A meta-analysis of hemicraniotomy for malignant infarction found that survival with a good functional outcome is most likely among younger patients [1, 3, 4].

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Chapter 16
Role of Jugular Venous Oxygen Saturation in Neuroanesthesia

Teruyuki Hiraki and Kazuo Ushijima

Abstract Although it is difficult to directly evaluate cerebral blood flow (CBF) and cerebral metabolism in patients that are at a risk of cerebral ischemia, measuring jugular venous oxygen saturation ($SjvO_2$) allows clinicians to determine the relationship between them [1, 2]. Catheters containing optical fibers are used for continuous $SjvO_2$ monitoring, and it was found that normal $SjvO_2$ values range from 55 to 75 % [3–5]. Low $SjvO_2$ levels are indicative of an increase in cerebral metabolism relative to CBF or of ischemia or hypoperfusion, which induces decreases in CBF relative to cerebral metabolism. In contrast, high $SjvO_2$ levels indicate either a decrease in cerebral metabolism relative to CBF or hyperemia, which induces increases in CBF relative to cerebral metabolism. As $SjvO_2$ is influenced by respiratory and circulatory dynamics, metabolic factors, the hemoglobin concentration, arterial carbon dioxide partial pressure, and arterial oxygen partial pressure, these factors must be considered when interpreting fluctuations in $SjvO_2$ levels. In this chapter, the usefulness of $SjvO_2$ monitoring, the significance of abnormal $SjvO_2$ levels, and relevant countermeasures are reviewed.

Keywords Jugular venous oxygen saturation • Cerebral blood flow • Cerebral ischemia

16.1 Introduction

Measurement of jugular venous oxygen saturation ($SjvO_2$) involves placing a catheter in the internal jugular vein bulb to allow continuous monitoring of the balance between cerebral circulation and cerebral oxygen metabolism [1, 2]. Combining various parameters such as intracranial pressure makes it possible to evaluate intracranial information in a range of pathologies. However, $SjvO_2$ is not suitable for understanding pathologies in localized areas of the brain. It is important

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to understand that $SjvO_2$ represents the overall balance between cerebral circulation and oxygen metabolism [6].

16.2 Monitoring Methods

16.2.1 Equipment

To evaluate $SjvO_2$, a catheter for oxygen saturation measurement, a sheath and introducer, and an oxygen saturation measuring device are required [3–5]. A system for delivering a continuous infusion of heparinized saline solution, which prevents coagulation within the catheter, is also necessary. Many facilities use a Vigilance II Monitor (Edwards Lifesciences Corporation, Irvine, CA) as the main measuring device. As no catheters for $SjvO_2$ measurement are currently available in Japan, many institutions use Swan–Ganz catheters, which were designed for use in children (Small French Oximetry Catheter 040HF4, Edwards Lifesciences Corporation).

Measurement of $SjvO_2$ involves directing two different wavelengths of light along an optical fiber filament within a catheter toward the blood flowing through the catheter tip. The light is then reflected back off the red blood cells within the blood and onto a photosensor in another optical fiber filament. As the degree of absorption of the two wavelengths of light differs depending on the deoxyhemoglobin/oxyhemoglobin state of the red blood cells, $SjvO_2$ can be assessed by analyzing the reflected non-absorbed light (Fig. 16.1).

16.2.2 Catheter Placement

It is important to note that the routine maneuvers used to insert catheters via the internal jugular vein, such as the Trendelenburg position, might be ill-advised in patients with elevated intracranial pressure. Instead, the sheath should be inserted in either a head-up or flat position under ultrasound guidance [6–9]. Although even a small amount of arterial pressure can lead to prostration or deviation of the carotid artery when venipuncture is performed while palpating the carotid artery, the operator can also adjust the force applied by visual confirmation.

While there is no consistent opinion regarding whether the catheter should be inserted into the left or right side of the internal jugular vein bulb, it is normally inserted into the right side because this is usually the side of dominant drainage from the brain to the jugular vein [10, 11].

The patient is placed in the supine position with their head turned left to expose the right side of their neck and to keep their chin from interfering with the procedure. The internal jugular vein lies in the groove between the clavicular and

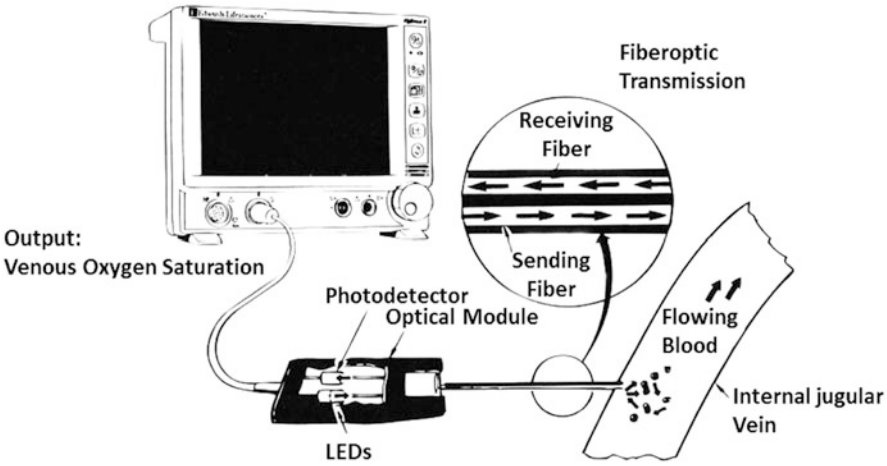

Fig. 16.1 Reflection spectrophotometry (Modified and reprinted with permission from *Quick Guide To Cardiopulmonary Care, Edwards Lifesciences Corporation*)

sternal heads of the sternocleidomastoid muscle. The needle is inserted at the apex of the triangle formed by the two heads of the sternocleidomastoid muscle and the clavicle. An intravascular catheter can then be inserted retrogradely, via the internal jugular vein, into the jugular bulb [12]. The catheter tip must be positioned in the internal jugular vein bulb (Fig. 16.2). The further the catheter tip is from the internal jugular vein bulb, the more external jugular vein blood contamination occurs (Fig. 16.3) [1, 13]. If the needle is inserted at the apex of the triangle formed by the two heads of the sternocleidomastoid muscle, the distance from the insertion site to the internal jugular vein bulb area is approximately 15 cm [4]. However, the operator will encounter some resistance if the catheter is inserted to this distance; thus, it should be withdrawn by approximately 5 mm so that the light intensity can be checked.

16.2.3 Checking the Position of the Catheter

The position of the catheter tip can be confirmed with a plain skull roentgenogram (frontal and lateral images) [14]. The tip should be primarily located in the center of the orbit on the frontal view and between the external acoustic foramen and mastoid process on the lateral view.

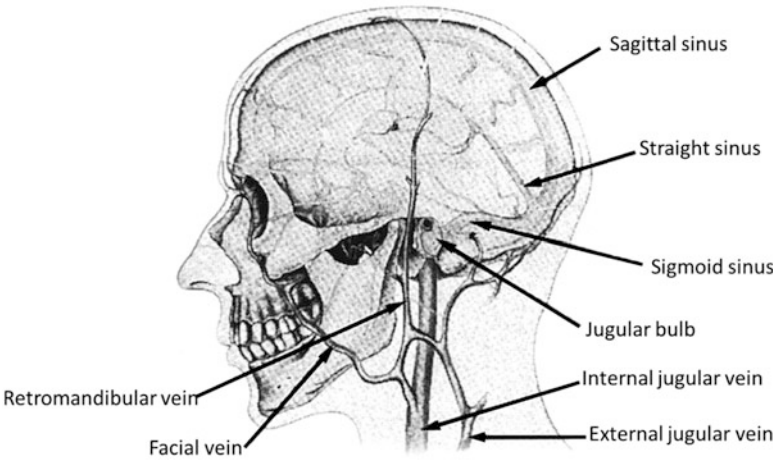

Fig. 16.2 Cerebral veins and dural sinuses. The jugular bulb is the dilated portion of the jugular vein just below the base of the skull that contains blood and shows little extracerebral contamination (15)

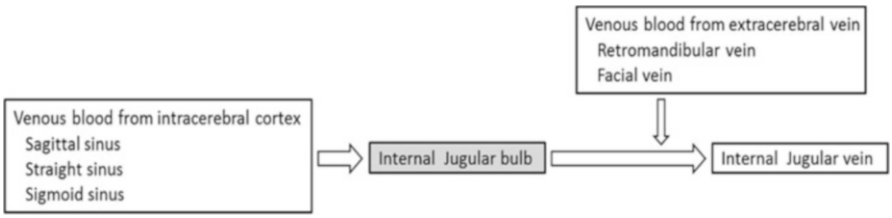

Fig. 16.3 Internal jugular bulb

16.3 What $SjvO_2$ Monitoring Reveals

$SjvO_2$ is determined by cerebral blood flow (CBF) and cerebral oxygen metabolism. In general, the relationship between the cerebral metabolic rate of oxygen ($CMRO_2$) and $SjvO_2$ is expressed by the following equation (SaO_2 = arterial oxygen saturation, Hb = hemoglobin): $SjvO_2 = SaO_2 - CMRO_2/(1.39 \times Hb \times CBF)$.

If SaO_2 and Hb are fixed, $SjvO_2$ is considered to represent the ratio of CBF to $CMRO_2$. Accordingly, low $SjvO_2$ levels indicate either an increase in cerebral metabolism relative to CBF or ischemia or hypoperfusion, in which decreases in CBF relative to cerebral metabolism occur. Moreover, high $SjvO_2$ levels indicate either a decrease in cerebral metabolism relative to CBF or hyperemia, in which increases in CBF relative to cerebral metabolism develop. Thus, $SjvO_2$ levels reflect both cerebral oxygen metabolism and cerebral circulation. The factors that

Table 16.1 Factors influencing $SjvO_2$

Decrease in $SjvO_2$	Increase in $SjvO_2$
1. Decrease in CBF	1. Increase in CBF
Sudden hypotension	Sudden hypertension
Hypotension with autoregulation impairment	Hypertension with autoregulation impairment
Hypocapnia	Hypercapnia
Increased blood viscosity	Decreased blood viscosity
Intracranial hypertension	
Cerebral vasospasm	
2. Increase in $CMRO_2$	2. Decrease in $CMRO_2$
Hyperthermia	Hypothermia
Seizures	General anesthesia
	Sedatives
3. Decrease in CaO_2	3. Increase in CaO_2
Decreased SaO_2, hypoxia	Increased SaO_2
Decreased hemoglobin	Increased hemoglobin
Anemia	Polycythemia

$SjvO_2$ = jugular venous oxygen saturation, *CBF* = cerebral blood flow, *$CMRO_2$* = cerebral metabolic rate of oxygen, *CaO_2* = arterial oxygen content, *SaO_2* = arterial oxygen saturation

cause variations in $SjvO_2$ levels must be continuously managed (Table 16.1, Fig. 16.4) [15].

16.4 Clinical Utility of $SjvO_2$

Table 16.2 shows the indications for $SjvO_2$ monitoring.

16.4.1 Head Injury

Serious cranial trauma decreases CBF rather than cerebral metabolism within a few hours of injury. During this time, the patient's intracranial pressure might increase because of cerebral hematoma and/or edema. Under such circumstances, without lowering CBF, the patient's intracranial pressure should be reduced by various methods such as head elevation, hyperventilation, the administration of osmotic diuretics, brain hypothermia, or surgery (e.g., ventricular drainage or decompressive craniectomy) [16–20]. However, head elevation and hyperventilation carry the risk of reducing CBF. Therefore, in hyperventilation therapy, the patient's breathing rate should be adjusted so that the $SjvO_2$ value does not fall below 55 % [21–24].

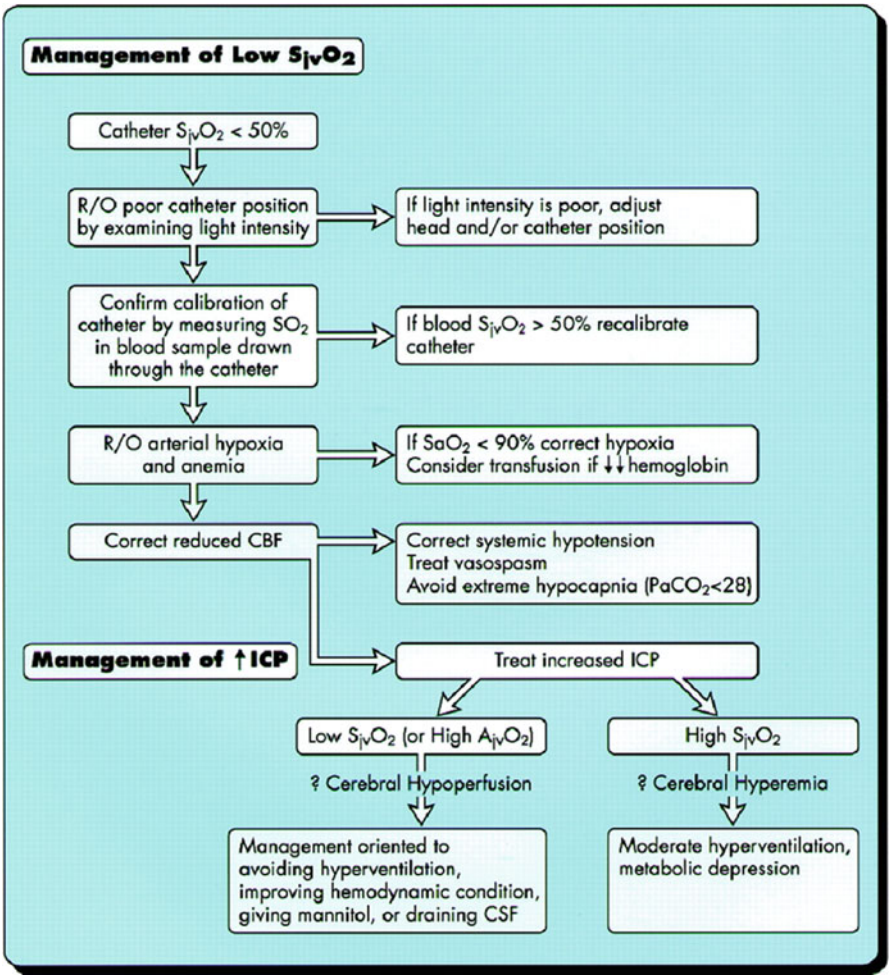

Fig. 16.4 Management of low $SjvO_2$. $SjvO_2$ = jugular venous oxygen saturation, R/O = rule out, SaO_2 = arterial oxygen saturation, CBF = cerebral blood flow, $PaCO_2$ = arterial partial pressure carbon dioxide, $AjvDO_2$ = the difference in oxygen content between simultaneously drawn samples of arterial and jugular venous blood (Reprinted with permission from *Schell (6)*)

16.4.2 Cerebrovascular Disease

Cerebral hemorrhaging and infarction induce abnormalities in local cerebral circulation and metabolism. However, unless they lead to increased intracranial pressure or extensive infarction, they do not affect the cerebral circulation or metabolism throughout the brain. Therefore, $SjvO_2$ monitoring is only useful when managing cases involving increased intracranial pressure or when conducting brain hypothermia therapy.

Table 16.2 Indications for $SjvO_2$ monitoring

1. Intracranial hypertension (especially severe head injury) – hyperventilation
2. Cardiovascular surgery with cardiopulmonary bypass
3. Neurological surgery
Carotid endarterectomy
Cerebral aneurysm clipping during temporary occlusion
Cerebral arteriovenous malformation extraction – evaluation of shunt blockage
4. Resuscitation from cardiopulmonary arrest – prognostic evaluation

$SjvO_2$ = jugular venous oxygen saturation

In cases involving subarachnoid hemorrhages, delayed cerebral vasospasm develops, resulting in cerebral infarction. As this is also a localized pathology, it is difficult to detect by $SjvO_2$ monitoring.

16.4.3 Neurological and Cardiovascular Surgery

$SjvO_2$ monitoring has been reported to be useful during various types of neurosurgical surgery, including carotid endarterectomy [25] and aneurysm surgery [26]. During the surgical extraction of arteriovenous malformations, $SjvO_2$ drops as the arterial inflow is cut off. Thus, $SjvO_2$ levels indicate the extent of arteriovenous shunt blockage to some degree [27, 28].

In cardiac surgery, the measurement of $SjvO_2$ revealed that oxygen desaturation during rewarming while the patient remained on cardiopulmonary bypass was associated with postoperative cognitive dysfunction [29–34].

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Chapter 17
Role of Microdialysis in Neuroanesthesia

Yasuhiro Kuroda, Nobuyuki Kawai, and Kenya Kawakita

Abstract Brain microdialysis is a well-established technique used to monitor the chemistry of the extracellular space in the brain during neurointensive care. Microdialysis may be useful in severe cases of traumatic brain injury, stroke, and hypoxic brain injury in which monitoring of intracranial pressure and cerebral perfusion pressure is required. The parenchymal concentrations of glucose, lactate, pyruvate, glutamate, and glycerol can be measured at the bedside. As the primary source of energy, glucose is an important marker of changes in cerebral metabolism and reflects systemic supply, which is influenced by capillary perfusion, ischemia, and blood glucose concentration. The lactate–pyruvate (L/P) ratio is a sensitive marker of changes in the redox state of cells brought about by ischemia. The glutamate concentration is an indirect marker of cell damage or ischemia. Glycerol concentration reflects cell membrane damage, as glycerol is an integral component of cell membranes. Loss of energy due to ischemia eventually leads to an influx of calcium and a decomposition of cell membranes, which liberates glycerol into the interstitial fluid. Microdialysis, when used with other brain monitoring techniques, may be a useful means of preventing and relieving secondary ischemic injury, predicting outcome and guiding therapy after severe brain damage. However, the value of microdialysis as a tool in routine neurointensive care decision-making remains unclear.

Keywords Microdialysis • Glucose • Lactate • Pyruvate • Glycerol

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17.1 Introduction

Brain microdialysis monitoring can detect adverse neurochemical conditions involving hypoxia/ischemia and seizure activity in subarachnoid hemorrhage (SAH), traumatic brain injury (TBI), thromboembolic stroke, and epilepsy. The measurement of parenchymal concentration of glucose, lactate, and pyruvate is used to quantify disturbances of cerebral glucose metabolism, and techniques are being developed to quantify excitotoxicity, cell membrane degradation, cellular edema, and blood–brain barrier dysfunction, although these need additional validation. The clinical utility of microdialysis depends on the choice of biomarkers, their sensitivity, specificity, and predictive value for secondary neurochemical events.

17.2 Principles of Microdialysis

Brain microdialysis requires a specialized catheter to be placed in the brain parenchyma. It is tipped with a semipermeable dialysis membrane, usually with a 20 kDa molecular weight cutoff (Fig. 17.1). The microdialysis catheter can be placed in areas of interest, which is of particular value when therapy is directed at attenuating secondary insults around the brain tissue at risk. The catheter tip should be located in the right frontal lobe after global hypoxic injury (e.g., post-cardiac arrest syndrome or diffuse TBI), the penumbral area of an ischemic stroke, the vascular territories of a ruptured cerebral aneurysm, or the pericontusional area of a focal TBI (Fig. 17.2). The microdialysis catheter is constantly perfused with a cerebrospinal fluid-like solution at a rate of 0.3 μL/min, thereby allowing regular (usually hourly) sampling of the patient's brain extracellular fluid into microvials and subsequent analysis at the bedside using a proprietary device [1].

17.3 Clinical Application of Microdialysis and Interpretation of Results

The time taken to analyze the samples means that in practice, the first results are not available until at least 1 h after catheter insertion, but thereafter, new technology allows online monitoring of dynamic changes in patients' neurochemistry. The small molecules demonstrated to have clinical utility as neurochemical markers used in the management of secondary cerebral injury are glucose, lactate, pyruvate (and the ratio between them, known as the L/P ratio), glutamate, and glycerol. Microdialysate glucose concentration depends on blood glucose and the blood supply to the region of interest. The L/P ratio is a sensitive marker of changes in the redox state of cells caused by ischemia (Fig. 17.3). Microdialysate glucose,

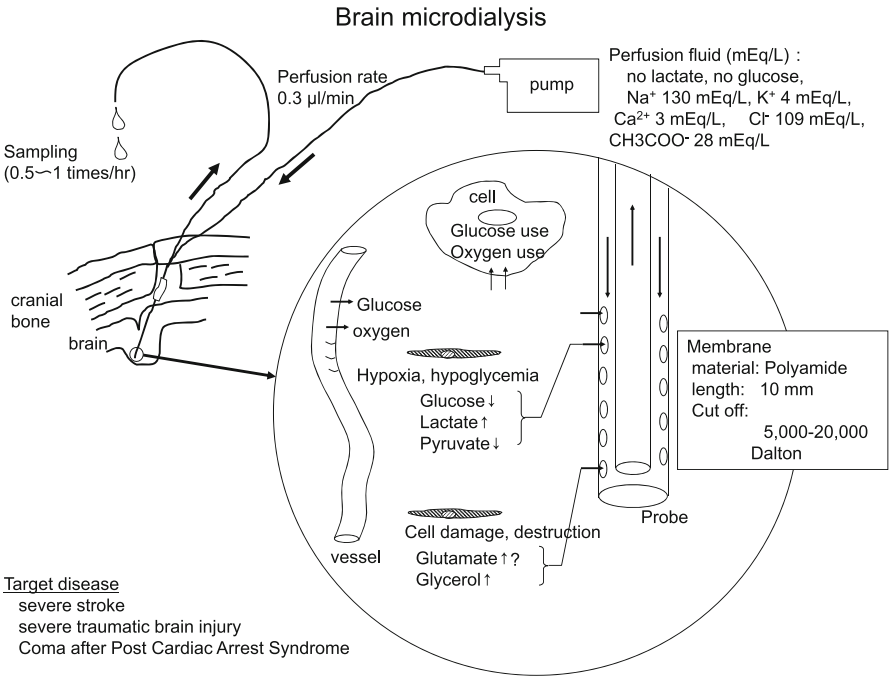

Fig. 17.1 Brain microdialysis

lactate and pyruvate concentrations, and L/P ratio may be indicators of secondary complications caused by persistent hypoxia or ischemia. Changes in the L/P ratio are classified into type 1 (in the presence of ischemia, implying anaerobic glycolysis) and type 2 (without ischemia, implying dysfunctional glycolysis; Fig. 17.4). Glutamate is a marker of ischemia and reflects excitotoxicity in the brain. Microdialysate glycerol concentration is a marker of cell membrane disruption and cell lysis, but may be affected by the use of glycerol as an intravenous osmotic diuretic.

Abnormal concentrations of molecules of interest in microdialysate fluid are considered to be: glucose $<$ 0.7–1 mmol/L, glutamate 10–20 μmol/L, and glycerol 100 μmol/L. An L/P ratio $>$35–40 is also considered abnormal (Table 17.1) [2, 3]. Biochemical changes observed in neurocritical care, including nonischemic glycolysis (Fig. 17.4) [4], are summarized in Table 17.2 [1]. A typical ischemic pattern includes a marked decrease in microdialysate glucose concentration, an increase in L/P and lactate/glucose ratios, and a moderate increase in brain lactate and a decrease in brain pyruvate concentrations [1]. Persistent episodes ($>$25 min) of profound brain tissue hypoxia (brain tissue oxygen tension [$PbtO_2$] $<$10 mmHg) are associated with marked metabolic changes (including decreased microdialysate glucose concentration and elevated L/P ratio) [5].

The degree of metabolic distress or crisis is reflected by the extent of the difference between energy supply and demand. Metabolic distress is commonly

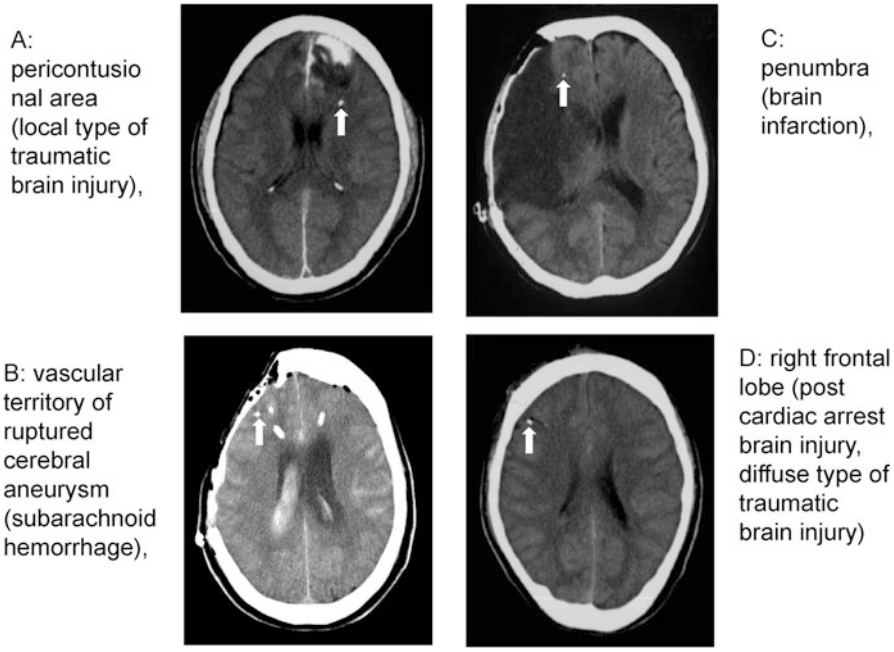

Fig. 17.2 Microdialysis probe location: (**a**) pericontusional area (focal traumatic brain injury), (**b**) vascular territory of ruptured cerebral aneurysm (subarachnoid hemorrhage), (**c**) penumbra (brain infarction), and (**d**) right frontal lobe (post-cardiac arrest brain injury, diffuse traumatic brain injury)

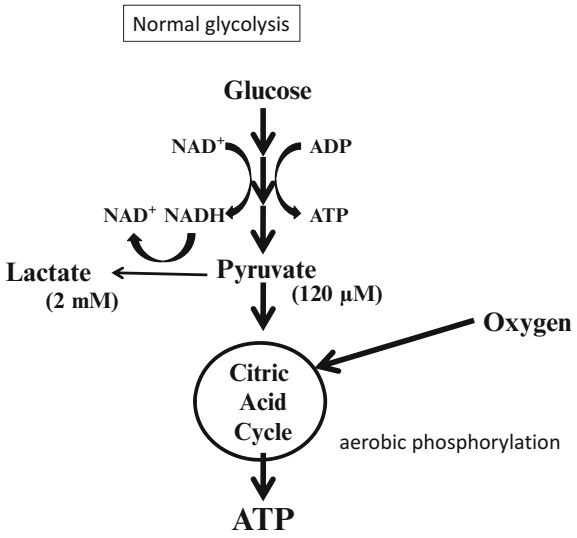

Fig. 17.3 Normal glycolysis

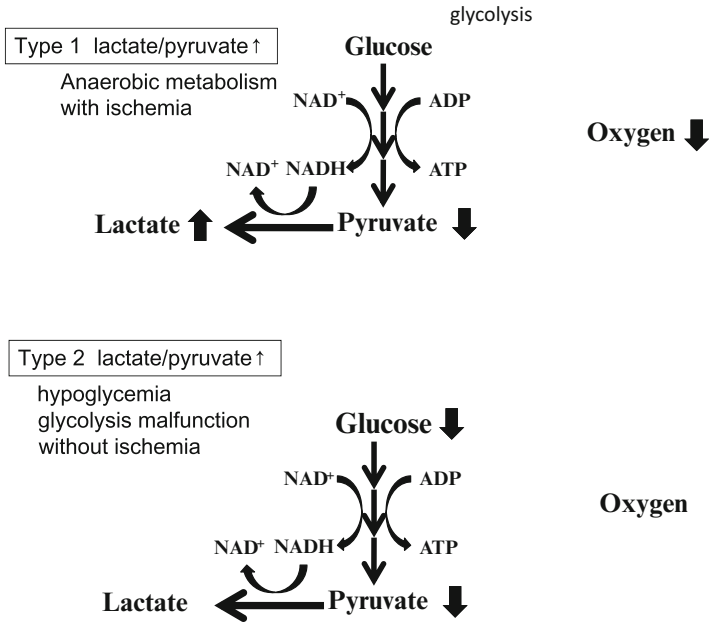

Fig. 17.4 Abnormal glycolysis and elevations in lactate–pyruvate ratio

Table 17.1 MD concentrations of each parameter in normal or ischemic human brain

Condition (perfusion rates)	Glucose (mmol/L)	Lactate (mmol/L)	Pyruvate (μmol/L)	Lactate/ pyruvate ratio	Glutamate (μmol/L)	Glycerol (μmol/L)
Anesthetized (1.0 μl/min)	1.2 ± 0.6	1.2 ± 0.6	70 ± 24	22 ± 6	17 ± 12	28 ± 16
Awake (1.0 μl/min)	0.9 ± 0.6	1.4 ± 0.9	103 ± 50	21 ± 6	7 ± 5	42 ± 29
Awake (0.3 μl/min)	1.7 ± 0.9	2.9 ± 0.9	166 ± 47	23 ± 4	16 ± 16	82 ± 44
Ischemia (0.3 μl/min)	0.1 ± 0.2	8.9 ± 6.5	31 ± 47	458 ± 563	381 ± 236	573 ± 427
Metabolic distress				>40		
Metabolic crisis	<0.7			>40		

Mean ± SD
Stahl (2001: 977) and Reinstrup (2000: 701)

defined as an L/P ratio >40, whereas metabolic crisis comprises a combination of L/P ratio >40 and microdialysis glucose concentration <0.7 mmol/L (Table 17.1) [1].

Table 17.2 Microdialysis parameters

MD parameter	Change direction	Interpretation	Etiology	Intervention
Glucose	Decrease	Reduced capillary perfusion	Ischemia/hypoxia, vasospasm, edema, ICP crisis, hyperventilation	Increasing brain perfusion (address vasospasm, improve CPP, osmotherapy, normocapnia)
		Decreased systemic supply	Decreased or normal blood glucose	Adjustment of blood glucose
		Increased cellular uptake of glucose	Seizure, ICP crisis, shivering	Antiepileptic drugs, osmotherapy, antishivering management, sedation
	Increase	Hyperemia	Reperfusion	No specific intervention needed
		Increased systemic glucose level (supply)	Hyperglycemia	
		Decreased cellular metabolism	Deep sedation	
Lactate	Increase	Anaerobic metabolism	Ischemia/hypoxia, ICP crisis, hyperventilation	
L/P	Increase with decreased pyruvate	Marker of ischemia	Ischemia/hypoxia, vasospasm, edema, ICP crisis, hyperventilation	Improving brain perfusion, osmotherapy, blood transfusion (?), normocapnia
		Decreased oxygen delivery	Hypoglycemia	Adjustment of blood glucose
		Decreased glucose supply	Glycolysis malfunction without ischemia	Improving glycolysis (?)
		Nonischemic glycolysis		
	Increase with normal or increased pyruvate	Increased oxygen consumption	Inflammation, fever, seizure	Fever control, temperature control, seizure control, sedation
		Mitochondrial dysfunction		
Glutamate	Increase	Excitotoxity	Marker of ischemia (vasospasm, stroke, hyperventilation, ICP crisis), seizure	Improving brain perfusion, normocapnia, seizure control
Glycerol	Increase	Destruction of cell membranes caused by energy failure	Ischemia/hypoxia (vasospasm, stroke), seizure	Improving brain perfusion, seizure control

From Hillered et al. [1]
ICP intracranial pressure, *CPP* cerebral perfusion pressure

17.4 Microdialysis in Post-Cardiac Arrest Brain Injury

In our experience of microdialysis in post-cardiac arrest brain injury, sustained increases in brain glycerol concentration and L/P ratio were observed in patients with unfavorable outcomes, even with the use of therapeutic hypothermia (unpublished data, Fig. 17.5). The increase in L/P ratio during rewarming could be explained by the concomitant restoration of cerebral metabolic demand and associated lack of balance between delivery and consumption of substrate and oxygen. We also found that microdialysate glycerol concentration increased transiently after intravenous infusion of glycerol as an osmotic diuretic, suggesting that it had crossed a permeable blood–brain barrier.

The concentration of glucose in microdialysate fluid correlates with that of in the blood (unpublished data, Fig. 17.6). Increased glycolysis and glucose utilization is frequently observed in patients who have suffered global cerebral ischemia [6], potentially leading to reduced availability of the brain's main brain substrate, glucose [7]. The critical threshold for microdialysate glucose concentration is generally considered to be 0.7 mmol/L. Multimodal neuromonitoring studies have shown that tight glycemic control may be associated with metabolic crisis in severely brain-injured patients [8]. Insulin therapy may decrease brain glucose concentration despite normoglycemia [9]. Combined monitoring of microdialysate and blood glucose concentrations is particularly helpful for the management of insulin infusion and glucose control in neurocritical care and allows glucose targets to be tailored to individual patients [8, 10].

17.5 Microdialysis in Traumatic Brain Injury

In a large cohort study of patients who had sustained a TBI, elevated L/P ratio was found to be associated with poor neurological recovery [11]. Poor outcome is also reportedly associated with elevated brain lactate and glutamate concentrations, raised L/P ratio, and low brain glucose concentration in TBI patients [7]. In our experience of TBI, sustained increases and fluctuations in L/P ratio are often observed in cases that ultimately have an unfavorable outcome (Fig. 17.7) [12].

17.6 Microdialysis in Subarachnoid Hemorrhage

Simultaneous elevation of brain L/P ratio and glutamate concentration has been used as an early indicator of delayed cerebral ischemia in patients with poor-grade SAH [13, 14]. Brain biochemistry may predict neurologic deterioration secondary to cerebral vasospasm hours before symptoms are manifest [15]. Microdialysis can be used in combination with $PbtO_2$ for the detection of delayed ischemia and to guide setting of blood pressure targets and transfusion requirements after SAH [16–18].

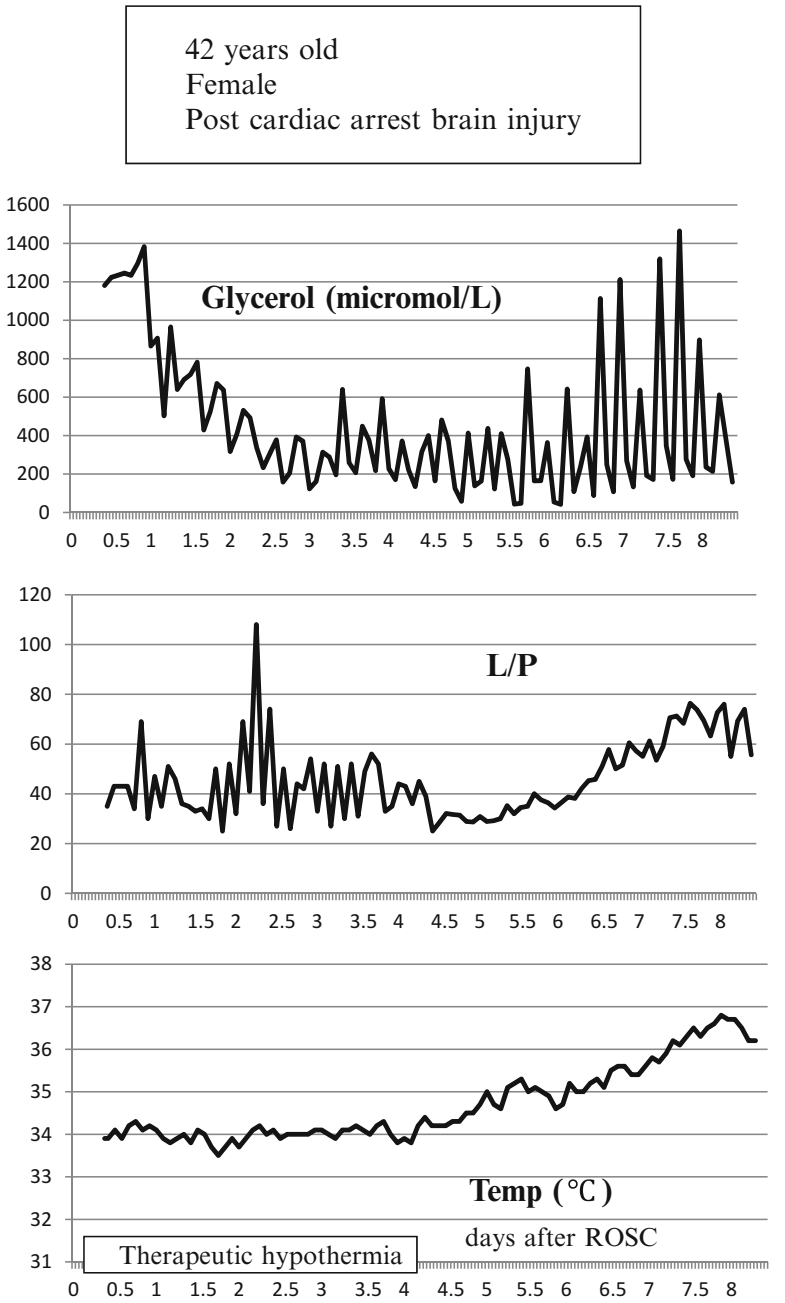

Fig. 17.5 Glycerol and lactate–pyruvate ratio in a case of post-cardiac arrest brain injury treated with therapeutic hypothermia. Repeated transient increases in glycerol concentration were likely caused by intravenous infusion of glycerol as an osmotic diuretic. Abbreviation: *ROSC* return of spontaneous circulation

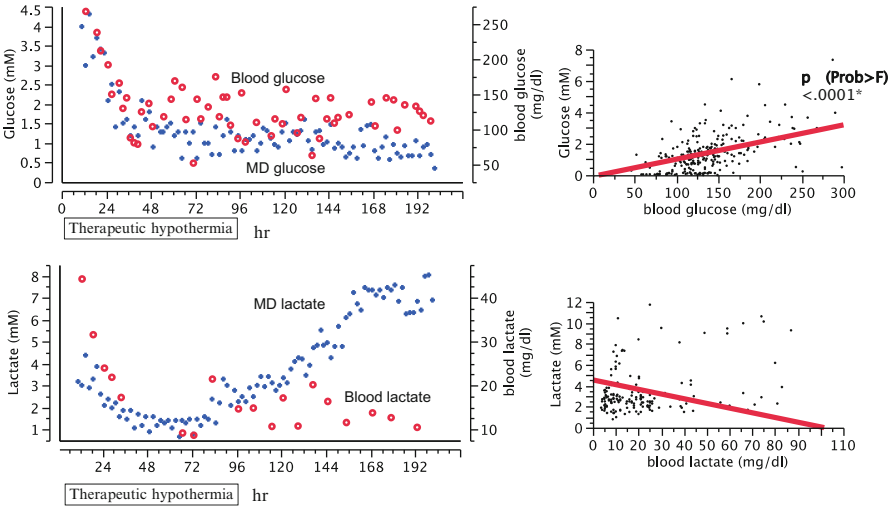

Fig. 17.6 Glucose and lactate: comparison between brain and blood concentrations in a case of post-cardiac arrest brain injury treated with therapeutic hypothermia

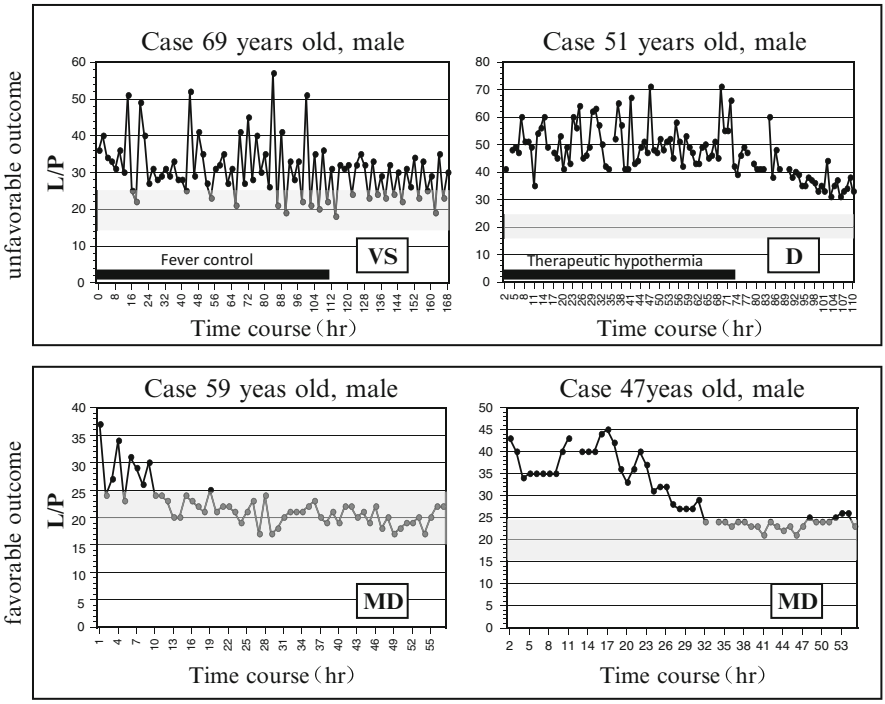

Fig. 17.7 Lactate–pyruvate ratio in traumatic brain injury. Abbreviations: *L/P* lactate/pyruvate ratio, *VS* vegetative state, *D* dead, *MD* moderate disability

Poor outcome has been associated with elevated brain lactate and glutamate concentrations, raised L/P ratio, and low brain glucose concentration in patients with SAH [19].

17.7 Microdialysis and Anesthesia

Recently, Bossers and colleagues reported that induction of anesthesia with propofol and subsequent tracheal intubation may cause an increase in L/P ratio and microdialysate glycerol concentration, which contrasts with the well-recognized phenomenon of general anesthesia suppressing brain metabolism. Microdialysis may become a useful tool to examine which anesthetic strategies might be best suited to preventing secondary brain injury [20].

Microdialysis, in conjunction with other techniques such as intracranial pressure and $PbtO_2$ monitoring, may be useful in preventing and relieving secondary ischemic injury, predicting outcome, and guiding therapy after severe brain damage. The value of microdialysis as a tool in routine neurointensive care decision-making, however, remains unclear.

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Chapter 18
Role of Evoked Potentials in Neuroanesthesia

Masafumi Fukuda and Yukihiko Fujii

Abstract Monitoring of motor evoked potentials (MEPs) is widely used in preserving motor function during neurosurgical procedures. Transcranial, transcortical, or trans-subcortical stimulation is applied according to the type of disease and surgical procedure involved. The electrodes are inserted into the peripheral muscles or cervical epidural space to obtain recordings. In most cases, intraoperative MEP findings correlate with postoperative motor function. However, we must be careful, as false-negative data caused not by intraoperative procedures but by secondary postoperative events are encountered in some patients. During skull base surgery, monitoring of facial MEPs (FMEPs) and pharyngeal MEPs (PhMEPs) is also useful in predicting postoperative facial motor and swallowing function. In this chapter, we describe how MEPs are elicited and discuss the interpretation of intraoperative findings and the usefulness of monitoring MEPs, FMEPs, and PhMEPs in predicting postoperative function.

Keywords FMEP • Intraoperative monitoring • MEP • Neurosurgery • PhMEP

18.1 Introduction

Many types of electrophysiological monitoring are widely used to preserve neurological function during neurosurgery. Visual evoked potentials allow us to monitor whether or not the optic nerve or visual pathway is affected intraoperatively. Monitoring of somatosensory evoked potentials (SEPs) provides useful information on how the sensory pathways are affected and is used to identify the central sulcus. This type of monitoring employs subdural electrodes attached to the brain surface. Auditory evoked potential monitoring is widely employed to preserve hearing function in patients with posterior fossa lesions or neurovascular compression syndrome. At present, the most important and most frequently used form of monitoring during neurosurgery is that of motor evoked potentials (MEPs). These potentials reflect intraoperative motor function and can be applied to the prediction

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of postoperative outcomes. In this chapter, we describe how monitoring of MEPs is carried out, the interpretation of intraoperative findings, and their usefulness and limitations in predicting postoperative motor function. In addition, we describe the utility of monitoring facial MEPs (FMEPs) and pharyngeal MEPs (PhMEPs) in preserving the facial and glossopharyngeal nerves, respectively, during skull base surgery.

18.2 MEP Monitoring

Application: This is applicable in tumors or vascular malformations involving or adjacent to the pyramidal tract (from the primary motor cortex to the spinal cord) or aneurysms in which the arterial branches originating adjacent to the aneurysmal neck supply the pyramidal tract.

Anesthesia: Following induction of anesthesia with a short-acting agent for neuromuscular blockade, neuroanesthesia is maintained by intravenous infusion of propofol and fentanyl or remifentanyl.

Stimulation methods: There are three methods of electrical stimulation – transcranial, transcortical, and trans-subcortical. Transcranial stimulation is used in patients with lesions somewhere other than the primary motor cortex: aneurysms or brainstem or spinal lesions, for example. When the lesions are adjacent to the primary motor cortex, transcortical stimulation is frequently employed after identification of the central sulcus using cortical SEPs. In patients with an intra-axial tumor adjacent to the pyramidal tract, subcortical stimulation is useful in confirming the distances from the stimulation sites to the pyramidal tract.

For transcranial stimulation, corkscrew electrodes are placed at positions C3, C4, or Cz. Paired stimulation of C3 or C4–Cz creates fewer motion artifacts than that of C3–C4. If motor function in the lower limbs is to be monitored, paired stimulation of C3–C4 should be used. The anode is always positioned on the affected side because this allows the cortex under the anode to be preferentially stimulated.

Transcortical stimulation is performed using subdural electrodes attached to the brain surface. Reversed N20 responses obtained from cortical SEPs allow surgeons to locate the central sulcus and hand motor area in the primary motor cortex. The anode serves as one of the subdural electrode contacts, allowing the maximum amplitude to be obtained (Fig. 18.1). The electrode placed at Fz is usually employed as the cathode. If information on somatotopy in the primary motor cortex is required, bipolar stimulation is preferred to monopolar stimulation.

When a lesion involves pyramidal tracts such as the corona radiata or internal capsule, trans-subcortical stimulation is useful in estimating the distance to the motor pathways. We use a stimulation-stick electrode during subcortical MEP monitoring. The anode is positioned at the stimulation sites and the cathode consists of the electrodes for the hand motor area.

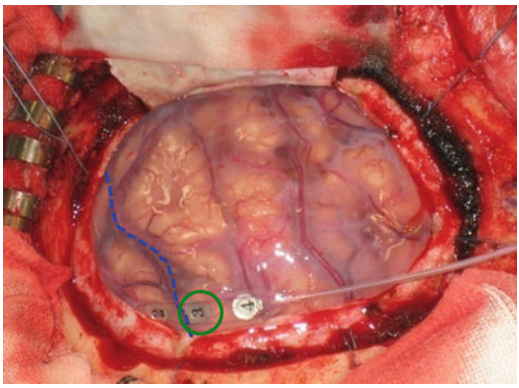

Fig. 18.1 Intraoperative photograph showing subdural electrode attached to the surface of the cortex and central sulcus (*dotted line*) and anode contact above primary hand motor cortex during motor evoked potential monitoring (*circle*)

A simulator is used to generate stimuli at a constant voltage in five rectangular pulses at 2-ms interstimulus intervals. The intensity of the stimulus is gradually increased until the amplitude of the MEPs obtained from the target muscles stabilizes before microsurgery. It is important that the stimulus not be increased to the maximum intensity as this might affect distal portions of the pyramidal tract, such as the internal capsule or brainstem, rather than the operative sites.

Recording methods: The electrodes may be inserted into two recording sites – the peripheral muscles or the cervical epidural space [1]. In the former, MEPs are usually recorded from the abductor pollicis brevis, radialis (ulnaris), abductor hallucis brevis, and tibialis (gastrocnemius) muscles through paired stainless-steel needle electrodes inserted subdermally. The band-pass filter is set at 5–3,000 Hz. The latter allows less variable responses (D-waves reflecting the action potentials of the primary motor neurons) to be obtained than those available from the muscles [2]. In addition, the responses are not likely to be affected by various drugs such as neuromuscular blockade agents. However, inserting the electrodes into the cervical epidural space represents a relatively high risk for the patient. Therefore, we exclusively use MEPs recorded from peripheral muscles for intraoperative monitoring of motor function.

Intraoperative evaluation: In general, amplitude is the parameter evaluated during MEP monitoring. Stable responses obtained before commencing microsurgery are taken as the baseline. During tumor dissection from a pyramidal tract or removal of a tumor adjacent to one, MEPs are recorded every 1–5 min. They are also frequently recorded during temporary clipping of the parent artery or after aneurysm clipping. If the amplitude of the MEPs decreases to 50 % or less of the baseline value, the surgeon assumes that the procedure may damage the pyramidal tract and temporarily abandons it or manipulates other lesions located elsewhere if present (Fig. 18.2).

Predicting postoperative outcome: The final-to-baseline MEP ratios are used to evaluate correlation with postoperative motor function in tumor patients. Several authors have reported that MEP monitoring is useful in predicting postoperative motor function. In 64 operations in 55 glioma patients, we found that an alteration

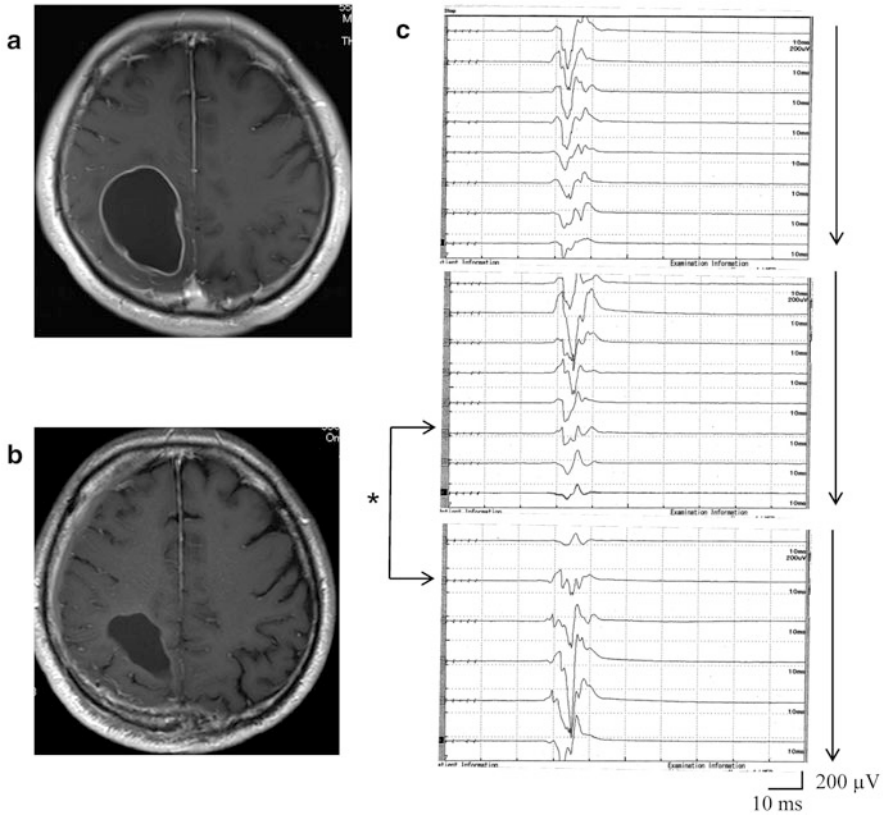

Fig. 18.2 Preoperative T1-weighted magnetic resonance imaging (MRI) with gadolinium enhancement showed cystic mass lesion in the right parietal lobe (**a**). Postoperatively, MRI demonstrated almost total removal of tumor capsule (**b**). Motor evoked potential (MEP) amplitude decreased by less than 50 % during resection of tumor capsule adjacent to posterior corona radiata (*). At final examination, MEP amplitude had returned to baseline level (**c**)

in MEPs correlated significantly with postoperative deterioration in motor function [3]. However, even if the MEPs remain stable throughout surgery, the patients may initially show deterioration in motor function, leading to a false-negative result. This type of deterioration is caused by postoperative hemorrhage, venous return dysfunction, postoperative convulsion, or resection of the supplementary motor area. This indicates the need to be careful in determining whether deterioration in postoperative motor function has been caused by intraoperative procedures or is attributable to secondary postoperative events.

18.3 FMEP Monitoring

Application: This is applicable in skull base lesions involved in or adjacent to the facial nerve.

Anesthesia: It is the same as in MEP monitoring.

Stimulation method: Corkscrew electrodes are placed at positions C3 or C4 and Cz. The cathode is always positioned at Cz, with the anode on the contralateral side. A stimulator is used to generate stimuli at a constant voltage in five rectangular pulses at 1-ms interstimulus intervals. The stimulation intensity is gradually increased until the amplitude of the FMEPs reaches a plateau before dural opening, with adjustment of the stimulus to supramaximal intensity.

Recording method: FMEPs are recorded from the orbicularis oculi and orbicularis oris muscles through paired stainless-steel needle electrodes inserted subdermally (Fig. 18.3). To avoid large and overwriting stimulus artifacts, the band-pass filter is set at 200–3,000 Hz. Setting an earth band between the stimulation and recording sites is also useful in avoiding stimulus artifacts.

Intraoperative evaluation: The highest value obtained before commencing microsurgery is taken as the baseline response. During tumor dissection from the facial nerve or removal of a tumor adjacent to the facial nerve, FMEPs are recorded every 1–5 min. If the MEP amplitude decreases to 50 % or less of the baseline value, the surgeon assumes that the procedure may damage the facial nerve and temporarily abandons it or manipulates other lesions located elsewhere if present (Fig. 18.4). If possible, compound muscle action potential is intermittently monitored by direct stimulation using a bipolar stimulating electrode to identify the anatomical location of the facial nerve.

Predicting postoperative outcome: The final-to-baseline FMEP ratios are used to evaluate correlation with postoperative facial function (House and Brackmann (HB) grade) [4] in patients with skull base tumors. In earlier studies of 26 patients with skull base tumors, we found that postoperative facial nerve function correlated significantly with the FMEP ratios in both the orbicularis oculi and orbicularis oris

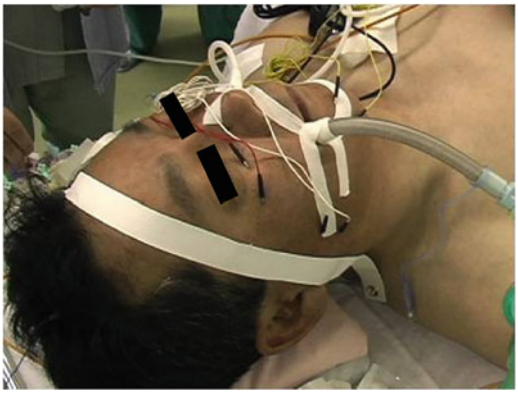

Fig. 18.3 In order to record facial motor evoked potentials (FMEPs), paired stainless-steel needle electrodes are inserted subdermally through orbicularis oculi and orbicularis oris muscles. An earth band between stimulation and recording sites is attached to avoid large and overwriting stimulus artifacts

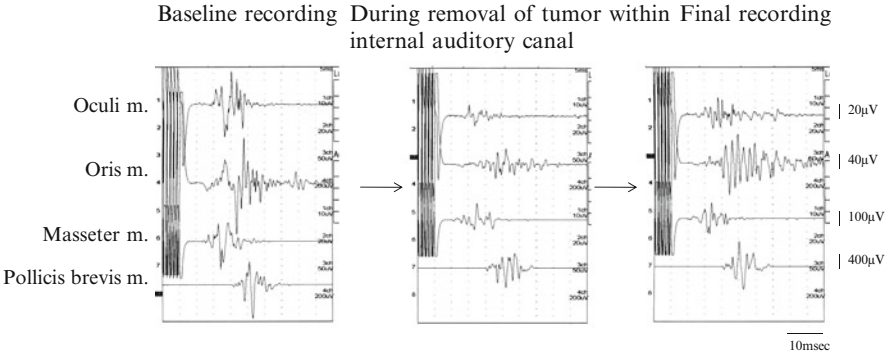

Fig. 18.4 Intraoperative FMEP monitoring in a patient with vestibular schwannoma. Representative electromyographic recordings from orbicularis oculi, orbicularis oris, masseter, and pollicis muscles before removal of tumor (*left*), during removal of intrameatal tumor (*middle*), and after removal (*right*). Note reduction in FMEP responses from both oculi and oris muscles during intrameatal tumor removal. Final FMEP ratios in both orbicularis oculi and orbicularis oris muscles were less than 50 %

muscles [5, 6]. An FMEP ratio <50 % consistently predicted immediate postoperative facial palsy, and all patients had satisfactory facial nerve function (HB grades I and II) postoperatively if it remained >50 %. Intraoperative FMEP monitoring also predicted not only immediate facial function but also long-term outcome [7].

18.4 PhMEP Monitoring

Application: This is applicable in skull base lesions involving or adjacent to the glossopharyngeal and vagus nerves.

Anesthesia: It is the same as in MEP and FMEP monitoring.

Stimulation method: It is the same as in FMEP monitoring.

Recording method: PhMEPs are recorded from the posterior wall of the pharynx through a modified endotracheal tube (Fig. 18.5). Adhesive surface electrodes (contacts 1, 2, 3, and 4, from the distal to proximal sites) are placed on the endotracheal tube and then positioned as surface electrodes attached to the pharyngeal musculature on the side ipsilateral to the lesion. PhMEPs are recorded from three pairs of the four contacts (contacts 1 and 2, 2 and 3, or 3 and 4). The band-pass filter is set at 200–3,000 Hz. Intraoperative monitoring is based on the PhMEP with the largest amplitude among the responses obtained from the three sets of paired contacts.

Intraoperative evaluation: It is the same as in FMEP monitoring.

Predicting postoperative outcomes: The final-to-baseline PhMEP ratios are used to evaluate correlation with postoperative swallowing function in patients with skull base tumors. Warning signs are a decrease in amplitude to less than 50 % of baseline, the same as in MEP or FMEP monitoring (Fig. 18.6). In an earlier study of

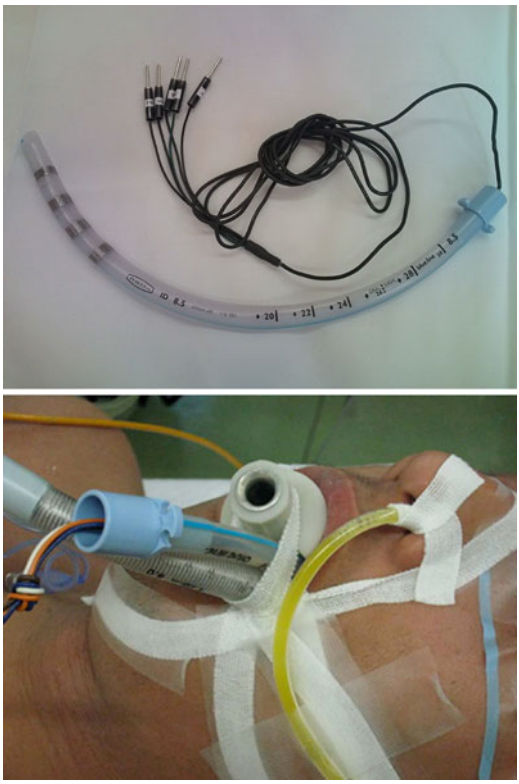

Fig. 18.5 Modified endotracheal tube with adhesive surface electrodes (contacts 1, 2, 3, and 4 from distal to proximal sites) (*upper*). Tube was positioned with surface electrodes attached to pharyngeal musculature on the side ipsilateral to the lesion (*lower*)

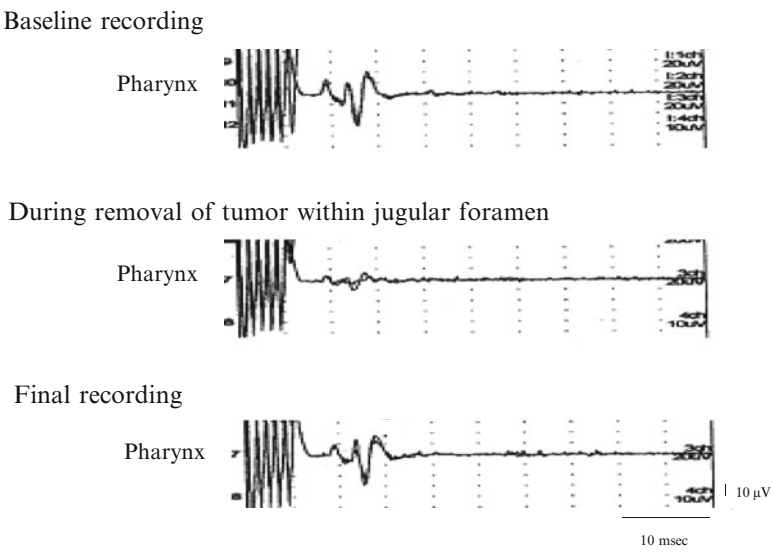

Fig. 18.6 Representative electromyograms obtained from the posterior wall of the pharynx before removal of the jugular foramen schwannoma (*upper*), during removal of the intrajugular foramen tumor (*middle*), and after removal (*lower*). Note marked reduction in pharyngeal motor evoked potential (PhMEP) responses during removal of the tumor located within the jugular foramen. Final PhMEP amplitude recovered almost fully to baseline value

21 patients with skull base tumors, we found that postoperative swallowing function correlated significantly with the final/baseline PhMEP ratio [8]. A PhMEP ratio of <50 % was recorded during 4 out of 22 procedures. All four of the patients experienced postoperative deterioration in swallowing function. PhMEP monitoring can be useful in predicting deterioration of swallowing function following skull base surgery, especially in patients with swallowing disturbances that are mainly due to reduced pharyngeal muscle motor function.

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Chapter 19
Role of Transcranial Doppler Ultrasonography in Neuroanesthesia

Kazuyoshi Ishida, Atsuo Yamashita, and Mishiya Matsumoto

Abstract Transcranial Doppler ultrasonography (TCD) allows easy bedside monitoring of cerebral circulation and can be used repeatedly and continuously at low cost. A high level of skill is required to obtain a sonogram of an individual blood vessel through the transtemporal bone window with this technique. However, the use of transcranial color duplex imaging and the power motion mode has further facilitated the measurement of blood flow velocity in the brain by this method. Cerebral autoregulation and cerebrovascular CO_2 reactivity can be determined by TCD and are useful prognostic indicators in patients with cerebral infarction, subarachnoid hemorrhage, or head trauma. Transcranial Doppler ultrasonography is also suitable in evaluating cerebrovascular stenosis, vasospasm following subarachnoid hemorrhage, vascular patency following cerebral infarction and cerebral circulation in patients with intracranial hypertension. Furthermore, microemboli that have disseminated to the brain during carotid endarterectomy or cardiovascular surgery can be detected by TCD as microembolic signals. New techniques to differentiate between gaseous and solid microemboli are currently under development. We anticipate that the utility of TCD as a useful bedside monitoring tool for evaluating cerebral circulation will become increasingly recognized.

Keywords Transcranial Doppler ultrasonography • Cerebral autoregulation • Cerebrovascular CO_2 reactivity • Vasospasm • Microembolic signal

19.1 Introduction

Transcranial Doppler ultrasonography (TCD) was established in 1982 by Aaslid et al., who reported successful transcranial measurement of blood flow velocity in the internal carotid artery (ICA), middle cerebral artery (MCA), anterior cerebral artery (ACA), and posterior cerebral artery (PCA) using 2-MHz pulsed wave

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Doppler [1]. TCD allows easy bedside monitoring of the cerebral circulation and can be used repeatedly and continuously at low cost without requiring a special dye.

In this chapter, we explain the measurement principles of and locations assessed by TCD, the parameters of physiological cerebral circulation, and the cerebrovascular responses that TCD can measure. We also provide an account of the changes that occur in cerebral blood flow velocity under various pathologic conditions, including vascular stenosis, vasospasm, and intracranial hypertension, and show how they are evaluated. In addition, we describe the characteristics of and methods for evaluating the intracranially disseminated microembolic signals that can be detected by TCD. Finally, we discuss the utility of TCD in surgical cases.

19.2 TCD Measurement Principles, Locations Assessed, and Procedures

Let us first look at the principles which underlie measurement in TCD. Rather than continuous ultrasonic waves, pulse waves are used to ultrasonically assess cerebral blood flow velocity. Based on the principle that ultrasonic waves are reflected by sites with substantially different acoustic impedances, TCD can isolate ultrasonic waves reflected by red blood cells circulating in a blood vessel. The frequency of these waves varies according to flow velocity (the Doppler effect), allowing the flow velocity of the circulating blood cells to be determined. Based on the known propagation velocity of ultrasonic waves in brain tissue (1,530 m/s), blood flow velocity at a given depth can be determined by measuring the propagation time of the pulsed ultrasonic waves reflected by blood cells. Ultrasonic waves at a frequency $\leq$2 MHz can pass through the skull, with lower frequencies penetrating deeper into the brain.

In terms of locations assessed, TCD can be used to insonate the ACA (A1), MCA (M1 and M2), PCA, and terminal portion of the ICA, as well as the anterior and posterior communicating arteries, through the temporal bone window. The ophthalmic artery can be visualized through the transorbital window, while the basilar artery and vertebral artery can be visualized through the transforaminal window. The external carotid artery can be insonated from the submandibular region (Fig. 19.1).

Doppler signals obtained by TCD can be visualized as sonograms by adjusting the depth of each target blood vessel (Fig. 19.2). From these sonograms, peak systolic velocity (PSV), end-diastolic velocity (EDV), and mean flow velocity (Vmean) can be determined, and, subsequently from these values, the pulsatility index (PI) can be calculated:

$$\mathrm{PI} = (\mathrm{PSV} - \mathrm{EDV}) \cdot \mathrm{Vmean}^{-1} \tag{19.1}$$

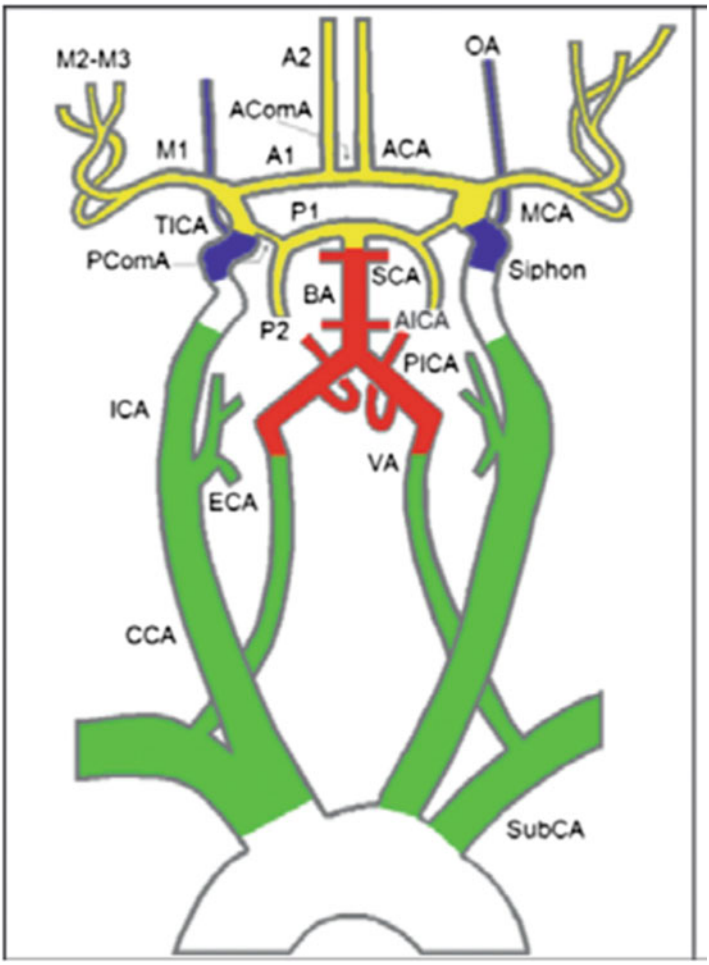

Fig. 19.1 Insonation area of cervicocerebral vasculature by transcranial Doppler. *Yellow*, through transtemporal window; *blue*, through transorbital window; *red*, through transforaminal window; and *green*, through submandibular region. *MCA* indicates middle cerebral artery, and M1, M2 and M3 are segments of this artery; *ACA* indicates anterior cerebral artery, and A1 and A2 are segments of this artery; P1 and P2 are segments of posterior cerebral artery: *CCA, ICA*, and *ECA* indicate common, internal, and external carotid arteries; *TICA* indicates the terminal portion of ICA; siphon indicates siphon portion of ICA; *SCA* indicates superior cerebellar artery; *AComA* and *PComA* indicates anterior and posterior communicating arteries; *BA* indicates basilar artery; *AICA* and *PICA* indicate anterior and posterior inferior cerebellar arteries; *OA* indicate ophthalmic artery; *VA* indicates vertebral artery; *SubCA* indicates subclavian artery. (Adapted and modified from reference [36])

Usually, the Vmean value in the MCA, where the ultrasonic irradiation angle is almost parallel to the blood flow, provides the most accurate estimate of blood flow velocity. Blood flow velocity in the MCA can be detected at a depth of 35–65 mm, with a Vmean of 45–70 cm/s. The MCA is the only artery whose Vmean can be constantly determined at a depth of $\geq$20 mm. However, since 10 % of patients lack

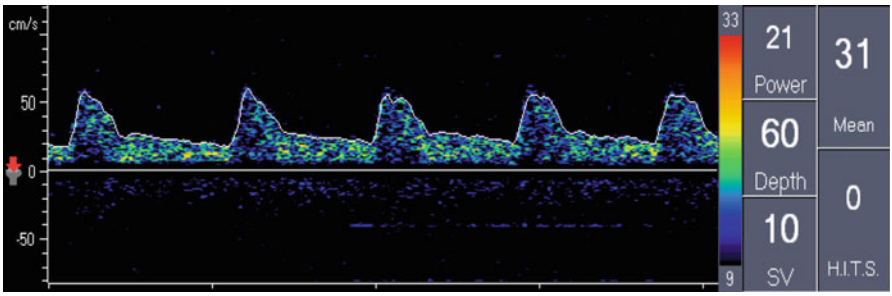

Fig. 19.2 Typical sonogram pattern of the middle cerebral artery blood flow velocity and envelope. *Top white envelope curve* indicates estimated maximum velocity

a temporal bone window, insonation of the MCA is difficult in some cases, especially in elderly and female patients [2].

Although a high level of skill is required to obtain a sonogram of an individual blood vessel through the transtemporal bone window by TCD, recent technical innovations have facilitated the visualization of blood vessels. One such innovation is transcranial color duplex imaging, where the depth and blood flow of blood vessels are transcranially visualized by color Doppler imaging (Fig. 19.3). With this technique, the depth, location, and sample volume of the target vessel can be determined. Another innovation is the power motion mode, which enables the identification and visualization of all blood vessels in the Doppler beam by collecting blood flow information from multiple sample volumes (usually 8) within the range of the set depth (Fig. 19.4).

19.3 Physiological Parameters Measurable by TCD

TCD measures only the blood flow velocity of insonated cerebral blood vessels, not actual blood flow. Thus, assuming that the diameter of the target blood vessel is not significantly affected by physiological changes, any change in cerebral blood flow velocity should reflect a relative change in cerebral blood flow. In fact, the diameter of the MCA, as measured by magnetic resonance imaging or visually by craniotomy, does not substantially change, even with a change in blood pressure, CO_2 load, or stand-up load [3–5]. Furthermore, Vmean as determined by TCD correlates well with cerebral blood flow velocity as measured by N_2O inhalation (as described by Kety and Schmidt) or ^{133}Xe inhalation [6], suggesting that changes in Vmean reflect relative changes in cerebral blood flow.

19.3.1 Evaluation of Cerebral Autoregulation

Cerebral autoregulation (CA) is a mechanism that maintains the cerebral blood flow at a constant level against varying mean arterial blood pressure (MAP). There are

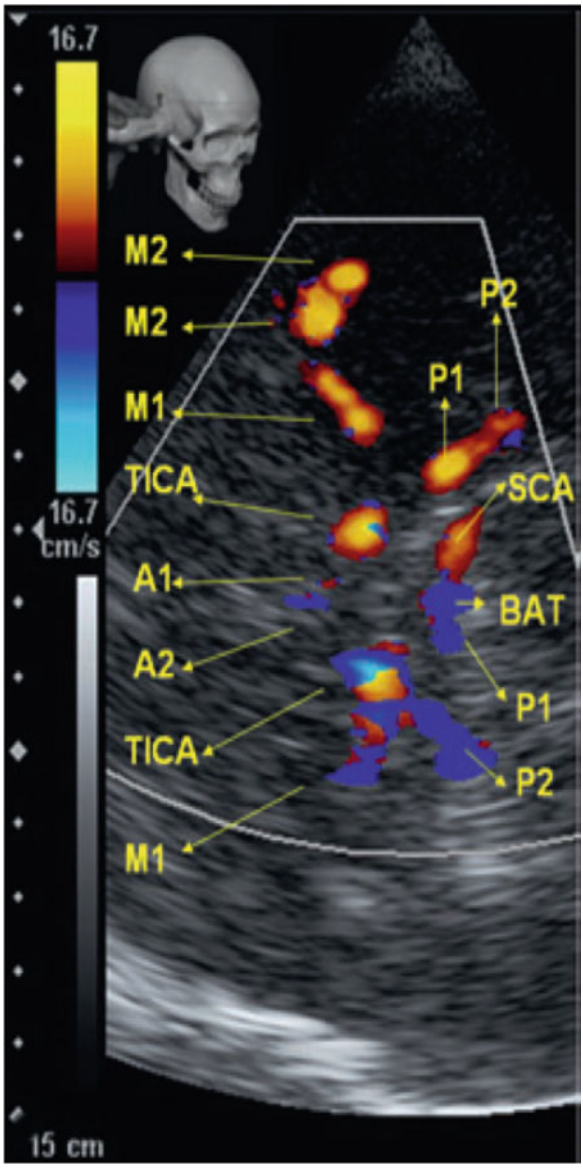

Fig. 19.3 Normal vessel appearance on transtemporal transcranial color duplex imaging *M1* and *M2* indicate M1 and M2 segments of the middle cerebral artery; *TICA* indicates terminal portion of the internal carotid artery; *A1* and *A2* indicate segments of the anterior cerebral artery; *P1* and *P2* indicate segments of the posterior cerebral artery; *SCA* indicates superior cerebellar artery; *BAT* indicates basilar artery. (Adapted and modified from reference [36])

two types of CA: static CA, which maintains cerebral blood flow against a mild change in MAP, and dynamic CA, which maintains cerebral blood flow against a rapid change in MAP. Evaluating CA is important because impaired CA results in either decreased blood pressure, which is associated with an increased risk of cerebral ischemia, or increased blood pressure, which is associated with an increased risk of cerebral hemorrhage.

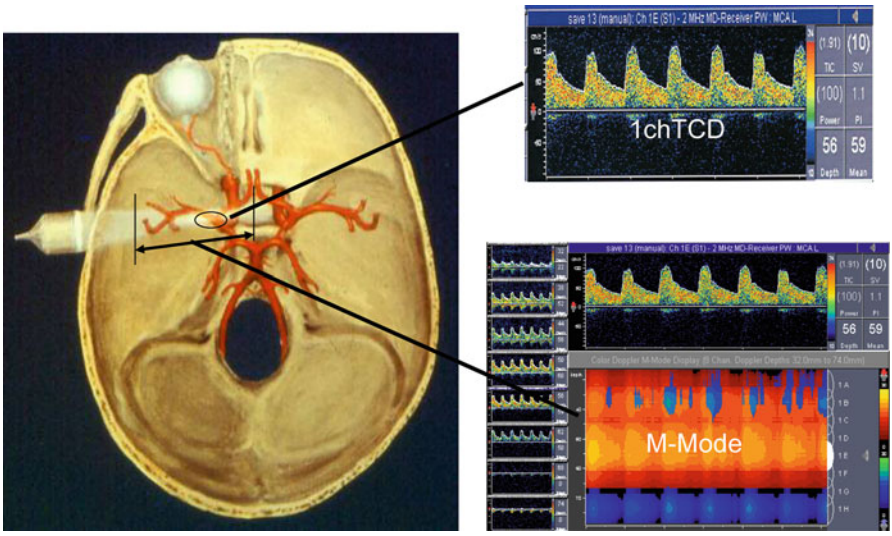

Fig. 19.4 Power motion mode enables identification and visualization of all blood vessels in Doppler beam by collecting blood flow information from multiple sample volumes (usually eight) within range of set depth

19.3.1.1 Evaluation of Static CA

Slow and continuous intravenous infusion of phenylephrine in increments of 20 mmHg gradually increases MAP. Mean arterial pressure and Vmean are measured before and after phenylephrine infusion. The percent change in cerebral vascular resistance (%CVR) per percent change in MAP (%MAP) is calculated as static CA (sCA%) using the following formulas:

$$\mathrm{sCA\%} = \mathrm{\%CVR} \cdot \mathrm{\%MAP}^{-1} \tag{19.2}$$

$$\mathrm{CVR} = \mathrm{MAP} \cdot \mathrm{Vmean}^{-1};$$

$$\mathrm{\%CVR} = (\mathrm{CVR\ pre} - \mathrm{CVR\ post})\ \mathrm{CVR\ pre}^{-1} \tag{19.3}$$

$$\mathrm{\%MAP} = (\mathrm{MAP\ pre} - \mathrm{MAP\ post}) \cdot \mathrm{MAP\ pre}^{-1} \tag{19.4}$$

Here, sCA% $\geq$20 is defined as normal vascular response [7].

It is typically understood that cerebral blood flow is regulated to maintain the MAP between 60 and 150 mmHg [8]. However, recent studies using TCD have shown that Vmean increases slightly depending on even this range of MAP at a constant rate [9].

19.3.1.2 Evaluation of Dynamic CA

Even after a rapid change in MAP, dynamic CA settles the cerebral blood flow to a constant level within 5 s. Dynamic CA can be evaluated by TCD by inducing a rapid change in blood pressure by mechanical or chemical stimulation or by making use of spontaneous fluctuations in MAP.

Suprasystolic Thigh Cuff Method

After inflating a thigh cuff to achieve a blood pressure of 30 mmHg above the systolic level and maintaining it for 2–3 min, rapid release of the cuff decreases MAP by about 15 mmHg. As a parameter of dynamic CA against this rapid change in MAP, the rate of regulation (RoR) is calculated as follows:

$$\mathrm{RoR} = \left(\Delta \mathrm{CVR} \cdot \Delta \mathrm{t}^{-1} \cdot \Delta \mathrm{MAP}^{-1}\right) \tag{19.5}$$

The change in MAP is measured over 2.5 s, from 1 to 3.5 s after cuff release, where CVR is calculated by multiplying MAP by Vmean^{-1} and Δt is 2.5 s (Fig. 19.5a) [10]. Vmean decreases with decrease in MAP over the first 1 s after cuff release, after which CVR decreases with continued decreases in MAP (Fig. 19.5b) and Vmean recovers to the level before cuff release. The normal value for RoR is 20 and a value close to 0 indicates impaired dynamic CA [10]. The autoregulation index is calculated by normalizing the pattern of change in Vmean over time so that evaluation can be made by determining which pattern most accurately describes the observed change in Vmean (Fig. 19.5c). An autoregulation index of $\geq$5 is defined as normal dynamic CA [10].

Valsalva Maneuver

The effect of the Valsalva maneuver on the systemic and cerebral circulation is manifested in four stages: stage I, in which holding of inspiration increases intrathoracic pressure, causing blood to be pumped out of the chest cavity and MAP and Vmean to increase; stage IIa, in which decreased venous return results in decreased cardiac output and MAP, while increased intrathoracic pressure results in increased intracranial pressure and decreased Vmean; stage IIb, in which sympathicotonia results in increased cardiac output and recovery of MAP, while Vmean also improves as a result of improved blood pressure and dynamic CA; stage III, in which a decrease in intrathoracic pressure following expiration of intrathoracic air results in decreased MAP due to blood inflow into the chest cavity; and stage IV, in which improved venous return leads to an increase in MAP and Vmean (Fig. 19.6). To evaluate dynamic CA, the autoregulatory slope index (ASI) is calculated by

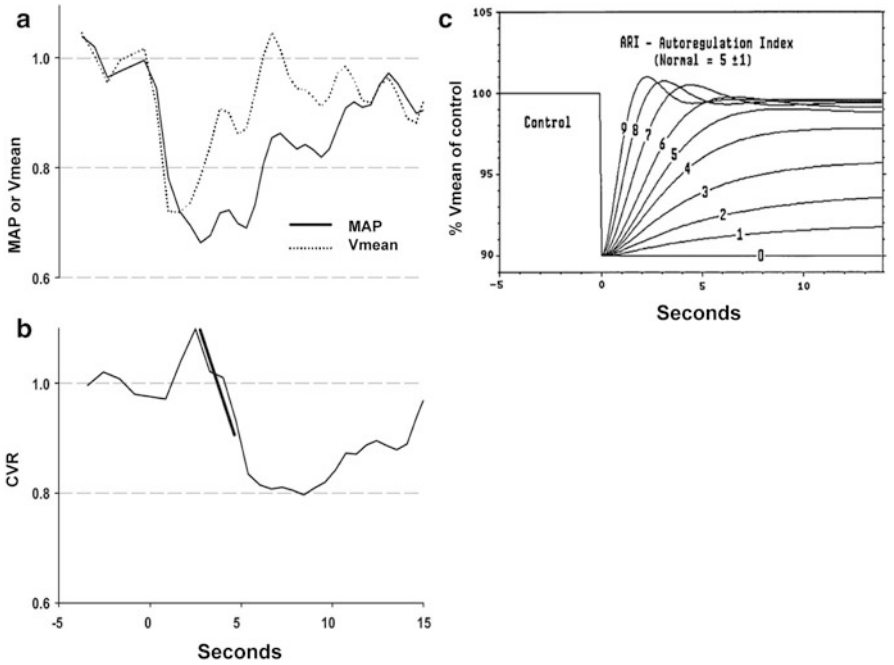

Fig. 19.5 Typical changes in mean arterial pressure (MAP), mean flow velocity (Vmean) (**a**), and cerebrovascular resistance in response to suprasystolic thigh cuff deflation to determine dynamic cerebral autoregulation (**b**). MAP and Vmean decreased simultaneously during first second after tight cuff was released following earlier recovery of Vmean during next seconds than MAP (**a**). All tracings are shown in normalized units relative to control prerelease values from −4 to 0 s. Straight line (*bold line*) through cerebral vascular resistance curve (**b**) was determined by regression analysis of data obtained from 1 to 3.5 s after thigh cuff release and used to calculate rate of regulation. Autoregulation index was calculated by normalizing pattern of change in Vmean over time so that evaluation could be made by determining which pattern most accurately described observed change in Vmean (**c**) (Adapted and modified from reference [10])

incorporating the duration of stage IIa and the degree of improvement in MAP and Vmean into the following formula:

$$\begin{aligned} \mathrm{ASI} = \{ [(\mathrm{Vmean}_{(\mathrm{IIa+3s})} - \mathrm{Vmean}_{(\mathrm{IIa})}) \cdot \mathrm{Vmean}_{(\mathrm{IIa})}{}^{-1} \\ - (\mathrm{MAP}_{(\mathrm{IIa+3s})} - \mathrm{MAP}_{(\mathrm{IIa})}) \cdot \mathrm{MAP}_{(\mathrm{IIa})}{}^{-1}] \times 100 \} \end{aligned} \tag{19.6}$$

The normal range of ASI in healthy individuals has been reported to be 22 ± 14 % [11].

Postural Alterations

Standing up from a supine, sitting, or squatting position can cause MAP to change by up to 35 mmHg. Dynamic CA can be evaluated based on changes in MAP and Vmean determined by this *postural alterations* method.

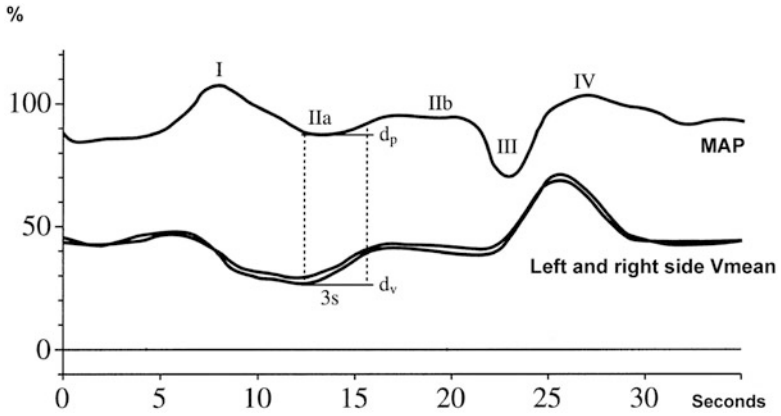

Fig. 19.6 Recordings of MAP and Vmean during Valsalva maneuver. Phase I, increased intrathoracic and MAP; phase IIa, fall in arterial blood pressure due to decreased atrial filling; phase IIb, rise in MAP due to increased heart rate; phase III, sudden decrease in MAP due to release of intrathoracic pressure; and phase IV, overshoot in MAP with resumed atrial filling. Derivation of autoregulatory slope index is shown: d_v, difference between minimum Vmean and Vmean reading 3 s later, and d_p, difference between MAP readings in the same time interval (Adapted and modified from reference [11])

Transient Hyperemic Response Ratio

The transient hyperemic response ratio (THRR) is calculated by dividing the mean PSV from the average of two heart beats after the release of 5-s common carotid artery compression (PSV hyperemia), as measured by ipsilateral TCD, by the mean PSV from the average of five heart beats before compression (PSV baseline), as follows:

$$\text{THRR} = \left(\text{PSV hyperemia} \cdot \text{PSV baseline}^{-1}\right) \tag{19.7}$$

With normal dynamic CA, cerebral blood vessels on the compressed side will be dilated to increase blood flow during carotid artery compression, resulting in transient hyperemia after releasing compression. The normal range for THRR is 1.2 ± 0.04, and a value close to 1 indicates impaired dynamic CA [12].

Spontaneous Fluctuations in Blood Pressure

Blood pressure fluctuates finely, even at rest. CA has been evaluated by examining the correlation between low-frequency MAP fluctuation ($\leq$2.0 Hz) and Vmean. The correlation coefficient between the average values of Vmean and MAP over 5–10 s is calculated as the mean velocity index (Fig. 19.7a). Impaired dynamic CA is associated with a higher positive correlation between Vmean and MAP

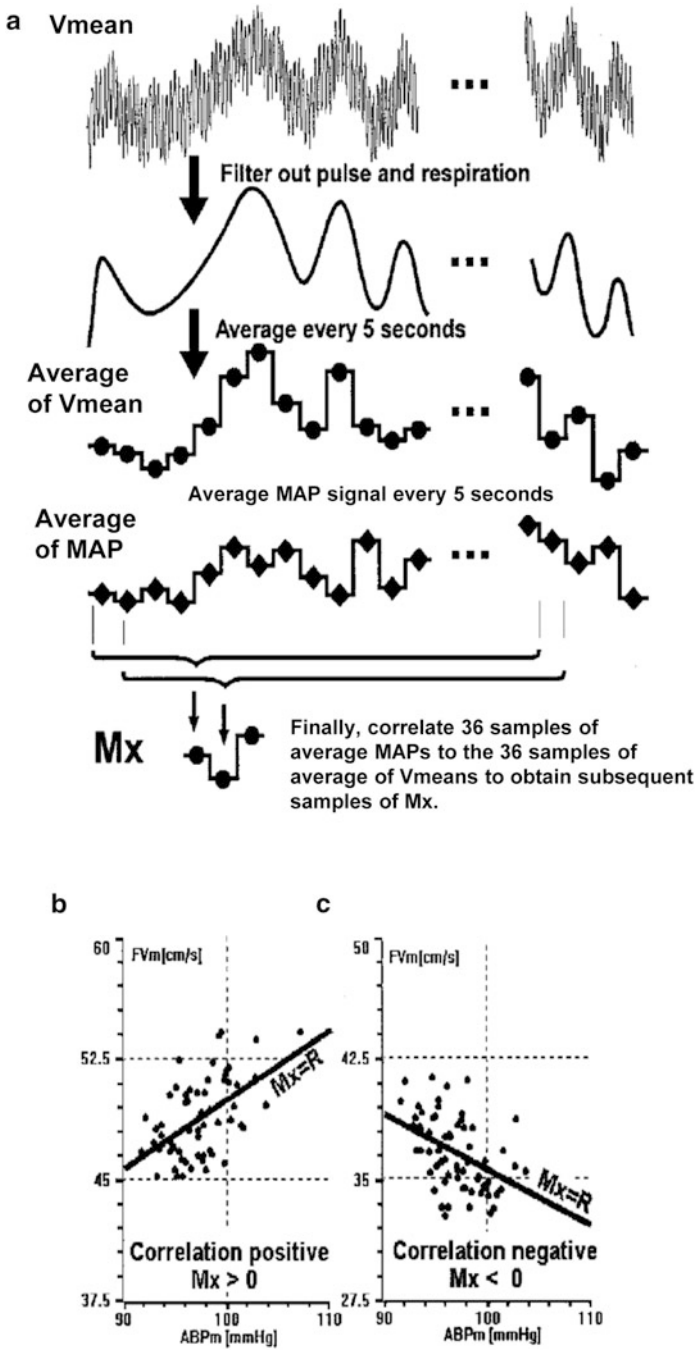

Fig. 19.7 Signal processing steps used to obtain subsequent samples of mean velocity index (Mx) (**a**). Two examples of linear regression plots with positive and negative values of Mx corresponding to non-autoregulating (**b**) and autoregulating (**c**) systems, respectively (Adapted and modified from reference [13])

(Fig. 19.7b), while normal dynamic CA is associated with no or a negative correlation (Fig. 19.7c) [13].

19.3.1.3 Effect of Anesthetics on CA

When evaluating CA by TCD during surgery, consideration should be given to the type of anesthetic being used. Volatile inhalation anesthetics typically used in clinical practice such as desflurane, sevoflurane, and isoflurane are known to impair CA in a dose-dependent manner. In contrast, intravenous anesthetic propofol reduces Vmean, but does not affect CA. Opioids such as fentanyl and remifentanil do not affect Vmean or CA [14].

19.3.1.4 Significance of Evaluating CA

Evaluation of CA by TCD has been performed under various pathologic conditions. Impaired CA is observed in the presence of cerebral vascular spasms in patients with post-subarachnoid hemorrhage [15]. Cerebral infarction, even involving small lesions, is also associated with impaired CA. The degree of impaired CA initially worsens over the first 5 days after the onset of cerebral infarction, but gradually improves over the 3 months that follow. There is also a correlation between the degree of impaired CA after cerebral infarction and the severity and prognosis of brain disorder [16]. Furthermore, CA evaluation has proven prognostic utility in patients with head trauma [17–19].

19.3.2 Evaluation of Cerebrovascular CO_2 Reactivity

Cerebrovascular CO_2 reactivity (CO_2 R) can be evaluated by challenge with chemicals such as acetazolamide or by changing the arterial partial pressure of CO_2 ($PaCO_2$) through respiratory regulation. Acetazolamide increases the tissue concentration of CO_2 by inhibiting carbonic anhydrase, an enzyme catalyzing the conversion of CO_2 and water to bicarbonate, thereby inducing metabolic acidosis in tissue.

Pa CO_2 can be changed by rebreathing of CO_2, administering CO_2, or changing the respiratory rate consciously to hypoventilation, apnea, and hyperventilation. CO_2 R is calculated as follows:

$$\text{Absolute } CO_2R = \Delta\text{Vmean} \cdot \Delta PaCO_2{}^{-1} \tag{19.8}$$

$$\text{Relative } CO_2R \text{ (percentage of baseline Vmean)} = \left(\text{absolute } CO_2R \cdot \text{ baseline Vmean}^{-1}\right) \cdot 100 \quad (19.9)$$

Here, Δ represents the change in each parameter before and after changing $PaCO_2$.

19.3.2.1 Effect of Anesthetics on CO_2 R

When evaluating CO_2 R by TCD during surgery, consideration should be given to the effect of anesthetics on CO_2 R, as in the case of evaluating CA. Volatile inhalation anesthetics such as desflurane, sevoflurane, and isoflurane are known to increase CO_2 R by increasing Vmean. In contrast, CO_2 R can be maintained with the intravenous anesthetic propofol, although the CO_2 R value will be slightly lower due to a reduced baseline Vmean. Opioids do not affect CO_2 R [20].

19.3.2.2 Significance of Evaluating CO_2 R

CO_2 R is decreased in patients with hypertension [21], obstructive apnea syndrome [22], central apnea syndrome complicated by heart failure [23], or carotid artery stenosis [24]. In addition, a correlation exists between an increased blood cholesterol level, a known precipitating factor for arteriosclerosis, and reduced CO_2 R in patients with a history of mild cerebral infarction or transient ischemic attack [25]. In patients with carotid artery stenosis and reduced CO_2 R, an increased incidence of cerebral infarction has been observed during follow-up [26–28]. Furthermore, impaired CO_2 R has been shown to correlate with the prognosis in patients with head trauma complicated by cerebral hemorrhage [29].

In patients with kidney disorder, however, controversy remains as to whether CO_2 R is maintained [30] or impaired [31]. Similarly in diabetic patients, some studies have reported an increased CO_2 R during general anesthesia [32], while others have reported a decreased CO_2 R [33]. Given that decreased CO_2 R during anesthesia is likely associated with postoperative cognitive dysfunction [34], evaluating CO_2 R is also important in predicting the risk of brain disorder and patient outcome.

19.4 Pathologic Conditions Evaluable by TCD

19.4.1 Intracranial Vascular Stenosis

Intracranial vascular stenosis can be detected by TCD as a localized area with an increase in PSV and Vmean. It has been reported that ≥50 % stenosis in the MCA

corresponds to a Vmean of 80–100 cm/s and 70 % stenosis corresponds to a Vmean of 110–120 cm/s [35]. A change in blood flow velocity in the distal part of the narrowing vessel can be detected as a decrease in Vmean to <30 cm/s and a decrease in PI to <0.6 (vasodilatation). A decreased Vmean and an increased PI are evident at the proximal part of the stenosis (Fig. 19.8). In the presence of severe stenosis in the ICA, the blood flow in the ipsilateral ACA is reversed, flowing from the contralateral side to the stenotic side through the circle of Willis.

19.4.2 Vasospasm

Vasospasm caused by subarachnoid hemorrhage can be easily detected and evaluated by TCD and occurs along a longer length of blood vessels than intracranial stenotic lesions. Vasospasm in the MCA can be most accurately detected by TCD as an area with increased Vmean and PSV. The criteria for identifying vasospasm are shown in Table 19.1. Since vasospasm is present even before a patient develops clinical symptoms or cerebral infarction, evaluating Vmean by TCD in post-subarachnoid hemorrhage patients is important in the early detection and treatment planning of vasospasm [36].

19.4.3 Acute Ischemic Stroke, Occlusion, Recanalization, and Reperfusion

TCD is useful in evaluating cerebrovascular patency in patients with cerebral infarction. The thrombolysis in brain ischemia [37] and consensus on grading intracranial flow obstruction criteria [38] are used to evaluate blood flow (Fig.19.9), and cerebrovascular patency based on these criteria is considered to correlate strongly with patient outcome.

19.4.4 Evaluation of Intracranial Pressure

TCD can be used to evaluate cerebral perfusion pressure and also to indirectly evaluate intracranial pressure (ICP). The initial sign of increased ICP is a combination of decreased EDV and increased PI. End-diastolic velocity becomes zero after ICP has exceeded diastolic blood pressure and decreases to negative values, with further increases in ICP (reverse diastolic flow), resulting in decreased PSV and eventually blood flow undetectable on TCD (Fig. 19.10). The sensitivity and specificity of undetectable blood flow on TCD for brain death are 95 % and 100 %, respectively.

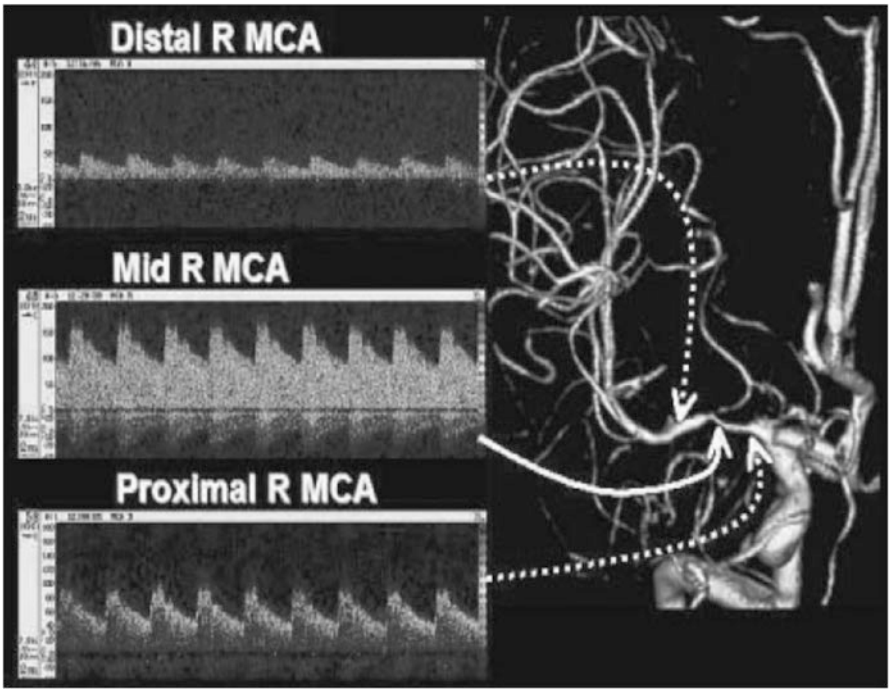

Fig. 19.8 Spectrogram changes in right middle cerebral artery with stenosis are displayed on corresponding magnetic resonance angiograph. Significant increase in flow velocities in stenotic region (peak systolic velocity 120 cm/s) and decrease in post-stenotic region are evident (Adapted and modified from *Neurosonology* 19:113–131, 2006, *in Japanese*; URL: https://www.jstage.jst.go.jp/article/neurosonology/19/3/19_3_113/_pdf)

Table 19.1 Criteria for identifying vasospasm

MCA (M1 and M2) vasospasm	Vmean (cm/s)	PSV (cm/s)	MCA/ECICA ratio
Severe	>200	>300	>6.0
Moderate	150–200	250–300	4.5–5.9
Mild	120–150	200–250	3.0–4.5

MCA middle cerebral artery, *Vmean* mean flow velocity, *PSV* peak systolic velocity, *ECICA* extracranial internal carotid artery

19.5 Detection of Microembolic Signals

The concept of microembolic signals (MES) was first introduced in 1965 by Austen et al., who detected signals that were stronger and shorter than those of blood flow sound in a cardiopulmonary bypass circuit using continuous ultrasonic waves [39]. Because they used a bubble-type oxygenation device for the cardiopulmonary bypass circuit, they assumed that these MES represented gaseous microemboli. In

Category	Appearance	Description
TIBI 0 COGIF 1		**ABSENT FLOW** No flow signal
TIBI 1 COGIF 2		**MINIMAL FLOW** Systolic spikes with variable velocity and duration; zero EDV; reverberating flow
TIBI 2 COGIF 3		**BLUNTED FLOW** Systolic upstroke delayed (duration >0,20 sec); EDV>0; PI<1,2
TIBI 3 COGIF 3		**DAMPENED FLOW** Vmean decrease greater than 30% of contralateral value; upstroke normal; EDV>0
TIBI 4 COGIF 4c		**HYPEREMIC FLOW** Segmentally increased flow velocities (Vmean >80 cm/s and/or >30% compared to the control side, no turbulence; low PI; no harmonics; low degree spectral broadening.
TIBI 4 COGIF 4b		**PSEUDOSTENOTIC FLOW** Focally increased flow velocities (Vmean >30% compared to the control side; EDV>0; Significant turbulence or flow disturbance.
TIBI 5 COGIF 4a		**NORMAL FLOW** Flow velocities normal or in the range of ±%30 of the control side. **[* Bar: 50 cm/sec]**

Fig. 19.9 Thrombolysis in brain ischemia (TIBI) and consensus on grading intracranial flow obstruction (COGIF) criteria: patients with absent flow (TIBI grade 0, COGIF grade 1), minimal flow with zero EDV (TIBI grade 1, COGIF grade 2), and low flow with either blunted (TIBI grade 2) or dampened (TIBI grade 3, COGIF grade 3) configuration show worse prognosis than patients with flow velocities equal to those of contralateral side (TIBI grade 5, COGIF grade 4a), flow velocities that increased segmentally (TIBI grade 4, COGIF grade 4c), or flow velocities that increased focally (COGIF grade 4b) (Adapted and modified from reference [36])

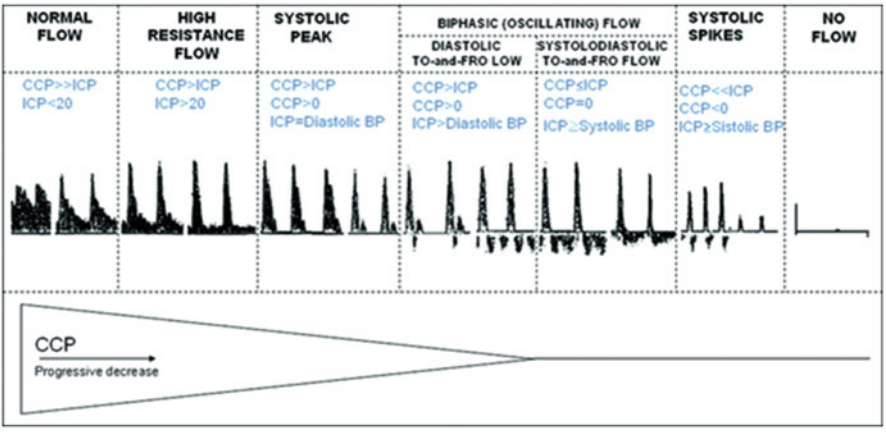

Fig. 19.10 Increased progressive waveform changes with intracranial pressure (ICP), eventually leading to cerebral circulatory arrest. If ICP significantly to level obviating spontaneous cerebral circulation (i.e., cerebral circulatory arrest or brain death), transcranial Doppler will show one of following specific flow patterns: (1) alternating flow with systolic forward flow, followed by complete reversal during diastole, indicating net zero forward flow, or (2) systolic peaks with only systolic hit to stagnant blood column but no flow: CPP, cerebral perfusion pressure. (Adapted and modified from reference [36])

1986, MES were detected during TCD-monitored carotid endarterectomy (CEA) [40]. This was the first study to detect intraoperatively disseminated microemboli in the brain by TCD. However, since this was observed after cutting the ICA, it was again considered that these MES represented gaseous microemboli. Subsequently, in 1990, MES with different acoustic properties than those of gaseous microemboli were detected during CEA. Because they were detected before cutting the ICA, these MES were considered to originate from solid microemboli such as a thrombus or atheroma. Patients in whom solid microemboli-derived MES were detected developed transient ischemic attack or cerebral infarction after surgery [41]. Subsequently, TCD was also applied in cardiovascular surgery to measure and detect MES.

19.5.1 Definition of MES

MES are defined as signals with a characteristic sound on a TCD sonogram. They are characterized by a signal intensity of $\geq$3 dB stronger than the background blood flow sound and a duration of $<$300 msec [42, 43] (Fig. 19.11). To detect MES, gain and ultrasonic power should be set as low as possible so that the background flow spectrum is barely visible.

19.5.2 Differentiation Between Gaseous and Solid MES

A number of attempts have been made since around 2002 to differentiate between gaseous and solid MES [44]. Because gaseous microemboli have very low acoustic impedance, Doppler signals are strongly reflected at the interface. Thus, MES representing gaseous microemboli are observed as strong signals on TCD [41]. However, it is difficult to differentiate relatively small gaseous microemboli from solid microemboli.

Microembolic signals comprise sine waves at a constant frequency (Fig. 19.11). It is believed that gaseous and solid MES can be differentiated to some extent by analyzing their frequencies, as gaseous MES emit relatively high-frequency sound ($>$400–500 Hz) (Fig. 19.11a, b), while solid MES emit sound at a lower frequency ($\leqq$400Hz) (Fig. 19.11c, d) [45]. Russel et al. differentiated the two types of MES by using ultrasonic waves of two different frequencies (2 MHz and 2.5 MHz) based on the fact that gaseous MES reflect 2-MHz ultrasonic waves more strongly than 2.5-MHz ones (Fig. 19.12a), while solid MES reflect ultrasonic waves of both frequencies to a similar extent (Fig. 19.12b) [44].

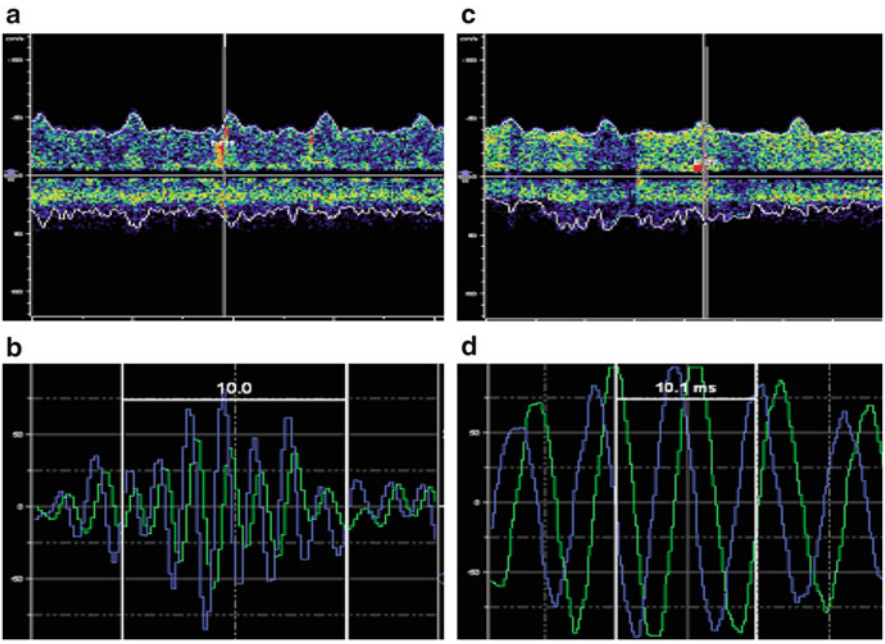

Fig. 19.11 Microembolic signals (MES) comprise sine waves of constant frequency. Gaseous and solid MES can be differentiated to some extent by analyzing their frequencies. For MES detected on sonogram in (**a**), MES comprising seven sine waves were detected over 10 ms (**b**). Therefore, their frequency was calculated as 700 Hz, indicating gaseous MES. For MES detected on sonogram in (**c**), MES comprising $\leq$2 sine waves were detected over 10 ms (**d**). Therefore, their frequency was calculated as $\leq$200 Hz, indicating solid MES [45]

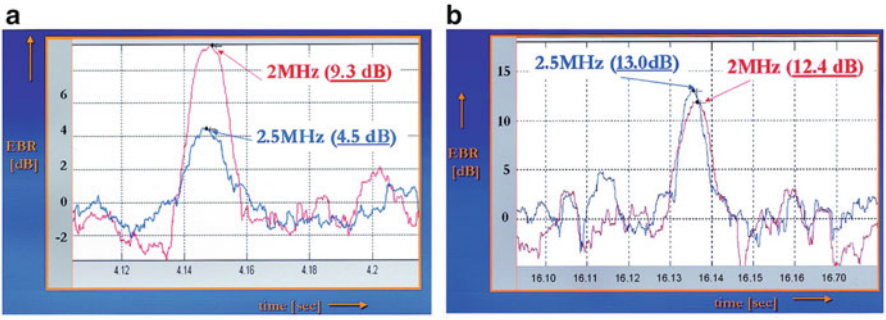

Fig. 19.12 Gas bubble reflecting 4.8-dB greater ultrasound at 2.0-MHz insonation (*red*) than at 2.5 MHz (*blue*) (**a**). Solid microemboli (80-μm plastic microsphere) reflecting only 0.6-dB greater ultrasound at 2.5-MHz insonation (*blue*) than at 2.0-MHz insonation (*red*) (**b**) (Adapted and modified from reference [44])

19.6 Usefulness of Intraoperative Monitoring by TCD

Transcranial Doppler ultrasonography is a useful monitoring tool that allows for the bedside monitoring of various parameters. However, it has limited use intraoperatively during neurosurgical procedures. Its utility has therefore been demonstrated mainly in CEA and cardiovascular surgery.

19.6.1 Usefulness of TCD in CEA

It is helpful to monitor Vmean in the MCA on the operated side during CEA. During CEA, an extreme decrease in Vmean from the baseline indicates the need to maintain blood pressure with drugs or use a shunt tube. A study investigating the relationship between Vmean of the MCA during carotid occlusion during CEA under local anesthesia and the occurrence of neurological complications suggested that a Vmean of <25 cm/s or a decrease to <48 % of the baseline value represents a risk of neurological complications [46]. A decrease in Vmean to <10 % of the baseline value during carotid occlusion and an increase in PI to >100 % after clamp release are associated with cerebral infarction in the perioperative period [47]. Furthermore, the detection of >50 MES during CEA is associated with cerebral ischemia [48].

Taken together, the evidence level of TCD in CEA is classes II to III, with a recommendation level of type B [49].

19.6.2 Usefulness of TCD in Coronary Artery Bypass Grafting Surgery

MES have been reported to occur during cardiovascular surgery in a number of cases, and their association with cerebral disorder or postoperative cognitive dysfunction has been examined. In coronary artery bypass grafting surgery (CABG) using cardiopulmonary bypass MES have been frequently detected during aortic cannulation, release of aortic cross-clamping, and heart displacement to identify the anastomotic site [50]. Furthermore, MES are even more frequently detected during valvular surgery involving cardiotomy [51].

The relationship between MES and postoperative cognitive dysfunction was confirmed in only 5 of 15 reports (1994–2009) that examined this relationship primarily in CABG cases [52]. Thus, the evidence level of MES detection by TCD during cardiovascular surgery is classes II to III, with a recommendation level of type B, while the recommendation level for the clinical significance of MES detection is type U [49].

One possible reason for the ambiguous relationship between MES detection and postoperative cognitive dysfunction after cardiovascular surgery is the small

sample size. Moreover, there have been no studies on the differential effect of gaseous and solid MES—which affect the brain differently—on the occurrence of postoperative cognitive dysfunction [52]. Fat globules aspirated from the surgical field during cardiovascular surgery can be disseminated to the brain via cardiopulmonary bypass [53]. Early and robust formation of cerebral edema in a rat model of fat emboli to the brain indicates the seriousness of such lipid dissemination [54]. It is, however, unclear whether fat emboli are detectable as MES. Further efforts to detect and differentiate MES to the maximum extent possible and prevent the dissemination of microemboli to the brain may improve the usefulness of TCD during cardiovascular surgery.

19.7 Conclusion

Inexpensive and noninvasive Vmean monitoring by TCD, which can provide various types of information at the bedside, is extremely useful in perioperative patient management. The use of transcranial color duplex imaging and power motion mode has further facilitated the determination of Vmean. New techniques for differentiating MES are also under development. We anticipate that the utility of TCD as a useful bedside monitoring tool will be increasingly recognized.

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Chapter 20
Role of Near-Infrared Spectroscopy in Neuroanesthesia

Ken Kuwajima and Kenji Yoshitani

Abstract Near-infrared spectroscopy (NIRS) provides information on regional tissue oxygen saturation (rSO_2) by measuring absorption of near-infrared light. Values of rSO_2 reflect the balance between oxygen supply and demand in the monitored region. The clinical application of NIRS has been frequently studied in the context of neuroanesthesia, such as assessment of cerebral ischemia during carotid endarterectomy or early detection of cerebral hyperperfusion. In addition, when a bolus of indocyanine green is injected and analyzed using specific NIRS software, blood flow index can be calculated, which indicates the relative measurement of cerebral blood flow. While NIRS has technical limitations and requires further development, it is noninvasive and relatively simple, thus providing advantages over other modalities. It has the potential to provide helpful information on cerebral function and improve perioperative outcomes in neuroanesthesia.

Keywords Tissue oxygen saturation • Cerebral blood flow • Blood flow index • Carotid endarterectomy • Indocyanine green

20.1 Introduction

Near-infrared spectroscopy (NIRS) provides information on regional tissue oxygen saturation (rSO_2) by measuring absorption of near-infrared light noninvasively and continuously. The clinical application of NIRS has been frequently studied in the context of neuroanesthesia, such as assessment of cerebral ischemia during carotid endarterectomy or early detection of cerebral hyperperfusion. In addition, when a bolus of indocyanine green is injected and analyzed using specific NIRS software, blood flow index can be calculated, which indicates the relative measurement of

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cerebral blood flow. In this chapter, clinical issues and importance of NIRS monitor would be clarified.

20.2 What Is Near-Infrared Spectroscopy?

Near-infrared spectroscopy (NIRS) uses near-infrared (NIR) light (680–800 nm). This region of the electromagnetic spectrum is also widely used in pulse oximetry, which monitors arterial oxygen saturation by measuring NIR light in the pulsatile component of the blood. Near-infrared spectroscopy, however, measures oxygen saturation in regional tissues such as arterial and venous blood, fat, or bone. The principle of NIRS is based on the difference in absorption spectra of oxygenated hemoglobin and deoxygenated hemoglobin [1]. Near-infrared light is generated by an emission probe and detected by a distant photodiode, as shown in Fig. 20.1. The attenuation of NIR light in idealized biological tissue is determined by the path length of the light and the absorption coefficient according to the modified Beer-Lambert law. Therefore NIRS can measure fractions of oxygenated and deoxygenated hemoglobin and calculate tissue oxygen saturation and the absolute tissue hemoglobin index (THI). Tissue oxygen saturation reflects the balance between oxygen supply and demand in the monitored region, and THI can also be a surrogate for regional blood volume. The application of NIRS has been frequently studied in the context of neuroanesthesia for monitoring cerebral regional oxygen saturation (rSO_2). There are several approaches to assessing cerebral perfusion, including transcranial Doppler (TCD), single-photon emission computed tomography (SPECT), and perfusion-weighted magnetic resonance imaging (MRI), but all are expensive or time-consuming. In contrast, the advantages of NIRS are its simplicity and noninvasiveness and the resulting fact that it is available for use in both the operation room and at the bedside.

20.3 Clinically Available NIRS Devices

Various manufacturers have developed NIRS devices, such as the INVOS (Somanetics, Troy, MI, USA) and NIRO series (Hamamatsu Photonics K. K., Hamamatsu, Japan). All these devices measure the transmission and absorption of

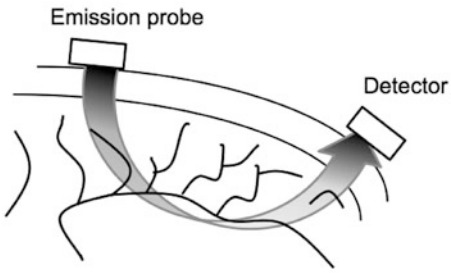

Fig. 20.1 Near-infrared light from emission probe scatters in biological tissue and reaches detector of near-infrared spectrophotometer

NIR light. However, there is variation in the transmitted wavelength, the number of wavelengths, the distance between diodes, and the algorithms used to derive physiologically relevant signals, that is, to exclude the influence of a superficial layer such as the skin or the skull. For example, the NIRO and INVOS series use the method of spatially resolved spectroscopy, whereas TRS-20 (Hamamatsu Photonics K. K., Hamamatsu, Japan) uses time-resolved spectroscopy. Thus, the optimum method and device remain to be determined, and further development is now in progress.

20.4 Clinical Application in Neuroanesthesia

20.4.1 Carotid Endarterectomy

Carotid endarterectomy (CEA) is an operation for moderate or severe stenosis of the internal carotid artery to reduce the risk of neurological symptoms such as transient ischemic attack and ischemic stroke. Anesthesiologists should be careful of further neurological complications perioperatively, because the internal carotid artery is cross-clamped during endarterectomy, exposing the ipsilateral brain to the risk of ischemia. In most cases, neurological consequences are avoided in CEA by collateral perfusion via the circle of Willis. In addition, temporary carotid shunting can be placed from the common carotid artery to the distal internal carotid artery to maintain cerebral perfusion. In any case, it is preferable to monitor cerebral perfusion to detect intraoperative cerebral ischemia, and several methods have been used, including TCD, somatosensory evoked potentials, electroencephalography, and NIRS [2]. Details of methods other than NIRS can be found in the other chapters. Near-infrared spectroscopy is a noninvasive and simple technique that can be used continuously during surgery. Previous studies demonstrated that rSO_2 values correlated with TCD [3–5] and electroencephalography [6–8]. Moritz et al. demonstrated that TCD, stump pressure, and NIRS showed similar accuracy for cerebral ischemia during CEA with regional anesthesia and that the cutoff of 20 % reduction of the baseline NIRS value provided 83 % sensitivity and 83 % specificity for detection of cerebral ischemia [9]. However, the criteria for carotid shunting vary among studies, and the indications for cervical shunting have not been determined. Similarly, the threshold of rSO_2 for tolerating cerebral ischemia has not yet been established.

20.4.2 Prediction of Cerebral Hyperperfusion Syndrome

Cerebral hyperperfusion syndrome (CHS) can occur after carotid revascularization and causes clinical manifestations such as intracerebral hemorrhage and seizures (3–5 %) [10]. The mechanism underlying CHS is an acute change in cerebral blood

flow. In the setting of chronic cerebral ischemia, the cerebral vessels dilate to compensate for the ischemia and maintain cerebral blood volume. After CEA, cerebral blood flow will increase rapidly and cerebral perfusion pressure may be elevated. The chronically dilated vessels cannot respond to the acute change due to impaired autoregulation, and the ipsilateral cerebral hemisphere may be exposed to hyperperfusion, which may result in brain edema and intracerebral hemorrhage. Therefore hyperperfusion must be detected early if devastating events are to be avoided. Computed tomography and MRI are the gold standard for diagnosis of CHS, but more simple and convenient approaches are required at the bedside. Near-infrared spectroscopy has been studied in the assessment of cerebral hyperperfusion, as this may cause a relative increase in O_2 supply, inducing an increase in rSO_2. Two previous studies comparing NIRS and SPECT demonstrated the effectiveness of NIRS in predicting postoperative cerebral hyperperfusion. Komoribayashi et al. showed that reduced preoperative cerebrovascular reactivity and reduced rSO_2 during internal carotid artery clamping were independent predictors of post-CEA hyperperfusion [11]. Ogasawara et al. also showed that increases in cerebral rSO_2 immediately after internal carotid artery declamping and at the end of the procedure were significantly correlated with increases in cerebral blood flow (CBF) immediately after CEA [12]. In addition, Pennekamp et al. compared rSO_2 with TCD-derived mean middle cerebral artery blood velocity (Vmean) to predict the onset of CHS [13]. Both rSO_2 and Vmean increased more in CHS patients than in non-CHS patients. The increases in rSO_2 and Vmean were independently related to the occurrence of CHS. These data suggest that NIRS could be an alternative modality to other methods for prediction of CHS, but the thresholds for hyperperfusion have yet to be determined.

20.5 NIRS-Based Method

20.5.1 Indocyanine Green Injection

Injection of indocyanine green (ICG) in conjunction with NIRS is also useful in assessing CBF. Absorption of NIR by chromophores such as ICG may be detected by this method. This particular dye has an absorption peak at 805 nm [14] and is limited to the intravascular compartment if injected intravenously [15]. These properties enable NIRS to monitor the passage of injected ICG as a tracer. In addition, ICG is rapidly cleared from blood by hepatic uptake and biliary excretion, which makes it a suitable tracer for repetitive measurements as it does not accumulate [16]. The concept of ICG injection is based on the method of fluorescein flowmetry [17]. Specific NIRS software (Hamamatsu Photonics) using this method can measure absolute concentration changes in ICG. In each measurement, parameters including rise time and maximal changes in ICG concentration can be calculated. Rise time is defined as the time interval between 10 % and 90 % of

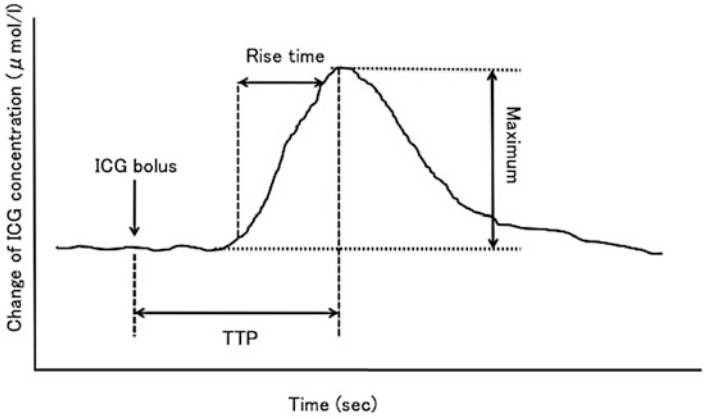

Fig. 20.2 Rise time is defined as interval between 10 and 90 % of maximal change in indocyanine green (ICG) concentration when ICG bolus is injected intravenously. Time to peak (TTP) is defined as interval between 0 and 100 % of maximal change in ICG concentration

the maximal change in ICG (Fig. 20.2). The blood flow index (BFI) can then be calculated as follows: BFI = maximal change in ICG/rise time. The BFI is proportional to the blood flow, but the proportionality factor is unknown, which may mean that BFI is comparable within a subject, but not between subjects. When NIRS is applied to the forehead and a bolus of ICG is injected intravenously, NIRS can measure the changes in ICG concentrations in the frontal lobes and also calculate BFI, that is, the relative, but not absolute, measurement of CBF. The bolus dose of ICG is 0.1 mg/kg and 50 measurements can be performed daily.

Several reports have examined the validity of the ICG-BFI technique. In animals, previous reports comparing BFI with TCD or radioactive microsphere methods suggested that BFI may be a valuable tool for estimating CBF [18, 19]. In human studies, BFI has also correlated with CBF obtained by perfusion-weighted MRI [20]. On the other hand, Schytz et al. showed that, compared with SPECT, ICG-BFI obtained by NIRS did not reflect changes in CBF after acetazolamide infusion in healthy humans [21].

In addition to BFI, time to peak (TTP) obtained by NIRS has also been investigated as a marker of CBF. Time to peak is defined as the time between 0 % and 100 % of the maximal change in ICG concentration when the ICG bolus is infused intravenously. Several studies stated that TTP was significantly correlated with perfusion-weighted MRI and might be a useful parameter for monitoring CBF [20, 22].

20.6 Limitations

In clinical use, NIRS has some potential limitations. One is problems with the signal from extracranial tissues such as the skull and skin [23]. To avoid this issue, the INVOS series uses two detecting photodiodes and excludes superficial signals

using a subtraction-based method. The NIRO series uses spatially resolved spectroscopy, measuring the difference between the signals of the two detectors. However, no NIRS device completely avoids the risk of signal contamination from extracranial tissue. Yoshitani et al. also demonstrated that rSO_2 values obtained by INVOS were influenced by skull thickness and area of the cerebrospinal fluid layer compared with NIRO [24], suggesting that rSO_2 values might depend both on regional anatomy and the NIRS device used.

Another potential difficulty with NIRS is interindividual variability. The technique may be useful for trend monitoring, but we should be careful about comparing NIRS data from a number of patients. One approach to dealing with this problem may be to convert rSO_2 values to a percentage change from baseline, but the most favorable definition of rSO_2 values (absolute values vs. relative values such as percentage change) is unclear.

20.7 Conclusion

Near-infrared spectroscopy can measure rSO_2, which reflects the balance between oxygen demand and supply in the monitored region. In addition, NIRS is a noninvasive and simple technique for monitoring cerebral perfusion, with advantages over other modalities. Clinical use of NIRS has been frequently studied in the context of neuroanesthesia, such as assessment of cerebral ischemia during CEA or early detection of cerebral hyperperfusion. The ICG-BFI technique with specific NIRS software is also useful in calculating BFI, the relative measurement of CBF. Further research and development are required, but in the future NIRS may play a significant role in providing helpful information on cerebral function and improving perioperative outcomes in neuroanesthesia.

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Chapter 21
Role of Pressure Reactivity Index in Neurocritical Care

Marek Czosnyka and Celeste Dias

Abstract Direct arterial blood pressure (ABP) and intracranial pressure (ICP) are two fundamental variables most often selected for brain monitoring after severe traumatic brain injury (TBI). Otherwise, cerebral perfusion pressure (CPP = ABP-ICP) and ICP-oriented therapy is not efficient. Additional information can be derived from the pressure reactivity index (PRx) which is calculated from the continuous correlation between slow waves (20 s to 2 min periods) of ICP and ABP. Positive PRx indicates impaired cerebrovascular reactivity, whereas negative PRx reflects intact reactivity. PRx can be interpreted as a surrogate for continuous index of cerebral autoregulation. In such a paradigm, dynamic changes in ICP (slow waves) are evoked by changes in cerebral blood volume which are in turn modulated by changes in cerebral blood flow. Impaired cerebrovascular reactivity was observed in patients who died following TBI. PRx stays close to +1 during temporal episodes (plateau waves) or before/during refractory intracranial hypertension. Distribution of PRx along varying CPP values shows a distinctive U shape with minimum PRx (best cerebrovascular reactivity) indicating the optimal value for CPP. This is important as patients with CPP below optimal level have an increased mortality rate, while patients with CPP above optimal CPP are at a higher risk of severe disability. The highest percentage of favorable outcome can be seen in those patients for whom current CPP was close to optimal value of CPP. These findings await further analysis by prospective randomized trial.

Keywords Cerebral blood flow • Autoregulation • Cerebrovascular reactivity • Cerebral perfusion pressure • Outcome

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21.1 Introduction

The brain is a highly metabolic active organ that requires a constant blood supply with oxygen, nutrients, and perfect functional neurovascular coupling (Fig. 21.1). In adults, the brain receives approximately 15 % of the cardiac output and accounts for almost 20 % of total body oxygen consumption. In neonates, the brain receives up to 30 % of cardiac output and accounts for 50 % or more of total oxygen consumption. The brain has no metabolic storage and is unique in its intolerance to diminished blood flow. To maintain constant cerebral blood flow, in spite of systemic changes, the cerebral vasculature has developed an active vasoregulatory response.

Knowledge of the normal mechanisms that regulate cerebral blood flow and the modifications induced by aging, brain lesions, and medical interventions such as anesthesia is fundamental to the adequate management of patients in the operating theater and intensive care unit.

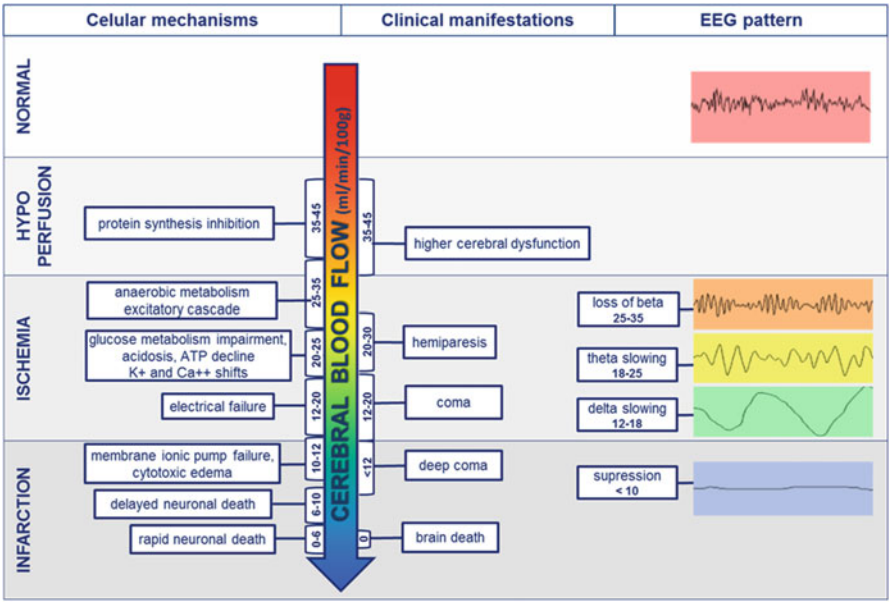

Fig. 21.1 General scheme showing gradual sequence of cellular mechanisms, clinical manifestation, and changing electrophysiological pattern with decreasing cerebral blood flow from normal to deep ischemic levels

21.2 Cerebral Blood Flow and Cerebrovascular Reactivity

In healthy young adults, global cerebral blood flow (CBF) is approximately 50 ml/min/100 g but CBF varies with age. Newborns have 40 ml/min/100 g, and at 2–4 years, CBF reaches a peak of 100 ml/min/100 g and then starts to decline in adult life [1] (Table 21.1). Regional cerebral blood flow to the gray matter is higher (80 ml/100 g/min) than to the white matter (20 ml/100 g/min) [2].

21.3 Cerebral Perfusion Pressure and Intracranial Pressure

Cerebral perfusion pressure (CPP) is the driving force of blood flow through the cerebrovascular bed. In clinical practice, CPP is calculated as the difference between mean arterial blood pressure (MAP) and mean intracranial pressure (ICP).

$$\mathrm{CPP} = \mathrm{MAP} - \mathrm{ICP}$$

The normal range for MAP, ICP, and, subsequently, CPP varies with body posture, clinical condition, and also with age [4, 5].

Normal values of ICP, in supine position, are 1.5–6 mmHg for term infants, 3–7 mmHg for young children, and less than 15 mmHg for older children and adults.

Generally accepted normal CPP values are >40 mmHg for newborns, 40–60 mmHg for infants/toddlers, 50–60 mmHg for children, 60–70 mmHg for adolescents, and >60–70 mmHg for adults [6–8] (Table 21.2).

According to the Monro-Kellie doctrine, intracranial volume is constant and equal to the volume of brain tissue, blood, CSF, and, in pathology, mass lesions. Therefore, an increase in the volume of one of these compartments can raise ICP and so reduce CPP and CBF. Intracranial compliance and the pressure-volume curve also vary with age [9]. In infants that have open cranial fontanelles or sutures, the cranial vault will compensate by expansion. During childhood, adolescence and in the adult life, normal intracranial compliance changes according to brain volume, CSF production, and CSF outflow [10]. However, in situations with high intracranial pressure, the compromised intracranial compliance decreases with age [11].

Table 21.1 Cerebral blood flow changes according to age [3]

Age	Global CBF (ml/min/100 g)
Newborn	40
1–6 months	64
6 months–2 years	80
2–12 years	100
13–60 years	50
>60 years	40

Table 21.2 Mean arterial pressure, intracranial pressure, and cerebral perfusion pressure changes according to age

Age	MAP (mmHg)	ICP (mmHg)	CPP (mmHg)
Newborn	>30–50	<2	>30
Infant	45–55	1.5–6	40–50
Toddlers/child	55–65	3–7	50–60
Adolescent	65–75	<15	60–70
Adult	75–95	<15	>60–70

21.4 Cerebrovascular Reactivity: Autoregulation and Vasoreactivity

The three major mechanisms that regulate CBF are cerebral perfusion pressure (CPP), arterial pressure of carbon dioxide ($PaCO_2$), and arterial oxygen content ($CaO_2 = 1.34*Hb*SaO_2 + 0.003*PaO_2$) [12] (Fig. 21.2).

In 1959, Lassen defined *cerebral autoregulation* as the intrinsic capacity of the cerebral vasculature to provide constant cerebral blood flow by changing cerebral vascular resistance (CVR) and cerebral blood volume (CBV), despite changes in cerebral perfusion pressure (CPP) [13].

In adults, CBF remains constant between the lower limit of autoregulation (LLA = 50 mmHg) and the upper limit (ULA = 150 mmHg). This pressure autoregulatory range varies with age and in pathologic conditions such as arterial hypertension or with the presence of an acute brain lesion [14]. The lower limit of autoregulation in neonates is approximately 30 mmHg, but the upper limit is much lower for infants than adults (90 mmHg). Outside these limits of CPP, flow is pressure dependent and cerebral autoregulation is lost. Autoregulation protects the brain, and the upper and lower limits of autoregulation are highly individual [15]. The risk of a secondary lesion increases for CPP values below the LLA due to hypoperfusion and ischemia. Similarly, CPP values above the ULA induce hyperemia and edema due to damage of the blood-brain barrier (Fig. 21.3).

Cerebral vascular response to changes in $PaCO_2$ and CaO_2 is defined as *cerebral vasoreactivity*. Hypercapnia produces vasodilation and decreases CVR, whereas hypocapnia produces vasoconstriction. Within a $PaCO_2$ range from 20 to 100 mmHg, a change in 1 mmHg of $PaCO_2$ induces a 2–3 % average change in CBF [16]. A decrease in normal arterial oxygen content (14–20 g/dl) induces a decrease in CBF [17]. This response is a complex sum effect of variations of PaO_2, SaO_2, Hb concentration, Hb dissociation curve, and blood viscosity.

Autoregulation is influenced by vasoreactivity: hypercapnia and low oxygen content impairs autoregulation [18]. However, autoregulation is a more vulnerable mechanism than vasoreactivity which may still be present despite autoregulation impairment. A modification of the autoregulatory response, with a right shift of the lower and upper limits of CPP, is observed in situations with high sympathetic tone, chronic hypertension, or during administration of vasodilatory drugs [19].

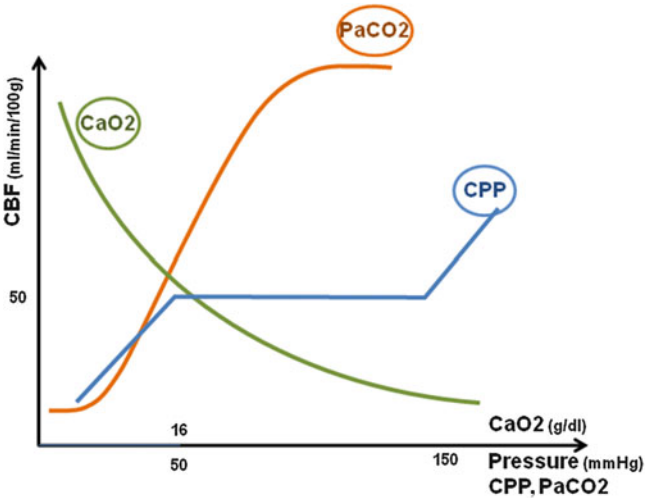

Fig. 21.2 Physiological relationship between cerebral perfusion pressure (CPP), arterial carbon dioxide content ($PaCO_2$), arterial oxygen content (CaO_2), and resulting cerebral blood flow (CBF)

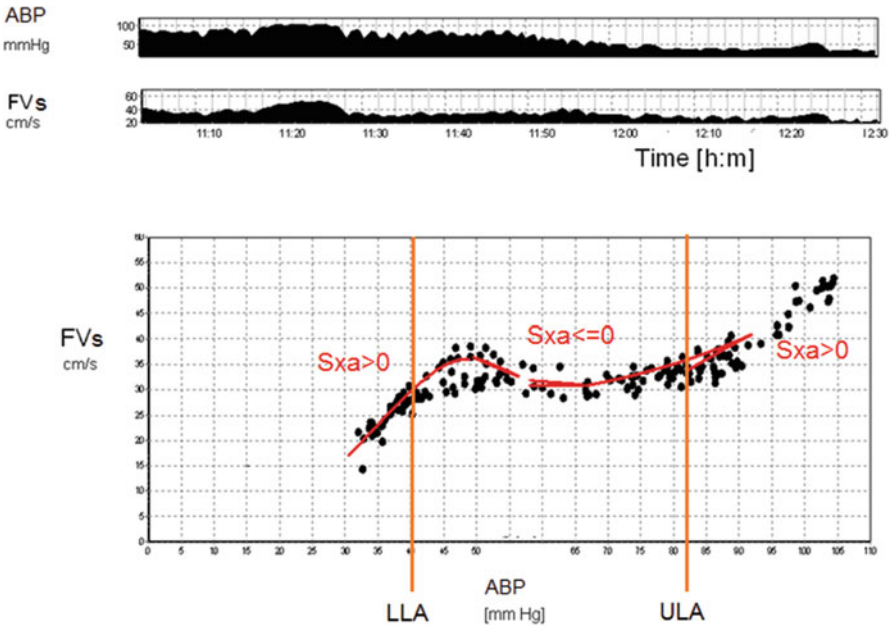

Fig. 21.3 Relationship between experimentally decreased arterial blood pressure (ABP) and systolic blood flow velocity (FVs) in the basilar artery of experimental animal (own material). FVs is a surrogate measure of CBF in this experiment. Time trends (upper panel) plotted as a scattergram (FV versus ABP – lower panel) suggest shape of Lassen's autoregulatory curve. Limits of autoregulation: lower (LLA) and upper (ULA) are not sharp thresholds but denote smooth transition between working and disturbed autoregulation. Sxa denotes index of autoregulation calculated as the correlation coefficient between systolic FV and ABP (30 consecutive 10 s averages), being positive outside autoregulatory range or negative/zero within ABP range for intact autoregulation

21.5 Cerebral Autoregulation and Anesthesia

Anesthetic agents affect cerebral metabolic rate and cerebral blood flow.

Intravenous anesthetic (propofol, thiopental and etomidate, except ketamine), opioid analgesic, and sedative drugs (midazolam and dexmedetomidine) reduce CBF and cerebral metabolic rate (CMR) in a parallel way, maintaining metabolic and neurovascular coupling. Autoregulation and vasoreactivity are generally preserved during the administration of these intravenous drugs [20–24].

Inhaled anesthetic drugs may produce uncoupling of cerebral metabolic rate and cerebral blood flow, with increase in cerebral blood volume and risk of increased intracranial pressure. With the exception of sevoflurane (up to 1.5 minimum alveolar concentration), for other volatile agents, impairment of autoregulation is dose related, although hypocapnia blunts this effect [19, 25, 26].

21.6 Cerebral Autoregulation and Pathologic Conditions

Systemic pathologic conditions and acute neurological lesions frequently impair cerebral autoregulation, but we will focus only on the most clinically relevant for neuroanesthesia.

In chronic arterial hypertension, cerebral autoregulation is shifted to the right but the dynamics of autoregulation appears to be preserved [27]. However, in patients with malignant hypertension, dynamic autoregulation is impaired [28]. In long-term type 2 diabetes, impairment of cerebrovascular reactivity is related to microvascular disease and autonomic neuropathy [29], but it seems that cerebral autoregulation impairment may be an early manifestation of brain microangiopathy [30].

Traumatic brain injury, spontaneous subarachnoid hemorrhage, and large ischemic stroke are associated to dysfunctional cerebrovascular reactivity, and impaired autoregulation correlates to worse outcome [31–35].

21.7 PRx – Continuous Assessment of Cerebral Autoregulation

One of the key mechanisms responsible for autoregulation is cerebrovascular pressure reactivity which is the ability of vascular smooth muscle to respond to changes in transmural pressure [15]. In theory, a change in arterial blood pressure (ABP) should induce reactive change in CVR with a change in CBV and subsequently in ICP. Some authors have suggested that cerebrovascular pressure reactivity, and therefore autoregulation, could be derived from the transmission of characteristic pulse waveform from ABP to ICP [36]. However, this has never

been demonstrated to work in clinical practice, perhaps because pulse-related changes in ABP are too fast (a fraction of a second) to mobilize an active vasoregulatory response. Cerebrovascular pressure reactivity can be derived from the transmission of characteristic slow waves of arterial blood pressure lasting from 20 s to 3 min, to intracranial pressure. The computer-aided approach to calculate cerebrovascular pressure reactivity index (PRx) and to monitor it continuously was introduced in 1997 [37]. Using computational methods, PRx is determined by calculating the moving correlation coefficient between 30 consecutive, time-averaged data points (10-s periods) of ICP and ABP in a 5-min window. A positive PRx signifies a positive gradient of the regression line between the slow components of ABP and ICP, which has been shown to be associated with a passive behavior of a nonreactive vascular bed. A negative value of PRx reflects normally reactive cerebral vessels, as ABP waves provoke inversely correlated waves in ICP [38] (Fig. 21.4).

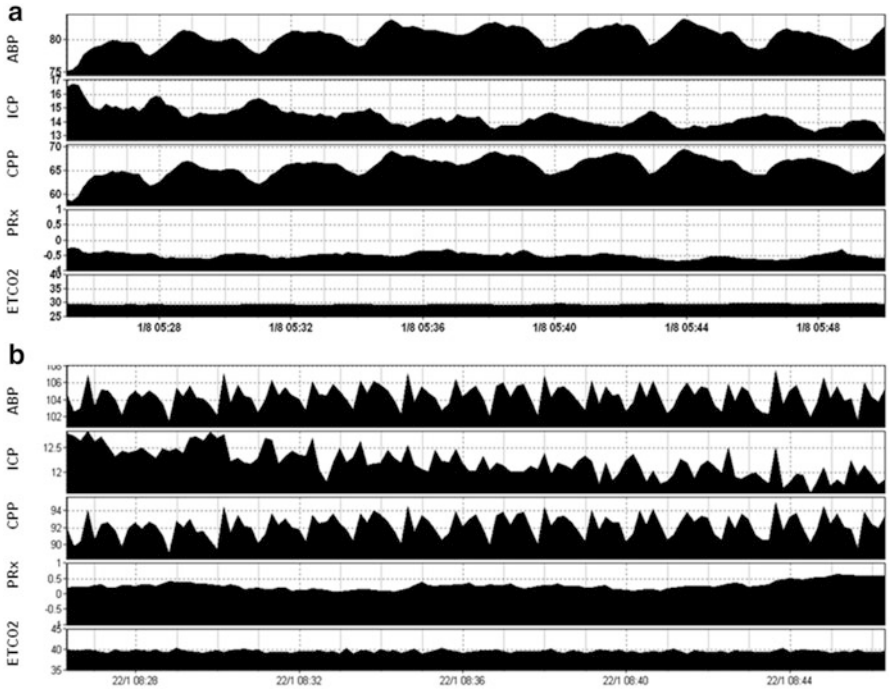

Fig. 21.4 Example of two multimodality brain recordings (own material) performed in TBI patients: *ABP* arterial blood pressure, *ICP* intracranial pressure, *CPP* cerebral perfusion pressure, *PRx* pressure reactivity index, and $EtCO_2$ end-tidal carbon dioxide partial pressure. All variables in mmHg with exception of PRx which is dimensionless. X-axis: time in format date hour – minute. Upper panel: example of continuously negative PRx indicating good cerebrovascular reactivity – note inverse reaction of ICP to slow changes in ABP. Lower panel: gradually deteriorating cerebrovascular reactivity with PRx increasing from 0.2 to above 0.5. CPP is well above 90 mmHg, system works probably above the upper limit of autoregulation

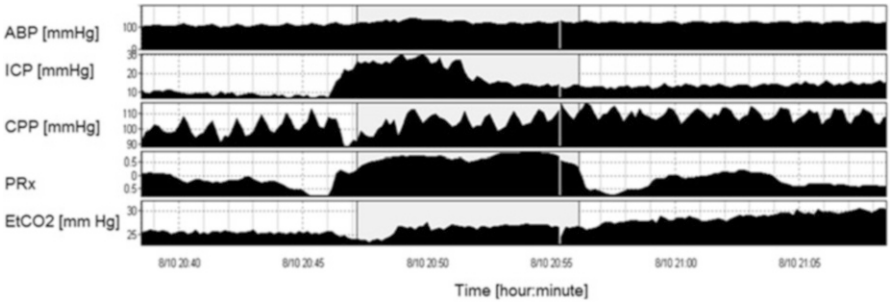

Fig. 21.5 Example of recordings with variables as described in Fig. 21.4, during shallow ICP plateau wave (ICP increasing from 10 to 30 mmHg), with PRx increasing from negative to positive values. This indicates loss of cerebrovascular reactivity during vasodilatation on top of plateau wave

The hypothesis that the PRx is an indicator of autoregulation has been validated in multiple studies.

- Observation of fast hemodynamic transients:
  - Time-related changes of PRx can be monitored during plateau waves with a change from negative to positive values indicating good reactivity before the wave and disturbed autoregulation during the wave when maximal vasodilatation takes place (Fig. 21.5).
  - During arterial hypotension, PRx incidentally increases to deeply positive values.
  - PRx deteriorates before refractory intracranial hypertension and improves after administration of hypertonic saline.
- Validation of PRx with other methods of assessment of autoregulation:
  - *PRx and Mx* – Budohoski et al. [31] showed highly significant correlation between PRx and transcranial Doppler mean flow index (Mx) autoregulation across a large number of patients and recordings.
  - *PRx and PET-based autoregulation* – Steiner et al. [39] compared PRx with PET-based static rate of autoregulation (SRoR), indicating strong association between both measurements ($r^2 = 0.31$; $p = 0.02$) in head injury.
  - *PAx and PRx* – Aries et al. [40] showed a significant correlation between PAx (moving correlation technique between slow fluctuations of ABP and ICP pulse amplitude) and PRx in severe TBI patients. Importantly, PAx is potentially more robust at lower values of ICP than PRx.
  - *PRx and LLA* – Brady et al. [41] indicated in laboratory model that the level of CPP below which PRx was very specific for loss of autoregulation. PRx increases above 0.3 coincide with CBF-assessed lower limit of cerebral autoregulation with area under the receiver-operator characteristics (ROC) curve of order 0.79.

- Comparison of PRx with measurement of CBF and cerebral metabolic rate:
  - *PRx and $CMRO_2$* – Steiner et al. [42] using PET measured global CBF, $CMRO_2$, and oxygen extraction fraction in 22 head injury patients. $CMRO_2$ showed an inverse association with PRx. The correlation between PRx and the O_2 extraction fraction was fitted to a quadratic model. This model suggests that both low O_2 extraction fraction (indicating luxury perfusion, hyperemia, or necrotic tissue) and high O_2 extraction fraction (representing poor perfusion or ischemia) are associated with disturbed pressure reactivity.
  - *PRx and microdialysis* – Timofeev et al. [43] in a group of 232 patients showed PRx was positively associated with lactate/pyruvate ratio (L/P), commonly used as a biochemical marker of ischemia. PRx, along with L/P, glutamate, glucose, ICP, and age, was included as an independent factor for a logistic model for mortality prediction.
- PRx in clinical practice:
  - *PRx and outcome* – Abnormal cerebrovascular pressure reactivity is associated with a fatal outcome after head injury [44], intracerebral hemorrhage [45], and subarachnoid hemorrhage [46]. In a retrospective analysis of 459 patients, PRx was worse in patients who died (22 %) compared with those who survived. Mortality modeled as a function of PRx was unevenly distributed. The PRx values > 0.25 indicated a mortality rate of 69 %, as opposed to a mortality rate < 20 % in patients with a PRx value < 0.25. In a stepwise multivariate analysis, PRx as well as ICP, age, and Glasgow Coma Score emerged as independent predictors of outcome.
  - *PRx and CT* – In a study comparing outcome with PRx and the CT classification [47] (according to the Marshall CT classification system), PRx showed a better correlation with outcome than the CT classification. Separating patients into 2 groups (one with positive and the other with negative PRx values) showed that the mortality rate differed considerably (28.6 % in those with positive PRx values vs. 9.5 % in those with negative PRx values), even though both groups did not show statistically significant differences in ICP and CPP values and CT scores.
  - *PRx and optimal CPP* – The relationship between cerebrovascular pressure reactivity and CPP shows a U-shaped curve (Fig. 21.6), suggesting that very low or high CPP values are unsuitable for maintenance of a good cerebrovascular reserve. Both too low (ischemia) and too high CPP (hyperemia and a secondary increase in ICP) are adversarial; CPP should be optimized to maintain cerebrovascular reactivity in the most favorable state. The question has been asked whether optimal CPP (the CPP that assures minimal, preferably negative PRx) can be identified in individual patients and followed over time. Steiner et al. [48] reported that in two thirds of patients with head injury, PRx plotted against CPP displayed a U-shaped curve. Consequently, optimal CPP can be evaluated in most individual cases. In this retrospectively evaluated cohort, patient outcome correlated with the difference between the

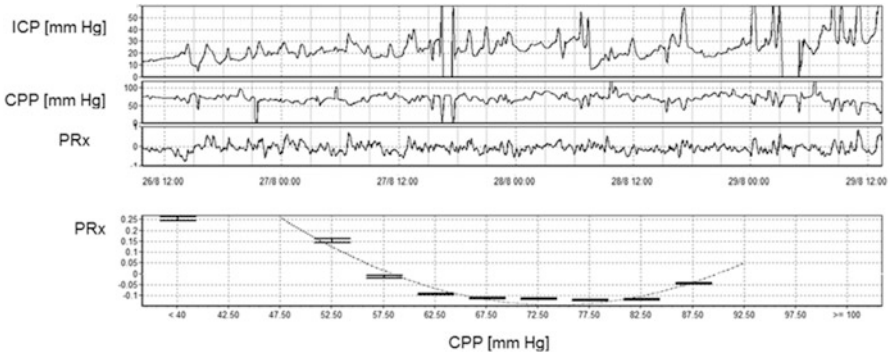

Fig. 21.6 Example of fitting U-shaped curve to CPP-PRx distribution using recording from 3 days monitoring of the TBI patient with unstable ICP (note variations ranging to 50 mmHg). Computer would suggest "optimal CPP" at 72.5 mmHg. However, minimum is quite wide. It would be probably more reasonable to choose minimal CPP optimizing PRx which equates to around 65 mmHg

averaged CPP and optimal CPP for patients who were treated on average below optimal. A later study of Aries et al. [40] validated the CPPopt algorithm by determining the association between outcome and the deviation of actual CPP from CPPopt in 327 traumatic head injury patients. Patient outcome correlated with the continuously updated difference between median CPP and CPPopt (chi-square = 45, $p < .001$; outcome dichotomized into fatal and nonfatal). They also demonstrated that patients treated at CPP lower than CPPopt had increased risk of mortality and those treated at CPP above CPPopt were more likely to attain a severe disability score. The highest rate of favorable outcome was recorded in those patients whose average CPP was not different from CPPopt +/− 5 mmHg.

– *PRx and decompressive craniectomy* – Decompressive craniectomy is an advanced treatment option for ICP control in patients with traumatic brain injury. The pressure-volume curve has an exponentially increasing shape, which is particularly steep after head injury. This curve becomes flat after decompressive craniectomy, which makes the prerequisite assumption for PRx as an index of cerebrovascular reactivity probably invalid. In a retrospective study with 17 patients submitted to decompressive craniectomy, PRx deteriorated postoperatively initially and improved in the later postoperative course [49].
– *PRx and hypothermia and rewarming* – The clinical benefit of hypothermia in the treatment of refractory intracranial hypertension is not yet clear. In 24 patients with head injuries, PRx was monitored during hypothermia/rewarming. Hypothermia helped to control increased ICP and did not impair pressure reactivity. Slow rewarming up to 37.0 ° C (rate of rewarming 0.2 °C/h) did not significantly increase ICP or PRx. However, in 17 of 24 patients who underwent rewarming and whose brain temperature exceeded

37 ° C, ICP remained stable, but the average mean PRx increased above 0.3, indicating a significant derangement in cerebrovascular pressure reactivity [50].

Continuously monitored ICP is an essential modality in neurointensive care for acute brain lesion assessment as it evolves in time. Some of these severe patients may need surgical interventions. PRx is a secondary index, calculated using ICP and ABP and can be used as a surrogate marker of cerebrovascular impairment. Continuous monitoring of PRx allows the determination of the CPP at which cerebrovascular pressure reactivity reaches its optimal value in individual patients and may be useful during anesthesia management in the operating theater.

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Part V
Anesthetic Management: Specific Issues for Neuroanesthesia

Chapter 22
Preoperative Assessment

Hiromichi Naito and Naoki Morimoto

Abstract In this chapter, we discuss the major principles of preoperative anesthetic assessment in patients undergoing neurosurgical procedures due to their importance in ensuring a favorable outcome. The focus of the patient's medical history, the physical examinations and tests required, instructions on preanesthetic medication, and policies on preoperative fasting are described. Neurosurgical procedures should ideally be preceded by a comprehensive neurological assessment. This should include a general neurological evaluation such as according to the Glasgow Coma Scale. The reaction of the pupils and motor and sensory function should also be assessed. If there is evidence of elevated intracranial pressure, the appropriate evaluation should be made. Focal neurological assessment can help identify neurological deficits and other abnormalities of the related nerve systems. Determining the patient's history of and predisposition to seizures may also be helpful. Imaging, such as by computed tomography or magnetic resonance imaging, can provide additional information regarding pathological lesions and other visible morphological abnormalities of the brain. In cases involving emergency surgery, a complete preoperative evaluation may not be possible. Nonetheless, the anesthesiologist should still attempt to perform the most critical evaluations in such patients.

These evaluations involve multiple assessments performed with the aim of anticipating intraoperative or postoperative complications. Many problems can be anticipated and avoided with adequate preoperative assessment and planning.

Keywords Evaluation • Medical history • Physical examination • Medication • Fasting

22.1 Introduction

The aim of preoperative assessment in patients undergoing neurosurgery and anesthesia is to improve outcome by evaluating existing medical complications and predicting anesthetic difficulties. The extent and timing of this assessment is

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sometimes determined by the urgency of the neurosurgery to be performed. Many intraoperative and postoperative problems can be both anticipated and avoided with adequate preoperative assessment and planning.

22.2 Medical History

The information listed below should be obtained from the interview and medical records: (1) anesthesia history (anesthesia and other drugs used in the past; tracheal intubation; postanesthesia headache, nausea and vomiting, hoarseness, and delayed return of consciousness; and unexpected admission to intensive care unit), (2) allergy history (alimentary allergies [soy oil, egg yolk, fish, and seafood]; allergies to local anesthetic, antibiotics, or nonsteroidal antiinflammatory drugs; allergic symptoms, including skin symptoms such as flushing or itching, swelling of face or oral mucosa, difficulty in breathing, wheezing, or circulatory collapse), (3) family medical history (neurological disease, hypertension, cardiac disease, diabetes mellitus, tuberculosis, cancer, allergy, asthma, and malignant hyperthermia), and (4) use of tobacco and alcohol (number of cigarettes smoked per day and number of years a smoker, alcohol consumption).

22.3 Physical Examination and Tests

22.3.1 Airway

A detailed physical examination should be conducted of the airway, with particular regard to the range of motion of the cervical spine and the jaw, the size and shape of the jaw and tongue, the condition of the teeth (loose or damaged teeth or crowns), the thyromental distance, the posterior pharyngeal space, tracheal deviation, and cervical mass. A number of measures are available for predicting potential difficulty in tracheal intubation, including the Mallampati classification [1] and Intubation Difficulty Scale [2]. Although such scales may aid in predicting potential problems, none can guarantee identification of potential difficulties in intubation. Predicting such difficulties in an emergency setting may also present problems. Moreover, extension of the neck is contraindicated in patients with head trauma or suspected cervical spine injury. Flexible fiberoptic bronchoscopy and video laryngoscopy offer two useful alternatives in securing the airway in such patients.

22.3.2 Respiration

Pulmonary disease increases the risk of perioperative complications, and increased attention must be paid to obtaining a focused medical history and carefully observing respiratory condition (rate, depth, and pattern) in patients with symptoms of dyspnea, chronic cough, or exercise intolerance. Predictors of perioperative risks include smoking, poor general health status, older age, chronic obstructive pulmonary disease, and asthma [3]. Examinations such as chest X-ray and the pulmonary function test can be useful in these patients.

22.3.3 Circulation

Cerebrovascular disease is often comorbid with cardiovascular diseases such as hypertension and coronary artery disease. Predictors for the risk of perioperative cardiac complications are listed in Table 22.1. Nonemergency surgery should be postponed for medical management if a major risk predictor is present. In patients judged as being at intermediate clinical risk, exercise tolerance should be taken as indicating the need for further testing. Noninvasive testing should be carried out in patients in whom such risk factors are either minor or absent if they have poor functional status or the planned surgical procedure is high risk. The results of such tests should help determine whether medical management is required such as preoperative cardiac catheterization, which can lead to coronary revascularization or even cancelation or delay of the planned operation. Some anesthetic and surgical procedures such as controlled hypotension or seated-position surgery should be avoided if ischemic heart disease is diagnosed.

22.3.4 Liver, Kidney, and Endocrine

Biochemical and electrolyte examination is required when hepatic, kidney, and/or endocrine dysfunction is suspected from the medical interview or history. Hepatic dysfunction due to the use of anticonvulsants and renal dysfunction due to hypovolemia are common disorders requiring attention in patients with neurological disorders.

22.3.5 Blood Products and Electrolytes

In neurosurgical procedures with the potential risk of blood loss, individual clinical indications such as age, poor nutrition status, history of hematologic disorders and

Table 22.1 Clinical predictors of increased perioperative cardiovascular risk (myocardial infarction, heart failure, death)

Major
Unstable coronary syndromes
Acute or recent myocardial infarction with evidence of important ischemic risk by clinical symptoms or noninvasive study
Unstable or severe angina
Decompensated heart failure
Significant arrhythmias
High-grade atrioventricular block
Symptomatic ventricular arrhythmias in the presence of underlying heart disease
Supraventricular arrhythmias with uncontrolled ventricular rate
Severe valvular disease
Intermediate
Mild angina pectoris
Previous myocardial infarction by history or pathological Q waves
Compensated or prior heart failure
Diabetes mellitus
Renal insufficiency
Minor
Advanced age
Abnormal ECG (left ventricular hypertrophy, left bundle branch block, and ST-T abnormalities)
Rhythm other than sinus (e.g., atrial fibrillation)
Low functional capacity (e.g., inability to climb one flight of stairs with bag of groceries)
History of stroke
Uncontrolled systemic hypertension

Data are from Eagle et al. [4]
ECG electrocardiogram

bleeding, cardiac/pulmonary/hepatic/renal disease, chemotherapy or radiation treatment, and steroid or anticoagulant therapy should be taken into account when evaluating the blood count. Sufficient blood preparations are needed when performing procedures for conditions which may involve extensive blood loss such as massive brain tumor and trauma. Preoperative "Type and Screen" is useful and cost effective when the likelihood of transfusion is low and the antibody screen is negative. Postponing elective surgery should be considered when anemia of uncertain cause is present.

Preoperative use of loop or osmotic diuretics may cause a loss of water and sodium ions, leading to a dehydrated/hypertonic (elevated hematocrit) state and electrolyte abnormalities. Electrolyte abnormalities, especially in sodium ions, can also be caused by head trauma, tumor, or hematoma.

22.3.6 Coagulation and Platelets

A coagulation test and platelet count are essential in cases of head trauma, intracranial hemorrhage, or other surgical procedures with anticipated bleeding, a medical history of a bleeding disorder, hepatic disease, poor nutritional status, use of anticoagulants or other drugs that affect coagulation, and/or anticipated use of anticoagulant therapy during the perioperative period.

22.4 Neurological Assessment

Patients undergoing neurosurgical procedures may present with a variety of symptoms, and a general neurological examination should be performed. This should include an evaluation of the patient's psychiatric state, cognition, Glasgow Coma Scale (GCS) score, papillary findings, and motor and sensory function (paralysis); the presence or absence of seizures should also be determined. Evidence of increased intracranial pressure (ICP) should be assessed at the preoperative visit (Table 22.2). In addition, other preoperative data such as those obtained from computed tomography (CT) and magnetic resonance imaging (MRI) should also be reviewed for signs of increased ICP.

22.4.1 Evaluation of Increased ICP

It is important to determine whether there is an increase in preoperative ICP, with particular attention to potential early-phase symptoms. Intracranial mass lesions such as a tumor, hematoma, and abscess may induce an increase in ICP. Brain edema and disturbances in cerebral autoregulation can occur, even in unaffected areas surrounding the mass. A further increment in ICP may cause herniation and brain stem ischemia. Brain herniation frequently presents with abnormal posturing

Table 22.2 Preoperative signs of elevated ICP

Positional headache
Nausea and vomiting
Hypertension
Bradycardia/tachycardia
Altered level of consciousness
Abnormal breathing pattern
Papilledema
Personality alteration
Oculomotor nerve palsy
Abducens nerve palsy

ICP intracranial pressure

(decerebrate/decorticate) or hemiplegia and a lowered level of consciousness as indicated by a low GCS score. The pupils may be dilated and fail to constrict in response to light, and oculomotor or abducens paralysis may occur in these patients. They may also present with abnormal irregular respiration or hypertension with bradycardia or tachycardia. Vomiting can occur due to compression of the medulla oblongata.

22.4.2 Focal Neurological Deficits

Motor/sensory paralysis or verbal disorder occurs when the corresponding area is compressed by a tumor or hematoma. Diseases of the brain stem area can result in abnormalities in cranial nerve function, and pituitary disease can result in optic or trigeminal nerve abnormalities. Cranial nerve palsy can indicate brain aneurysms in some cases; for example, oculomotor nerve palsy can occur in an internal carotid-posterior communicating aneurism.

22.4.3 Seizures

Various conditions requiring neurosurgery such as a brain tumor, aneurysms, arteriovenous malformations, stroke, infections, and classic epilepsy may cause seizures. The type of seizure (focal or generalized), frequency, and symptoms (movement, sensation, and awareness) should be evaluated. Furthermore, the level to which the seizures can be controlled and the side effects of anticonvulsants should also be assessed. Poorly controlled or new-onset seizures may require appropriate dose adjustment.

22.4.4 Neuroimaging Assessment

Preoperative preliminary CT/MRI images should be assessed. Cerebral midline shift and ventricular/cisternal compression indicate a reduction in intracranial compliance. If an intracranial space-occupying lesion (tumor mass/hematoma) is present, the blood vessels of the surrounding pathological lesion should be observed and the area assessed for edema. The pathological characteristics of the intracranial tumor mass may influence perioperative management; for example, intraoperative bleeding may increase during surgeries for well-vascularized masses (meningioma or metastatic brain tumor). Surgery for an invasive malignancy tumor may lead to severe postoperative brain edema, which would require a considerable restriction of intravenous fluids. If the pathology is near the venous sinuses, there is a risk of

Table 22.3 Location-based interpretation points of CT/MRI findings

Extracranial lesion	Subcutaneous hemorrhage and swelling, infection, and abscess
Cranial bone	Fracture and dissociation of suture, previous operation
Brain surface lesion	Bleeding and hemorrhage (epidural hematoma, subdural hematoma, or subarachnoid hemorrhage), abscess, and pneumocephalus
Intraparenchymal lesion	Site, size, shape, density, bilateral difference (existence of midline shift), diagnosis (brain tumor, brain contusion, or intracerebral hematoma) of space-occupying lesion, abnormal blood vessel
Ventricular lesion	Bilateral difference (existence of midline shift), compression (slit), expansion, and hemorrhage of ventricle
Cisternal lesion	Narrowing of basilar cistern (compression of brain stem), bleeding, and pneumocephalus

CT computed tomography, *MRI* magnetic resonance imaging

venous air embolism. A systematic interpretation of CT/MRI findings in patients scheduled to undergo neurological surgery is presented in Table 22.3.

22.5 Medication

Medication may be required in treating some patients with neurosurgical disease or comorbidities. Depending on the type of medication used, this may have a positive or negative effect intraoperatively, and discontinuation of a medication can also have a detrimental effect in this regard. Therefore, it is important to take the surgical procedure and comorbidities into account in deciding whether to continue or discontinue a given drug. Table 22.4 shows which drugs should be continued and which should not. Osmotic or loop diuretics and steroids may be used to treat brain edema, and anticonvulsants can be used to treat seizures during perioperative neurosurgical management. These medicines should be continued during the perioperative period. However, careful attention must be paid to adverse effects such as hypovolemia, hyperglycemia, and liver dysfunction when using these medications.

Preoperative pharmacological premedications such as sedatives and opioids may induce ventilation depression, which can lead to increased partial pressure of carbon dioxide ($PaCO_2$) and a subsequent increase in ICP. Therefore, these medications should not be administered to patients in whom an ICP increase is expected.

22.6 Preoperative Fasting

Preoperative fasting requires that no clear fluids be orally ingested within 2 h or a light meal within 6 h prior to elective surgery [5]. These restrictions are not applicable to patients with conditions such as a history of gastroesophageal reflux,

Table 22.4 Preanesthetic medication

Discontinue before surgery	Continue until surgery
Antihypertensives	Antihypertensives
(ACE inhibitors or angiotensin receptor blockers)	(Beta blockers or calcium channel blockers)
Antiplatelet therapy or warfarin	Diuretics
(Heparin can be used as bridging agent)	Thyroid medications
NSAIDs	Insulin
Oral hypoglycemic medications	Anticonvulsants
Digitalis products	Asthma medications
Antipsychotic medications	Steroids
Supplements	Anti-Parkinson's medications
	Antiarrhythmic medications

NSAIDs nonsteroidal antiinflammatory drugs, *ACE* angiotensin converting enzyme

morbid obesity, diabetes mellitus, the use of specific medicines (L-dopa, phenothiazine, tricyclic antidepressants, calcium channel blockers, or opioids), or who are at risk of delayed gastric emptying.

In patients with impaired consciousness, a long fasting period may impair hydration and electrolyte balance, necessitating this to be determined and corrected if present.

22.7 Emergency Surgery

In many conditions requiring neurosurgical intervention such as ongoing intracranial hemorrhage, trauma, or other neurologic emergencies, the patient has to be transported to the operating room as quickly as possible, leaving little time to make a preoperative assessment. Additionally, the patient may have impaired consciousness or communication or be intubated before induction of anesthesia, making a precise assessment even more difficult. In such cases, preoperative assessment should at least involve determining any increase in ICP (as evidenced by nausea and vomiting, alterations in the level of consciousness, pupillary dilation, or decreased reactivity of the pupils to light), blood pressure, or pulse rate and any respiratory abnormalities. Further information obtained from the emergency physician or attending neurosurgeon can be valuable in these circumstances.

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Chapter 23
Neurosurgical Technique and Approach

Eiichi Suehiro and Michiyasu Suzuki

Abstract In a neurosurgical procedure, a suitable surgical environment should be established to conduct the operation in a comfortable position. Therefore, the satisfactory layout of surgeon, staff, and equipments is important.

It is difficult to maintain an intraoperative field in serious neurosurgical disease due to intracranial hypertension. It is necessary to choose the most appropriate surgical route to lesion and methods which drops intracranial pressure prior to operation in order to prevent brain damage. Further, additional attention is required in comparison with general surgery, because systemic circulation and respiration are also damaged due to intracranial hypertension, cerebrovascular autoregulation breakdown, and decreased circulating blood. There is a requirement to maintain the cerebral oxygen supply to prevent neurosurgical complications.

Keywords Neurosurgical procedure • Operation room • Intracranial hypertension

23.1 Introduction

In a neurosurgical procedure, the satisfactory layout of surgeon, staff, and equipments is important. Neurosurgeons have to prepare for various situations to make an operation successful. A neurosurgical procedure requires additional attention to prevent postoperative complication. A suitable surgical environment should induce the procedure of an operation smooth.

Further, it is necessary to choose the most appropriate surgical route to lesion and methods which drops intracranial pressure prior to operation in order to prevent brain damage. Systemic circulation and respiration are also required stable to maintain the cerebral oxygen supply to prevent neurosurgical complications.

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23.2 Layout of the Operation Room

A suitable surgical environment should be established to conduct the operation in a comfortable position. Anesthesia devices, microscope, surgical bed and equipment base, etc., should always be prepared under the same conditions in order to conduct each surgery in the same routine environment. If a surgeon feels physical discomfort with the introduction of a microscope, slight differences in layout, position, head rotation, up-down of the vertex, height of surgical chair, and degree of the microscope eyepiece should be considered. The operation should be conducted in comfort and the layout corrected until satisfaction is obtained. A surgeon should stand during the operation until the brain is opened and work in a seated position of an electric chair after the introduction of a microscope (Fig. 23.1). A nurse should then stand with a steerable equipment base on the right hand side of the surgeon, thereby allowing passage of devices to the surgeon (Fig. 23.1). Both the anesthesiologist and nurse should confirm surgical progression with two monitors (Fig. 23.1).

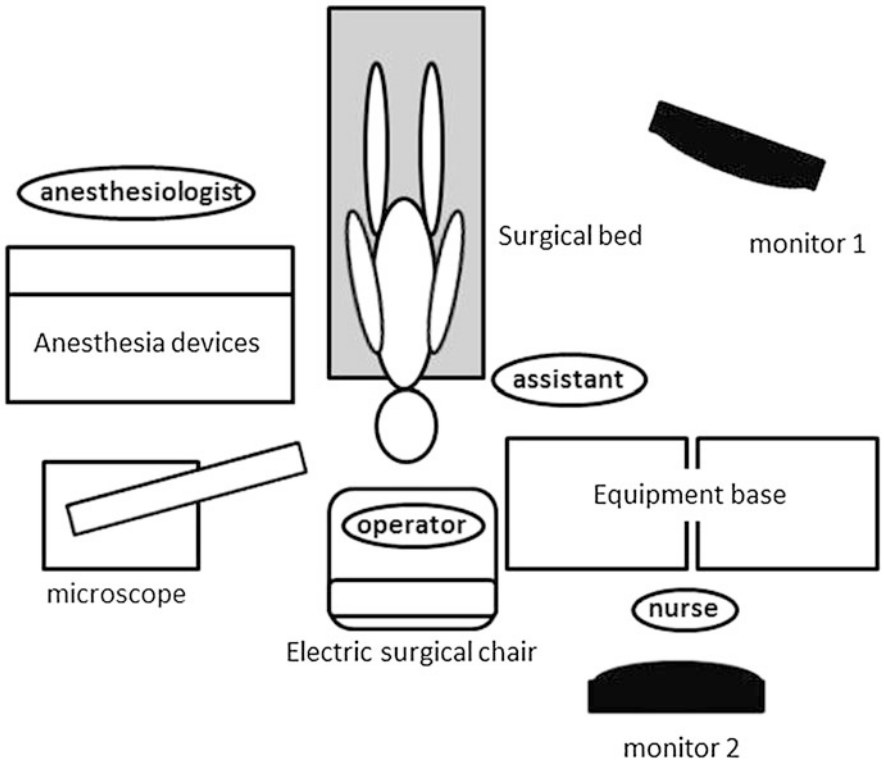

Fig. 23.1 Layout of the operation room

23.3 Position and Patient Stabilization

Both shoulders, hip, and lower limbs should be fixed, in order to prevent problems in turning a patient left or right and moving patient's head up and down on the operating table. A surgeon should not move but adjusts a patient to perform subtle operation without introducing a stress position. Confirm that the patient is lying on a surgical bed without risk by sloping the bed to the maximum of the motion range prior to surgery. Use an equipment base that is fixed with an operation table that is adjustable for the degree of motion required. An equipment base which allows a free change in the degree of operation table is necessary. A surgeon performs the operation in a seated position of an electric chair. He/she should be free from fatigue in order to do subtle operations by fixing the upper arms to the hands. The optical axis should be changed to the operative field from an overhung position to the direction of the skull base by changing the degree of microscope eyepiece and objective and moving the chair up and down simultaneously. The head position can be changed from the vertical to the horizontal position by rotating the operative table, providing multidirectional observation of the operative field. An electric chair is useful; however, caution should be exercised against accidental brain injury, unless a surgeon removes a brain retractor from the operative field, thereby producing a low-power field during replacement and rotation of the operative table.

23.4 Important Points in Neurosurgical Procedure

23.4.1 Cerebrovascular Disorder

In a neurosurgical procedure of a cerebrovascular disorder, cerebral and systemic circulation is damaged due to intracranial hypertension, cerebrovascular autoregulation breakdown, decreased circulating blood, and respiratory/circulatory complications. This requires additional attention in comparison with general surgery. There is a requirement to maintain the balance between cerebral oxygen supply and demand. However, the development of an operative field requires the evacuation of intracranial pressure, frequently resulting in decreased regional cerebral blood flow (rCBF). In order to prevent ischemia, it is important to maintain the level of systemic oxygenation and cerebral perfusion pressure at the appropriate threshold considering decreased rCBF during surgery. Cerebral aneurysm rupture due to increased blood pressure and backing at the induction of anesthesia and during surgery may cause catastrophic results and sometimes death. Therefore, appropriate caution should be paid, in particular, to this neurosurgical procedure. Recently, microsurgery and the frequency of cerebral aneurysm rupture have been improved due to intraoperative manipulation. Consequently, artificial hypotension is not required compared to previous procedures, but the maintenance of cerebral perfusion pressure during surgery is needed. However, specific cerebral aneurysms,

including a giant cerebral aneurysm, often require artificial hypotension and circulatory arrest during hypothermia. Serious neurosurgical disease is likely to cause intracranial hypertension. Consequently, it is difficult to maintain an intraoperative visual field. Forced expansion of the visual field causes new lesions due to strong evacuation of intracranial pressure and intravenous perfusion damage. Blind manipulation may cause ruptured aneurysm and vascular injury. Therefore, the operation under conditions of decreased cerebral volume (slack brain), by controlling intracranial pressure, provide cerebroprotective surgery. A transient block of blood flow, a common problem in surgery during a cerebrovascular disorder, is frequently used in neurosurgical procedures. In clipping the cerebral aneurysm, a brief transient block is performed to facilitate surgical manipulation by decreasing the pressure in cerebral aneurysm. Therefore, it is not clinically crucial. However, in unexpected aneurysm rupture, blood flow is blocked for a long time, and normal manipulation sometimes induces cerebral infarction. Therefore, it is recommended that precautions be made for the maintenance of cerebral perfusion pressure, the administration of cerebroprotective agents, and the treatment of hypothermia prior to surgery.

23.4.2 Brain Tumor

The objectives of surgery are roughly classified: (1) complete removal of tumor tissues for radical operation, (2) resection to support adjunct therapy or to relieve current symptoms, and (3) biopsy for histology. It is necessary to choose the most appropriate surgical route prior to operation in order to prevent brain damage, and it is also important to choose the most appropriate surgical site, which is suitable for surgery. Surgery of tumors in the frontal and temporal lobes is generally conducted in the supine position, whereas surgery in the parietal and occipital lobes is done in the lateral or prone position. Specific surgical manipulation includes the route via the sphenoid sinus for surgery of pituitary tumor, and operation of pineal tumor is performed in the sitting position. If severe edema is expected, larger-scale craniotomy in the head raised and slight hyperventilation are required. On the other hand, intracranial pressure is decreased by placing lumbar and ventricular drainage in place, prior to tumor resection or opening the basilar cistern and eliminating spinal fluid during an early stage of surgery. If massive bleeding is expected, it is necessary to conduct vascular embolization of tumor vasa vasorum prior to surgery by selecting the entering route to treat a diseased vessel earlier and reducing blood pressure. Skin incision and craniotomy are determined based on the lesion site and size. Malignant tumors including glioma are resected by separating a tumor from normal brain. However, the border is not always clear. The border is decided by color and stiffness. However, recent technology utilizes navigation and fluorescent dye. Tumor cells frequently invade the area that is considered to be a marginal brain area, due to the characteristics of tumor. Glioblastoma contains angiogenesis and arteriovenous shunts, and furthermore since it is hemorrhagic, the border is unclear

due to hemorrhagic necrosis, cysts, and soft lesions. In surgical procedures such as cerebral extraparenchymal tumor, including meningioma, the dura adhering to a tumor requires resection. Adjoining cerebral tissues are minimally tracted or resected, and the border between the brain and tumor is detached. If the tumor size is large and it is difficult to remove the tumor as a lump, the internal part of tumor is first removed, and the remaining tumor is detached and resected from the peripheral brain after decompression.

23.4.3 Head Trauma

Neurosurgical procedures for head trauma include trephining and craniotomy. Trephining is conducted when a patient has brain herniation due to intracranial hemorrhage and requires decompression as soon as possible and the patient cannot undergo craniotomy due to age or complication. Trephining is a surgical procedure for removing epidural and epidural hematoma and inserting a catheter into the cerebral ventricle by making a burr hole. A craniotomy is conducted to remove the skull for advanced intracranial hypertension. If the cause of intracranial hypertension is hematoma, hematoma evacuation is conducted by craniotomy and intracranial pressure is decreased. For diffuse injury without hematoma removal, decompressive craniectomy is conducted to remove bone flaps when intracranial pressure cannot be controlled by internal medicine or ventricular drainage. Intraoperative hypertension is not decreased because usually Cushing's syndrome is involved. The cerebral blood vessel is expanded by decreased blood pressure, while intracranial pressure is enhanced. Shock is likely not to be manifested due to Cushing's syndrome. It is noted that pressure is decreased when opening the brain; shock is manifested, resulting in marked hypotension. If cerebral perfusion recovers after incising the dura and the blood flow returns to the ischemic part, ischemia/reperfusion injury develops and cerebral edema is likely to develop due to vascular hyperpermeability. When using a pressor for hypotension in opening the brain, marked cerebral edema, brain swelling, and intracerebral hemorrhage occur, and the brain rapidly expands.

23.4.4 Functional Neurosurgery

Epilepsy surgery often consists of an operation to set intracranial electrodes and that for treatment of focal epilepsy. The latter includes epileptic focus and cortical focus resection, lobotomy, callosotomy, and hemispherotomy. Involuntary movement of Parkinson's disease, essential tremor, and dystonia are often improved by stereotactic surgery including deep brain stimulation.

23.4.5 Pediatric Neurosurgery

In pediatric neurosurgery, surgery is conducted to treat malformation, malformed condition, and hydrocephalus. In craniotomy for children, no scalp clip is used although it is used in adults. A pediatric scalp clamp is used for the galea aponeurotica. Coagulation is not usually used to prevent damage of the juvenile scalp. In opening the brain, a craniotome for children is used. The periosteum is conserved as much as possible considering a thin scalp. In pediatric craniotomy, the surgical procedure should be performed without blood aspiration by bleeding compression, keeping in mind not to lose a drop of blood, while completing within the bleeding volume treated by transfusion.

23.4.6 Spine and Spinal Cord Surgery

The basic rules for spine and spinal cord surgery are same as those for common surgery. However, the former targets improvement in social life including activities of daily living (ADL) and quality of life (QOL) rather than improvement in prognosis alone. Patients who undergo spinal surgery are often the elderly and have cardiovascular, respiratory, and metabolic complications including hypertension, ischemic heart disease, emphysema, and diabetes, regardless of primary disease. Patients who undergo surgery for cervical spine disease have a narrow cervical disk and vulnerable cervical cord. Consequently, limb dysfunction deteriorates by slight compression and force to the cervical cord by the cervical spine position and postural change. A surgeon and anesthesiologist should discuss the moving range of the cervical spine and airway management until intratracheal intubation and its procedure prior to surgery. Also in surgery for spinal trauma, decompression of the spinal cord is performed. In a patient with unstable vertebral fracture, attention should also be paid not to deteriorating symptoms but secondary damage to the spinal cord in setting the position.

Chapter 24
The Management of Intracranial Pressure and Cerebral Edema

Yasuhiro Kuroda, Kenya Kawakita, and Toru Hifumi

Abstract The brain is encased in a confined space, and an increase in the volume of the intracranial contents or any space-occupying lesion may lead to elevated intracranial pressure (ICP). As well as assessing the absolute value of ICP, neurointensivists should also consider the character of the ICP waveform: a poorly compliant waveform suggests that even minor changes in the patient's condition, such as head position or inadequately treated pain or agitation, may trigger an ICP crisis even when the ICP lies within the normal range.

ICP values should be considered together with cerebral perfusion pressure (CPP), which is calculated by subtracting ICP from the mean arterial pressure. In the setting of systemic hypotension, a CPP less than 50 mmHg may result in brain injury and poor outcome. Strategies to optimize CPP should be tailored to individual patients. Nevertheless, a higher CPP does not necessarily mean better cerebral blood flow.

The management of ICP should be undertaken in an organized, stepwise approach. A full understanding of the pathophysiology of elevated ICP is required to guide neurointensivists' decisions about the timing, duration, and magnitude of ventricular CSF drainage, sedation strategies, the need for osmotherapy, and control of cerebral vasodilation. Therapeutic hypothermia (with a target core body temperature of 32–34 °C) can be an effective method of reducing raised ICP that is refractory to other treatments.

Keywords Intracranial pressure • Cerebral perfusion pressure • Cerebral edema

24.1 Introduction

Any space-occupying lesion or an increase in the volume of the intracranial constituents may lead to elevated intracranial pressure (ICP), which should be considered along with cerebral perfusion pressure (CPP). The concept of the

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compliance of the ICP waveform is also important. Neurointensivists should appreciate that changes in ICP compliance can be used to guide interventions such as cerebrospinal fluid (CSF) diversion and ventricular drain management and guide medical therapy including therapeutic hypothermia.

24.2 Physiology of Intracranial Pressure

The brain produces 500 mL of CSF per day, two-thirds of which is secreted by the ependymal cells of the choroid plexus. The choroid plexus is a venous plexus that runs throughout all four cerebral ventricles, hollow structures inside the brain that are filled with CSF. The remainder of the CSF is produced by the surfaces of the ventricles and by the lining surrounding the subarachnoid space. CSF returns to the vascular system via the arachnoid granulations (or villi) and thence to the dural venous sinuses. As CSF is constantly reabsorbed, only 100–160 mL is present at any moment.

ICP is defined as the pressure exerted by the contents of the skull on the dura mater and is a reflection of the relationship between alterations in craniospinal volume and the ability of the craniospinal axis to accommodate added volume.

The intracranial volume (1.0–1.2 L) is normally occupied by brain parenchyma (70–80 %), blood (10–15 %), and CSF (10–15 %). The craniospinal axis is essentially a partially closed box with container properties that includes both viscous and elastic elements. The elastic or its inverse, the compliant, properties of the container will determine the volume that can be added before ICP begins to rise. An understanding of raised ICP requires an appreciation of the relationship between intracranial volume and craniospinal compliance.

24.3 Pathophysiology of Intracranial Pressure

Normal ICP varies with age, body position, and clinical condition. Normal ICP is pulsatile, as a consequence of intracranial arterial pulsations that reflect the cardiac and respiratory cycles. Based on largely intuitive considerations, the normal mean ICP is 0–10 mmHg in a supine adult, and it is considered abnormal if it exceeds 15 mmHg. Mean levels above 20 mmHg are moderately elevated and sustained levels above 40 mmHg are severely increased. In traumatic brain injury (TBI), it is more common to observe a rise in baseline pressure, rather than in the amplitude of the raised ICP waveform. If a cranial bone flap has been surgically removed, pressure readings can be unreliable. Normal ICP is 3–7 mmHg in children and 1.5–6 mmHg in term infants.

Intracranial hypertension (ICH) occurs as a result of expansion in the volume of the intracranial contents and/or a newly developed mass region. Common causes of ICH include an intracranial space-occupying mass lesion (subdural hematoma,

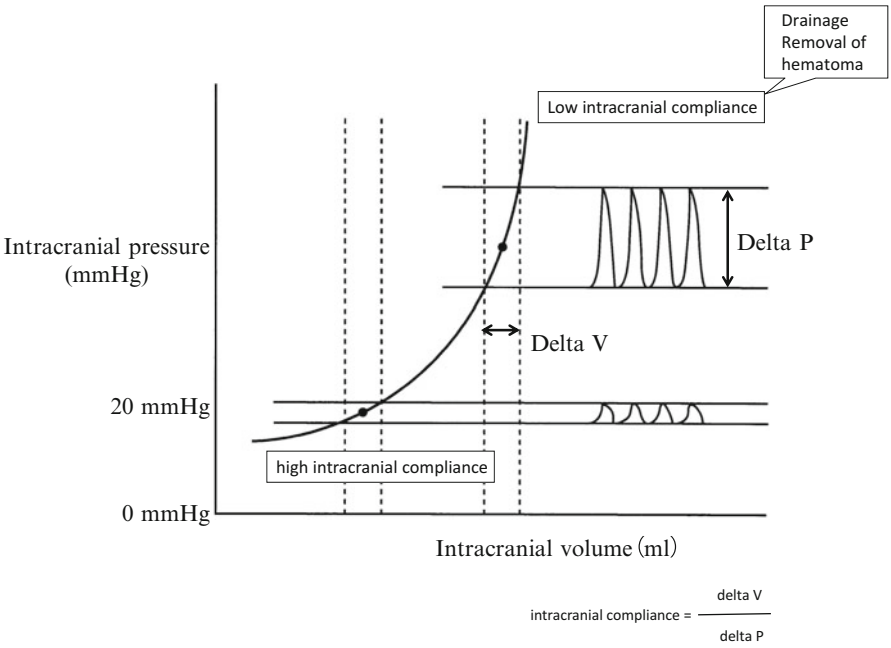

Fig. 24.1 Intracranial pressure-volume curve. If intracranial compliance is low, intracranial pressure increases exponentially even in the face of small increases in intracranial volume

epidural hematoma, brain tumor, intracerebral hemorrhage), increased brain volume (cerebral infarction, hypoxic-ischemic brain injury), increased brain and blood volume (TBI or subarachnoid hemorrhage [SAH]), and increased CSF volume (hydrocephalus). The pathophysiology of ICP elevation has been described by the Monro-Kellie hypothesis, which states that compensation mechanisms exist to moderate changes in ICP with increases in intracranial volume of 50–100 ml, but if this is exceeded, an elevation in ICP is inevitable (Fig. 24.1).

24.4 Cerebral Edema

Cerebral edema is traditionally divided into cytotoxic edema and vasogenic edema. Cytotoxic edema is defined as excess fluid within the intracellular space. After stroke, energy depletion produces cytotoxic edema by the failure of the Na-K ATPase to maintain transmembrane osmotic gradients. Osmotic diuretic therapy is the treatment of choice. Vasogenic edema is defined as excess fluid within the interstitial space and may be evident in a brain tumor or brain abscess or result from a progressive neuroinflammatory process (e.g., acute disseminated encephalomyelitis), disruption of the blood brain barrier, or diffusion of water into the interstitial space. Glucocorticoid therapy may partially attenuate vasogenic edema. After TBI,

cytotoxic edema is prominent within 24 h of injury, and vasogenic edema generally develops 48 h after the insult.

24.5 Autoregulation of Cerebral Blood Flow

The main negative consequence of elevated ICP is reduced cerebral blood flow (CBF) and secondary hypoxic-ischemic injury due to flow reduction. CPP is calculated by subtracting ICP from mean arterial blood pressure (MAP). CBF is determined by CPP and cerebral blood volume (CBV); normally, (static) autoregulation of the cerebral vasculature maintains CBF at a constant level between a CPP of approximately 50–150 mmHg by changing cerebral vascular resistance (Fig. 24.2). Dynamic autoregulation can also be detected using transcranial Doppler ultrasound (Fig. 24.3).

In patients with preserved cerebral autoregulation and a CPP of 60–70 mmHg, controlled increases in CPP may reduce ICP through increases in cerebrovascular resistance that in turn reduce CBV. Brain injury may impair cerebral autoregulation and cause CBF to adopt a more straight-line relationship with CPP (Fig. 24.2). In patients with impaired cerebral autoregulation and CPP >60 mmHg, controlled reductions in CPP to the 40–60 mmHg range can effectively reduce ICP (by decreasing CBF and CBV); however, such manipulations should only be undertaken if simultaneous cerebral oxygenation-ischemia monitoring has been

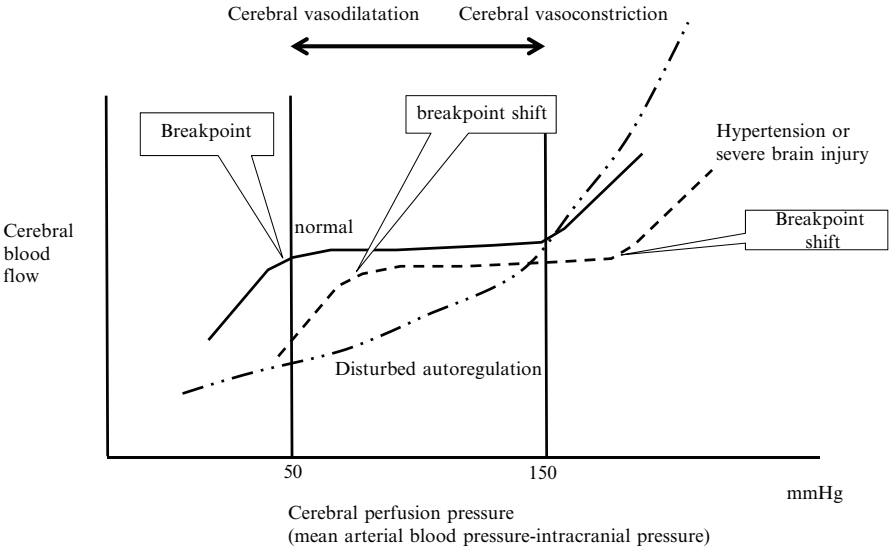

Fig. 24.2 Autoregulation of cerebral blood flow and its disturbance. Cerebral blood flow is maintained at a constant level between cerebral perfusion pressures of approximately 50–150 mmHg as a result of alterations in cerebral vascular resistance

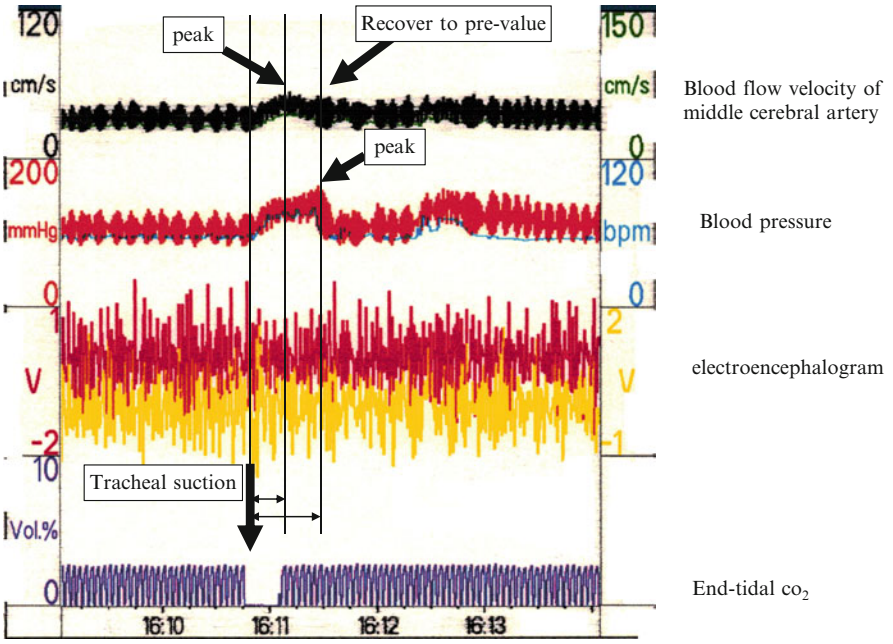

Fig. 24.3 Dynamic autoregulation of cerebral blood flow. The mean flow velocity of the middle cerebral artery increases transiently and then returns to its previous level during tracheal suction, despite persistent elevation of mean arterial blood pressure, suggesting dynamic autoregulation of cerebral blood flow

instituted. A CPP low enough to induce ischemia can trigger reflex vasodilation that raises ICP further. Conversely, a high CPP (>110 mmHg) can sometimes cause breakthrough cerebral edema and thus elevate ICP (Fig. 24.2). Although the optimal CPP for a given patient may vary, in general it should be greater than 60 mmHg (to avert ischemia) and below 110 mmHg (to avoid breakthrough hyperperfusion and cerebral edema).

As described below, if ICP is not controllable by basic treatment, attention should be directed to optimizing CPP.

24.6 Intracranial Pressure Monitoring

ICP monitoring is vitally important in the management of patients with severe TBI, particularly if computed tomography (CT) imaging of the brain is abnormal (e.g., if midline shift, compression of the basal cisterns, or hemorrhagic contusions are evident). Increased intracranial volume may result in brain herniation and reduction of CBF; high ICP is strongly associated with increased disability and mortality [1]. Although ICP can be evaluated noninvasively by transcranial Doppler or optic

nerve sonography, an invasive technique is needed for continuous online monitoring. Intraventricular and intraparenchymal devices provide equivalent pressure measurements, but intraventricular probes also allow CSF drainage. ICP monitors are cost-effective and have an acceptably low complication rate, particularly if inserted in the brain parenchyma.

A recent randomized control trial demonstrated equipoise in terms of major outcome endpoints (mortality and functional recovery) between an ICP monitoring-based management strategy and one based on clinical examination and repeated CT imaging without ICP monitoring. Nonetheless, ICP monitoring was more efficient in guiding therapy, since it reduced by half the number of ICP interventions made per patient as well as the number of intensive care unit (ICU) days during which patients received treatment for TBI [2]. There are numerous causes of elevated ICP [3] and different approaches to therapy [4]. The response to ICP therapy is an important determinant of final outcome: the effective reduction of ICP translated into good recovery. However, a subset of patients fails to respond to aggressive therapy and eventually has a poor outcome [5]. Careful evaluation of the effectiveness of ICP reduction allows interventions to be precisely tailored to individual patients' clinical situations.

24.7 Indications for Intracranial Pressure Monitoring

The diagnosis of increased ICP should not be made clinically, as clinical signs are not reliable and can vary. Instead, ICP must be measured directly, even though this requires invasive monitoring. ICP monitoring is indicated in all pathophysiological conditions in which raised ICP is known to impair outcome (Table 24.1). The routine clinical use of invasive ICP monitoring began with the management of patients with severe TBI, but its use is becoming more widespread in SAH, intracranial hemorrhage, large ischemic strokes, and meningoencephalitis, for example, although outcome data from clinical trials are lacking for these indications (Table 24.1). ICP monitoring is contraindicated in patients with severe coagulopathy.

24.8 Intracranial Pressure Monitoring: Location and Device

Several types of ICP monitors exist (Fig. 24.4). Each measures ICP in a different part of the brain, so the reliability of the ICP value and rate of complications differ between devices.

A ventricular drainage catheter is a standard means of monitoring ICP. It consists of a catheter placed through a burr hole into the anterior horn of the lateral

Table 24.1 Indications for intracranial pressure monitoring

1 The condition in which is recommended to monitor ICP	GCS score < 8
	Rapid neurologic deterioration plus clinical signs of increase ICP
	Hypotension (systolic blood pressure < 90 mmHg)
	Abnormal brain CT findings (midline shift, disappearance of cistern, space-occupying lesion, severe cerebral edema) suggesting at risk for high ICP
	Therapeutic hypothermia
	Barbiturate therapy
2 The condition in which is considered to monitor ICP	CT examination cannot be performed
	Cannot estimate consciousness level because of sedation, anesthesia, prolonged neurologic surgery, prolonged ventilation, or use of PEEP (e.g., ARDS)
3 Case with possible poor outcome	Abnormal posturing (decortication, decerebrate rigidity) in case (<40 years old) with normal brain CT finding

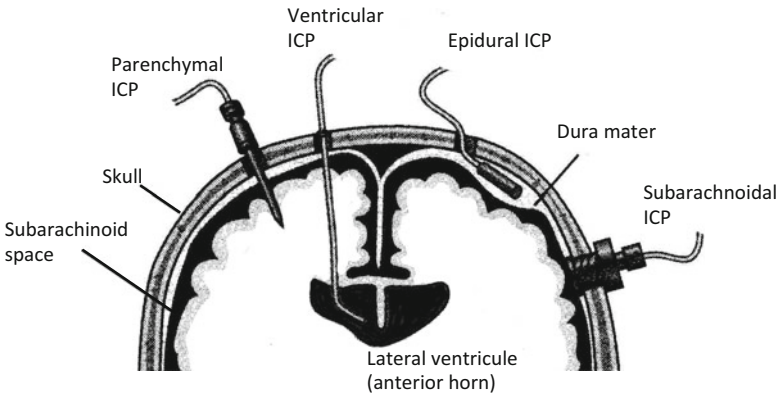

Fig. 24.4 Intracranial pressure monitoring device. Modified from Mayer SA. Management of increased intracranial pressure. In: Wijdicks EFM, Diringer MN, Bolton CF, et al, eds. Continuum: Critical Care Neurology. Minneapolis, MN: American Academy of Neurology, 1997:47–61

ventricle connected to a pressure transducer positioned at ear level, which approximates to the level of the foramen of Monro. This method is cheap and reliable and also allows for therapeutic CSF drainage. The technique is complicated by ventriculitis in 10–17 % of patients, and the risk steadily increases until the 10th day of use: the catheter may be tunneled subcutaneously to minimize the risk of infection. Bleeding may also occur, and positioning of the catheter may be technically difficult if the ICP is high.

ICP may also be measured using a microtransducer, which may comprise fiber optic (Integra LifeSciences, Plainsboro, NJ) or pressure (strain gauge) microsensors (Codman & Shurtleff Inc., Raynham, MA). These are also placed through a burr hole, but into the cerebral parenchyma. These devices provide very reliable ICP

measurements, even when ICP is extremely high. They are also less likely to become infected but are expensive and do not allow therapeutic drainage of CSF. The microtransducer technique can also be used in the cerebral ventricles or the subdural or epidural spaces.

Subdural and epidural ICP can only be measured using a microtransducer and the risk of intracerebral hemorrhage is low. However, the stability and reliability of subdural ICP monitoring is inferior, especially when the ICP is extremely high. The ICP may also be measured in the subarachnoid space using a traditional catheter, which is cheap but less reliable when ICP is very elevated. In current clinical practice, the microtransducer technique is used most often, and a separate ventricular catheter is added if CSF drainage is needed.

24.9 Management of Intracranial Hypertension (Fig. 24.5)

ICH is defined as an ICP >20 mmHg sustained for more than 5 min. ICH or clinical brain herniation must be addressed urgently. Critical signs of transtentorial herniation are the acute onset of unilateral or bilateral pupillary dilation with loss of light reactivity and loss of consciousness. Other clinical changes that indicate herniation include extensor posturing, arterial hypertension, bradycardia, and changes in respiratory pattern (Cushing's triad, Table 24.2 and Fig. 24.6).

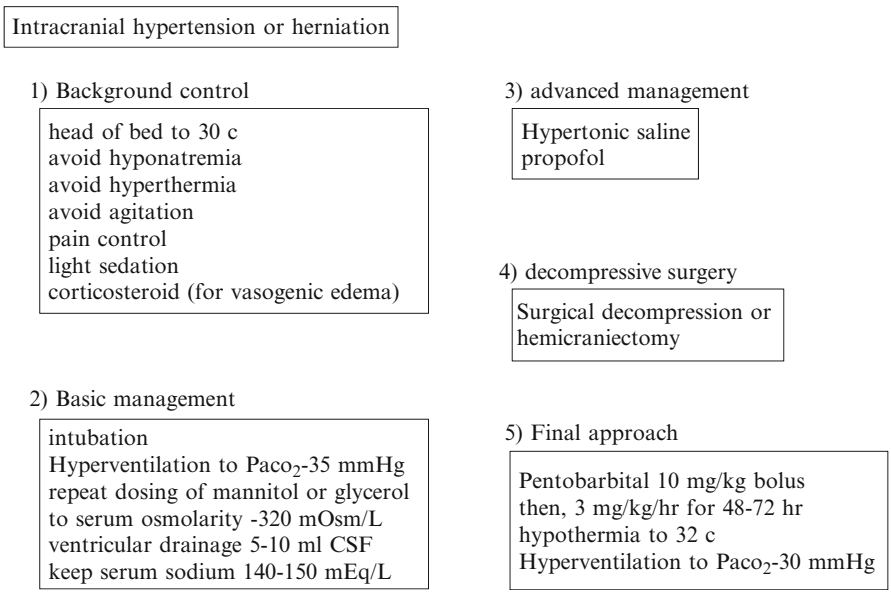

Fig. 24.5 Stepwise algorithm for the management of intracranial hypertension

Table 24.2 Brain herniation

Type	Clinical feature	Cause	Pathophysiology
Uncal (lateral transtentorial)	Ipsilateral cranial nerve III palsy	Temporal lobe mass lesion	The uncus (medical temporal lobe gyrus) shifts medially and compresses the midbrain and cerebral peduncle
	Contralateral or bilateral motor posturing		
Central transtentorial	Progressive from bilateral decorticate decerebrate posturing	Diffuse cerebral edema hydrocephalus	The diencephalon and midbrain shift caudally through the tentorial incisura
	Rostral-caudal loss of brainstem reflexes		
Subfalcine	Asymmetric (contralateral > ipsilateral) motor posturing	Convexity (frontal or parietal) mass lesion	The cingulate gyrus across midline under the falx cerebri
	Preserved oculocephalic reflex		
Cerebellar (upward)	Sudden progression to coma with bilateral motor posturing	Cerebellar mass lesion	The cerebellar shifts transtentorially (upward)
	Cerebellar signs		
Cerebellar, tonsillar (downward)	Sudden progression to coma with bilateral motor posturing	Cerebellar mass lesion	The cerebellar tonsil shifts caudally through the foramen magnum
	Cerebellar signs		

After simple measures have been taken, ICH is managed according to a stepwise algorithm, moving from basic to advanced interventions if necessary. The CPP should be maintained in the range of 60–70 mmHg to prevent cerebral ischemia, which can be achieved by lowering ICP or raising MAP by administering intravenous fluids or vasopressors or positive inotropic drugs.

CT images should be acquired to exclude bleeding, hydrocephalus, cytotoxic edema, or other sources of mass effect causing an acute elevation in ICP; CT is the preferred imaging method as it is quick and is normally easily accessible. As the patient needs to lie flat for during image acquisition, it is wise to ensure that the patient can tolerate lowering the head of the bed before transfer to the scanner. Imaging findings inform further conservative management decisions and the need for surgical intervention to place or revise an intraventricular drain (in the presence of hydrocephalus), perform decompressive craniectomy, or remove a mass lesion.

24.9.1 Simple Measures

The patient should be nursed with the head of the bed elevated at 30°. It is essential to correct hyponatremia and treat pyrexia. Elevation of ICP caused by agitation and pain or during tracheal toilet should be avoided whenever possible by giving

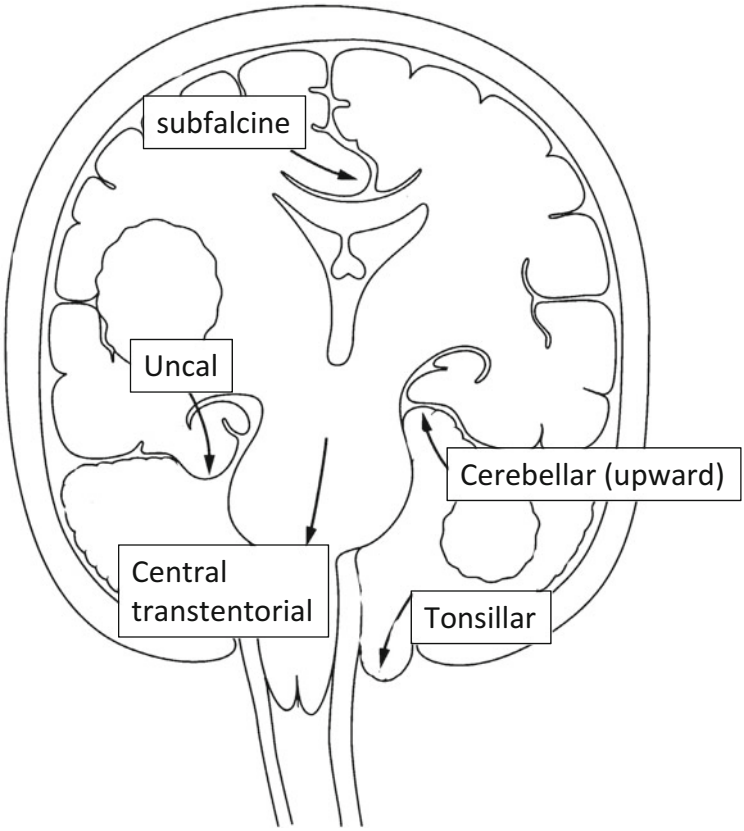

Fig. 24.6 Brain herniation

preemptive treatment with analgesics or sedatives, which should be short-acting if the stimulus is expected to be brief (Fig. 24.3). Consideration should be given to treating vasogenic edema with high-dose corticosteroid (dexamethasone 0.1 mg/kg every 6 h or methylprednisolone 0.5 mg/kg every 6 h).

24.9.2 Basic Management

The airway should be secured by intubating the trachea with a cuffed endotracheal tube and short-term hyperventilation may be instituted. Mannitol should be administered as a 0.5–1.0 g/kg intravenous bolus. If acute obstructive hydrocephalus is contributing to clinical deterioration, an external ventricular drainage system should be inserted. Serum sodium concentration should be maintained between

140 and 150 mEq/L using 2 % or 3 % NaCl, and serum electrolyte concentrations should be measured every 2–4 h.

24.9.3 Advanced Management

Boluses of hypertonic saline may be administered in concentrations ranging from 3 % to 23.4 % with the goal of maintaining serum sodium concentration between 140 and 150 mEq/L. Evidence supports rapid infusion in the event of transtentorial herniation or decreased ICP. Concentrations in excess of 2 % must be administered through a central venous catheter.

If ICP does not respond to hypertonic saline, a bolus of propofol 1–3 mg/kg may be given to reduce cerebral oxygen demand ($CMRO_2$), CBF, and ICP. However, propofol causes circulatory depression that may need to be addressed with intravenous fluid resuscitation or a vasopressor infusion to maintain CPP at its target level. Propofol may be continued as an infusion of 200 μg/kg/min.

24.9.4 Decompressive Surgery

More invasive surgical intervention may be required to decompress the brain if the measures above have failed. This may include evacuation of mass lesions or decompressive craniectomy in their absence. The decision to proceed with surgical decompression is made in consultation with neurosurgical colleagues, and it is prioritized for patients in whom there is a significant likelihood of meaningful recovery. For mass lesions, surgical intervention should be considered in carefully selected patients in whom rapid neurologic deterioration can be directly attributed to space-occupying lesions such as intracranial tumors or abscesses, ischemic stroke, and traumatic or nontraumatic intraparenchymal hemorrhage. Decompressive craniectomy may also be considered in the absence of a focal lesion, for example, if there is diffuse brain edema associated with aneurysmal subarachnoid hemorrhage, TBI, or meningoencephalitis.

24.9.5 Further Measures

Further interventions can be made in the presence of refractory elevated ICP that has not responded to the strategies outlined above, but carry the highest risk of adverse events. Barbiturates may be used to decrease $CMRO_2$; pentobarbital 10 mg/kg can be administered as an intravenous bolus over 30 min and then 5 mg/kg/h for 3 h with long-term maintenance if needed at 1–4 mg/kg/h titrated against the ICP goal. Barbiturates may be given for 24–96 h while the underlying process driving

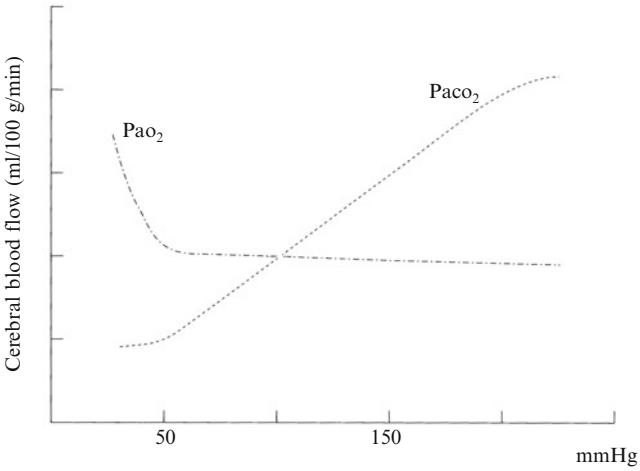

Fig. 24.7 Arterial blood gases and regulation of cerebral blood flow. Hypercapnia dilates cerebral vessels and increases cerebral blood flow, while hypocapnia causes cerebral vasoconstriction and decreases cerebral blood flow

ICP is treated or begins to resolve, but treatment is associated with respiratory depression, hemodynamic instability, immune suppression, and paralytic ileus.

Moderate hypothermia, with a target core temperature of 32–34 °C, may also be induced using external cooling devices, an intravenous infusion of cooled fluids, or with an intravascular cooling system. Treatment may be complicated by shivering, cardiac arrhythmia, sepsis, coagulopathy, or electrolyte disturbance.

Hyperventilation to moderate hypocapnia of an arterial partial pressure of CO_2 ($PaCO_2$) of approximately 30 mmHg may be considered in selected patients in whom all other management strategies have failed (Fig. 24.7). Hyperventilation should be undertaken in conjunction with cerebral oxygenation monitoring (jugular venous saturation [SjO_2] and brain tissue oxygen [$PbtO_2$]) in order to minimize the risk of cerebral ischemia. Prolonging hyperventilation for >6 h is unlikely to be beneficial and may cause harm.

24.10 Conclusion

The institution of ICP monitoring does not necessarily mean that effective therapy is being administered. Rather, ICP monitoring, if appropriately interpreted and guided by clinical experience, may help neurointensivists to provide judicious interventions and timely therapies [6].

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Chapter 25
Basics of Required Neuroimaging for Neuroanesthesia

Nobuyuki Kawai

Abstract Neuroimaging is a very important tool for the neuroanesthesiologist, allowing him or her to grasp intracranial factors influencing intracranial pressure and cerebral hemodynamics in patients with neurologic disease. While computed tomography (CT) provides excellent images of acute hemorrhages and bone and good visualization of neural elements, visualization of the structure of the posterior fossa, spinal cord lesions, early infarction, and subacute hemorrhages is relatively poor. Magnetic resonance imaging (MRI) provides an excellent tool for depiction of all neural elements, including lesions of the posterior fossa and spinal cord. Among MRI sequences, T2-weighted images in particular provide excellent visualization of fluids such as cerebrospinal fluid and brain edema. High intensity in diffusion-weighted images with a low apparent diffusion coefficient is particularly useful in the diagnosis of acute ischemic stroke. Computed tomography angiography and MR angiography provide noninvasive alternatives to conventional angiography. Angiography is playing a new role in interventional neuroradiology. Modern functional and metabolic imaging modalities such as positron emission tomography and single-photon emission tomography provide direct information on cerebral hemodynamics and metabolism. Functional MRI can detect increased blood flow in the brain associated with neuronal activation, which is useful in brain mapping, localizing motor and speech functions, and determining the relationships between various abnormalities in the eloquent regions of the brain.

Keywords Neuroimaging • Functional imaging • Cerebral hemodynamics • Brain edema

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25.1 Introduction

The primary goal in managing diseases of the central nervous system (CNS) is to prevent secondary brain damage due to neuronal hypoxia or hypoperfusion. Neuroimaging provides important information on the location, type, and severity of CNS abnormalities which may influence intracranial pressure (ICP) and cerebral hemodynamics in such patients. The modalities available include morphological and functional imaging. Neuroimaging allows us to better understand the condition of the brain, so familiarity with these modalities will enable us to better manage anesthesia and postoperative critical care. This can prevent complications during neuroanesthesia and improve the outcomes of critical care management by precise manipulation of three of the main components of the CNS: the brain, blood, and cerebrospinal fluid (CSF). This chapter gives a basic outline of the neuroimaging modalities available and the pathologies to which they can be applied from the viewpoint of neuroanesthesia.

25.2 Imaging Modalities

25.2.1 Computed Tomography

Since its development in the early 1970's, computed tomography (CT) has remained one of the most useful types of radiological examination in the assessment of the pathology of the living brain. Non-contrast CT is excellent for detecting acute hemorrhage and bone lesions, including fractures, and is often the modality of first resort in an acute or emergency setting. Contrast-enhanced CT involves intravenous injection of iodinated contrast material and is useful for imaging intracranial mass lesions such as tumors and abscesses, as these readily leak the contrast material due to damage to the blood–brain barrier (BBB). Meanwhile, the technique of CT angiography (CTA) provides useful information on vascular structure and abnormalities such as aneurysms and arteriovenous malformations (AVMs). However, while CT is adequate for making management decisions regarding neuroanesthesia in an acute or emergency setting, it does have some disadvantages, including relatively poor visualization of the structure of the posterior fossa, spinal cord lesions, early infarction, and subacute hemorrhages.

25.2.2 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) uses radiofrequency pulses within a strong magnetic field and is therefore contraindicated in patients with ferromagnetic implants (recent intracranial implants are mostly MR compatible), pacemakers, or

metallic foreign bodies in the body. This imaging modality offers high sensitivity to minute alterations in brain water content and blood products, allowing it to illustrate the complex structures of the brain and reveal damage that would be invisible on CT. T1-weighted images provide excellent visualization of the soft tissue, and T2-weighted images provide excellent visualization of fluids such as those found in CSF and brain edema. Magnetic resonance angiography (MRA) provides vascular information without the need for contrast material. Diffusion-weighted imaging (DWI) can be particularly useful in the diagnosis of hyperacute ischemic stroke. Acute infarction can be detected as high-intensity areas in DWI with a low apparent diffusion coefficient (ADC). Contrast-enhanced MRI involves intravenous administration of gadolinium and is useful for imaging intracranial mass lesions resulting from disruption of the BBB. Its major and uniquely important role in anesthesia is in diagnosing diseases of the spine and spinal cord such as cervical spondylotic myelopathy and canal stenosis, which may cause spinal cord damage during tracheal intubation in the neck extension position. However, structures very close to metallic implants such as aneurysm clips cannot be visualized with MRI, even if they are MR compatible.

25.2.3 Angiography

Angiography uses intra-arterial contrast material to visualize normal vasculature and vascular lesions such as aneurysms and AVMs. Computed tomography angiography and MRA provide noninvasive alternatives to conventional angiography, with capabilities for three-dimensional reconstruction. Angiography is not performed very often for brain tumors these days. However, it is an important neuroimaging modality for some types of brain tumor as it can provide useful information on which blood vessels are supplying the tumor and how. Moreover, angiography is often the modality selected in coil embolization for aneurysms, nidus embolization for AVMs, and feeding artery embolization for vascular-rich brain tumors such as meningiomas. Anesthesia for interventional neuroradiology is another challenge for the neuroanesthesiologist.

25.2.4 Functional and Metabolic Imaging

Positron emission tomography (PET) and single-photon emission CT (SPECT) are sensitive functional imaging modalities used in the assessment of the altered metabolism and blood flow that are prevalent in many types of brain disease. Single-photon emission CT uses conventional γ-emitting tracers with multiple detectors to generate tomographic images and is commonly employed to investigate cerebral blood flow (CBF). The technique is simple and three-dimensional, but the images produced are of relatively low resolution and generally nonquantitative.

Positron emission tomography measures the accumulation of positron-emitting radioisotopes in the brain. Tracers can be administered via an intravenous or inhalational route for imaging. ^{15}O-labeled gases are employed to measure CBF and cerebral oxygen metabolism, whereas ^{18}fluorodeoxyglucose is used to measure glucose metabolism. This modality provides higher-resolution images and is quantitative. Functional MRI (fMRI) uses differences in radiofrequency signals between oxygenated (by increased blood flow) and deoxygenated (by increased oxygen metabolism) blood to detect activated regions in the brain. It is especially useful in brain mapping, localizing motor and speech functions, and determining the relationships between various abnormalities in the eloquent regions of the brain.

25.3 Imaging Pathology

25.3.1 Intracerebral Hematoma

Intracerebral hematoma (ICH) most commonly involves idiopathic (hypertensive), hemorrhagic or traumatic contusions, or hemorrhagic infarctions. However, it may also result from hemorrhage into or around other lesions such as tumors or AVMs or moyamoya disease. It represents 20–30 % of first-time strokes in Asian populations and 10–15 % in Western populations and has a 30-day mortality rate of 35–50 %. On CT, acute hemorrhage is seen as an area of hyperdensity with surrounding hypodense brain edema. As the clot ages, brain edema gradually develops. This occurs within 24 h of the ictus, and the edema will continue to develop over the next couple of days, eventually becoming isodense with the brain over a period of several weeks. A fluid-fluid level within a hematoma indicates clot liquefaction and is seen in patients with coagulopathy or receiving anticoagulant therapy. As ICH always entails some brain destruction, surgery has limited merits for deep hemorrhages involving the putamen and thalamus. Lobar hemorrhages coming to the surface with clinical deterioration, however, sometimes merit surgical intervention. Hemorrhage into other lesions such as tumors may be difficult to distinguish from idiopathic hemorrhage or hemorrhagic infarction. The neoplasms most commonly associated with ICH are high-grade gliomas, especially glioblastoma, and certain metastatic brain tumors such as lung, melanoma, breast, and renal cell carcinomas. Contrast-enhanced MRI often reveals the underlying neoplasm associated with ICH (Fig. 25.1).

25.3.2 Epidural Hematoma

Epidural hematoma (EDH) constitutes a hemorrhage occurring between the skull and the dura, usually in direct association with a skull fracture. Blood coming from

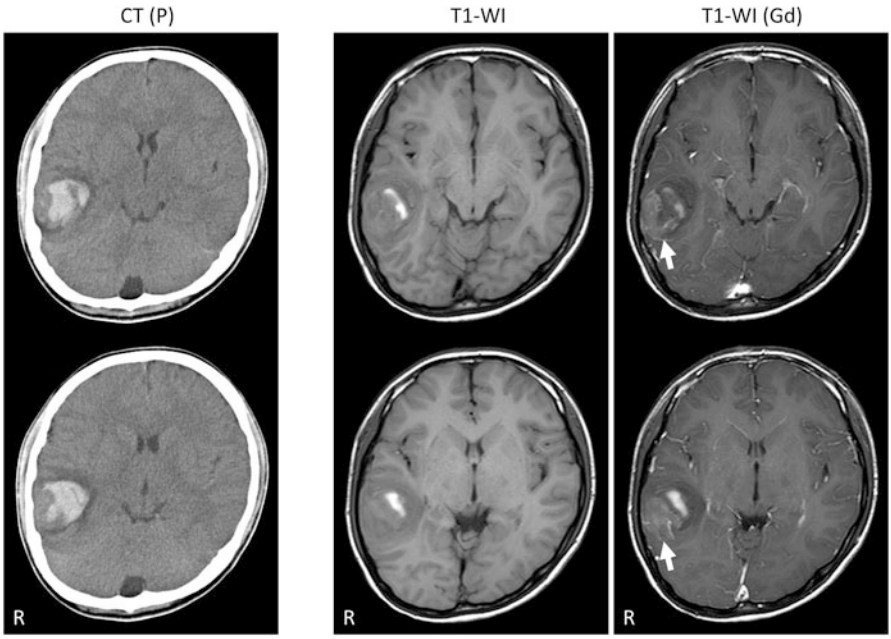

Fig. 25.1 A 10-year-old boy presented with abrupt onset of headache and nausea. Plain computed tomography (CT) scan revealed intracerebral hemorrhage in right temporal lobe. T1-weighted MR image with gadolinium enhancement showed faintly enhanced area in hematoma (*arrows*). Craniotomy revealed malignant glioma tissue in hematoma

torn meningeal arteries or veins or from laceration of the dural sinuses generates a clot that further strips the dura from the skull and is usually limited in its extent by sutures, where the dura is tightly attached to the skull, but may cross the midline (sagittal suture) in the case of vertex EDH. On CT, an EDH typically appears as a uniformly high-density biconvex-shaped lesion resting against the vault of the skull. Clinically, EDHs are characterized by a lucid interval after the injury occurs, during which time the patient's neurological status remains intact. Deterioration from then on, however, is rapid, with the patient eventually becoming comatose. Surgical evacuation of the hematoma should be performed immediately if it is diagnosed. The patient often shows excellent recovery.

25.3.3 Subdural Hematoma

With a subdural hematoma (SDH), blood collects between the arachnoid membrane and the dura. There are two types of SDH with completely different clinical settings: acute and chronic. Acute SDHs occurring after severe head trauma should be treated by rapid surgical intervention. They are usually the result of tearing of the

fragile veins that bridge the subdural space, but they can also arise directly from adjacent brain contusions with arterial bleeding and subarachnoid lacerations. Acute SDHs commonly have a high-density convex or crescent-shaped appearance on axial CT. Subdural hematomas cross suture lines and spread out over the surface of the brain, but do not cross the midline. In general, if the hematoma is more than 1 cm in thickness, or if a greater than 5-mm shift is observed in the midline, emergency surgical intervention is required, comprising large decompressive craniectomy and duraplasty. Such patients often require long-term postoperative intubation and ventilation and days or weeks in the intensive care unit. Moreover, the neurological outcome of treatment is often very poor. On the other hand, the prognosis in older patients with chronic SDH resulting from minor head trauma, or, as is often the case, with no history of such due to associated memory loss is more positive. These patients present with high, low, or mixed density convex or crescent-shaped lesions with midline shift on CT, making diagnosis easy. Occasionally, isodense chronic SDH will be present, and the absence of clear demarcation between the hematoma and the underlying brain may make diagnosis difficult on CT. With MRI using T1-weighted sequencing, however, hematomas with hyperintense lesions are clearly distinguished from the underlying brain (Fig. 25.2). Chronic SDHs are judged according to their size, degree of mass effect

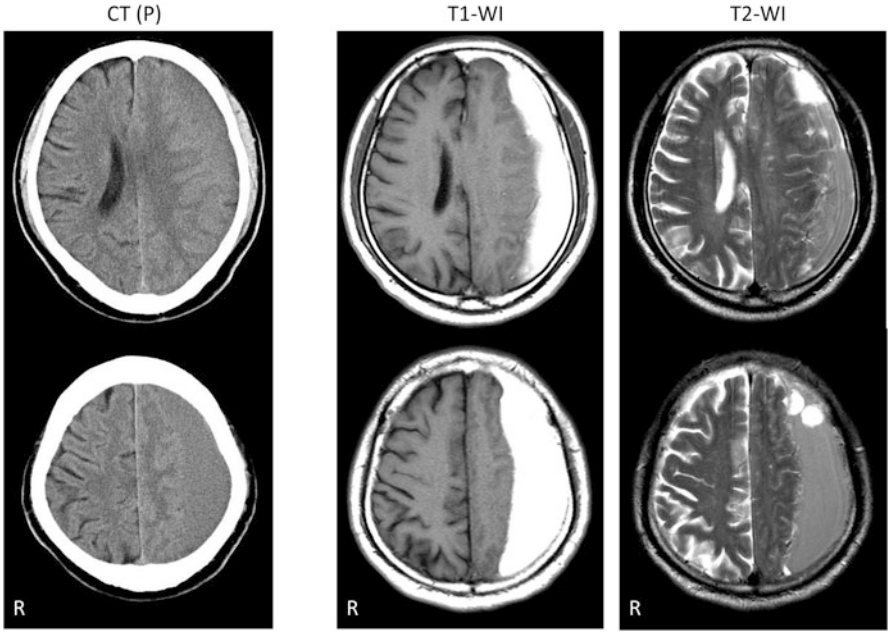

Fig. 25.2 A 76-year-old man presented with right hemiparesis and speech disturbance. Plain CT scan revealed isodense area in left frontoparietal lobe compressing lateral ventricle. T1- and T2-weighted magnetic resonance imaging (MRI) revealed convex-shaped high-intensity area in the left frontoparietal lobe, suggesting chronic subdural hematoma

or midline shift, and clinical symptoms. When a patient presents with neurological signs or symptoms such as hemiparesis, gait disturbance, or cognitive impairment, hematoma removal from a small burr hole is performed with excellent neurological outcome. Antiplatelet agents or anticoagulants increase the likelihood of SDH formation. Again, the pathology and outcome in patients with acute and chronic SDH are completely different.

25.3.4 Subarachnoid Hemorrhage

Subarachnoid hemorrhages (SAH) are most commonly aneurysmal but sometimes traumatic or due to other causes. Differentiation of aneurysmal and traumatic SAH may be difficult, but the patterns of hemorrhage and concomitant injury are sometimes diagnostic. Aneurysmal SAHs are mainly located in the basal and Sylvian cisterns, while traumatic SAHs usually present over the convexities associated with local hemorrhage or cerebral contusion. Traumatic SAH, however, is occasionally found isolated in the basal cistern in cases of skull-base fracture. Patients with aneurysmal SAH commonly present with abrupt onset of thunderclap headache and nausea/vomiting. However, SAHs may appear innocent when the bleeding is very minor and causes little direct neuronal damage. The enduring effects on brain physiology can be devastating, however. Massive SAHs may occur within a few days (mostly within 24 h) of minor bleeding and cause devastating neuronal damage. On CT, they typically present as a diffuse hyperintense lesion in the basal cistern, sometimes with blood refluxed in the fourth, third, and lateral ventricles. They do not routinely show on MRI in the acute stage because of high oxygen tension in the blood, but if FLAIR sequence is selected, even minor bleeding that would be invisible on CT will show (Fig. 25.3). Early angiography or CTA is necessary to identify the ruptured aneurysm. Hypertension should be avoided to prevent rebleeding from the ruptured aneurysm before aneurysmal obliteration. The aftereffects of SAHs include brain edema, vasospasm, and hydrocephalus; SAHs can also cause rapid-onset cardiac dysfunction (wall-motion abnormalities, myocardial ischemia) and pulmonary dysfunction (edema, acute respiratory distress syndrome) due to excess sympathetic activity, which presents further challenges in their management.

25.3.5 Brain Infarction

Infarction represents the majority of acute strokes, occurring in 70–80 % of all strokes. Magnetic resonance imaging is much more sensitive than CT for detecting acute infarction. When acute infarction is suspected, DWI images should be obtained as they reveal cytotoxic edemas as bright (white) lesions within 30 min, whereas changes on CT are not clearly visible until 3–6 h after onset. However,

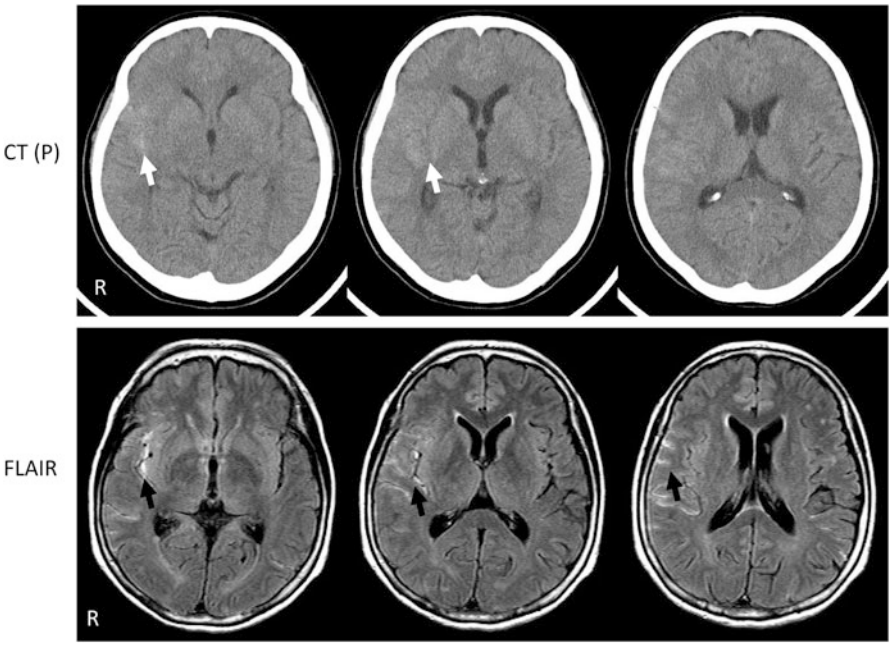

Fig. 25.3 A 48-year-old man presented with abrupt onset of severe headache and nausea. Plain CT scan showed faint high-density area in right Sylvian cistern (*white arrows*). FLAIR image revealed high-intensity areas in right Sylvian and cortical cisterns (*black arrows*), indicating subarachnoid hemorrhage

high-resolution CT can detect abnormalities within 3 h of onset, including hypoattenuation of the cortex and basal ganglia and swelling of focal tissue (early CT sign) (Fig. 25.4). In younger patients, ischemic infarctions are often embolic but may also result from moyamoya disease, especially in Asian populations, whereas in older patients they are most commonly occlusive (arteriosclerotic). Arterial infarctions typically involve a distinct arterial territory, the most common of which is that of the middle cerebral artery (MCA). Increased attenuation of an arterial segment, the "hyperdense MCA sign," is highly specific for MCA occlusion by thrombus on CT. If a patient presents with cerebral infarction, MRA of the carotid and intracranial arteries should be performed. When major vascular lesions are identified, functional imaging using SPECT or PET is necessary to evaluate residual CBF. Normotension and normovolemia should be maintained during neuroanesthesia to prevent ischemic complications in these patients.

25.3.6 Mass Lesions and Edema

Mass lesions of concern to the neuroanesthesiologist are most commonly neoplastic. Neuroimaging provides clinically useful information on mass lesions which can

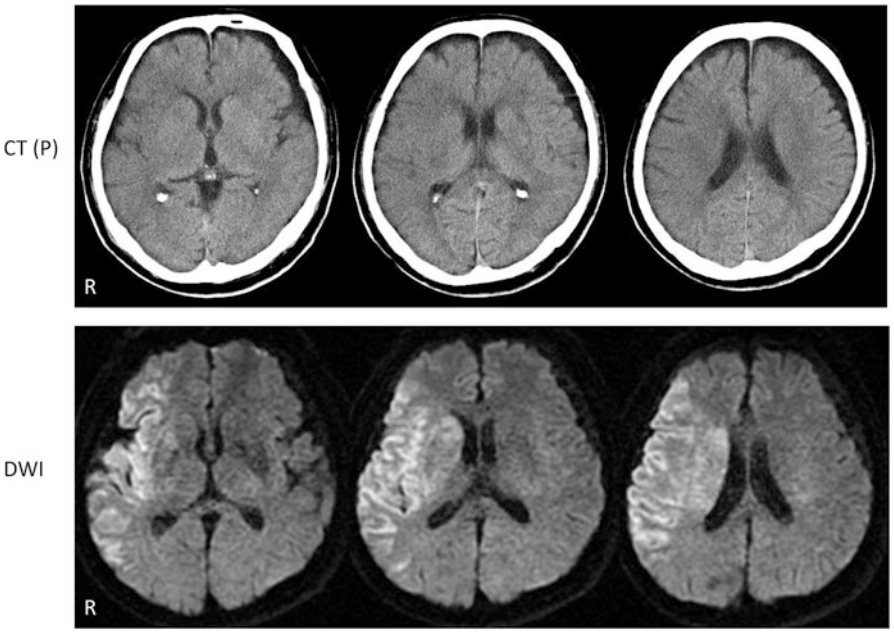

Fig. 25.4 A 62-year-old woman presented with left hemiparesis. Plain CT scan showed faint low-density area in the right fronto-temporo-parietal lobe. Diffusion-weighted MR image revealed high-intensity area in the right fronto-temporo-parietal lobe, indicating acute ischemic stroke

be of benefit in anesthetic management, including on their size and location, and concomitant brain edema. Edema and infarction have a similar hypodense appearance on CT and are sometimes difficult to distinguish, except by pattern. Edemas associated with neoplasms are usually vasogenic. They are restricted to the white matter and can disappear when the neoplasm is removed. Hyperosmotic solutions such as mannitol or glycerol are effective in reducing water content in brain edemas and temporarily lower increased ICP. Steroids are also effective in reducing vasogenic edema by restoring damaged BBB function.

25.3.6.1 Extra-axial Tumors

Meningioma represents about 25 % of all intracranial tumors and is the most common histologically benign brain tumor and most common extra-axial tumor in adults. Meningiomas commonly attach to the dura and are well enhanced homogenously with contrast material. Characteristically slow growing, they can reach an impressive size before becoming symptomatic in silent brain regions such as the frontal skull base. Pituitary adenoma is another common benign extra-axial brain tumor accounting for 15 % of all intracranial tumors. Pituitary adenomas commonly arise from the anterior pituitary gland. They expand superiorly,

compressing the optic chiasma, which results in bitemporal homonymous hemianopsia. These tumors commonly exhibit a less-enhanced effect than normal pituitary gland. Pituitary adenomas occasionally present with apoplexy in the tumor, demonstrating high density on CT. Some patients, especially those with a large pituitary adenoma, exhibit panhypopituitarism. In such cases, it is necessary to replace glucocorticoids before, during, and after surgery to compensate for adrenocortical insufficiency.

25.3.6.2 Intra-axial Tumors

Gliomas represent about 25 % of all intracranial tumors in adults and are the most common primary intra-axial tumors. Ring-like enhancement is the most typical characteristic of malignant gliomas and usually indicates a rapidly growing lesion with central necrosis. Non-enhancing or weakly enhancing lesions are more likely to be lower grade and slower growing than those which are strongly enhancing. Gliomas typically originate from the white matter and invade according to the white matter tracts as they increase in size. Low-grade astrocytomas appear as poorly marginated low-density tumors on CT and are isointense or hypointense on T1-weighted images and hyperintense on T2-weighted MRIs. Glioblastomas typically demonstrate irregular, inhomogeneous, and poorly marginated ring-like enhancement on CT and MRI with contrast material. As they are very aggressive tumors, often with extensive brain edema, necrosis, and hemorrhage, they are usually associated with increased ICP. Therefore, particular attention must be paid to maintaining adequate cerebral perfusion pressure and hemodynamic stability in patients undergoing surgery for resection of such lesions.

25.3.7 Spine and Spinal Cord Lesions

Although the spine protects the spinal cord and nerve roots, spinal lesions often directly compromise neural elements because of the small space involved and the eloquence of spinal tissue. The most common spine lesions resulting in neural element compromise are degenerative changes in the spine or disc, although tumor and injury may also result in neural compromise. Anesthetic challenges particular to cervical spinal lesions include securing and maintaining the airway while maintaining the neck in a neutral position. Extreme extension of the neck for tracheal intubation may compromise neural elements further. Cervical spine lesions may produce significant dysautonomia, particularly in patients with craniocervical junction spinal cord or lower medullary lesions. Stability is best assessed by flexion and extension X-ray of the cervical spine. Computed tomography and MRI are the best imaging modalities for assessing spinal lesions: CT for bone and MRI for neural elements. T2-weighted MRI is particularly useful in assessing spinal neural elements.

Chapter 26
Positioning of Neurosurgical Patients

Hiroyuki Jimbo and Yukio Ikeda

Abstract In order to reach the lesions through the minimal invasive corridor, patients are sometimes immobilized in specific postures that seem nonphysiological during neurosurgical procedures. There is concern that these positions may result in peripheral neuropathy and formation of pressure ulcers. The limitations of movements in the diaphragm and rib cage may affect respiratory functions. It is not uncommon that the skull is placed in anteflexion or greatly rotated, thus causing inhibition of venous return and increased intracranial pressure. If the head position is elevated extremely high and the pressure in the venous sinus becomes negative, there is a risk of the development of an air embolism.

To avoid these problems, the checkup points and physiological effects in the basic positioning of neurosurgical procedures are mentioned in this chapter.

Keywords Positioning • Venous return • Intracranial pressure • Air embolism

26.1 Introduction

During neurosurgical procedures, the method of approach is selected so that it is minimally invasive to healthy brain tissue and by considering how to reach the intracranial lesions. As a result, patients are sometimes immobilized in specific postures that seem nonphysiological [1, 2]. Patients are often forced to maintain that posture for many hours. Even when there is excessive load or compression to a localized region, hyperextension of joints, or impairment of blood flow, patients under general anesthesia are unable to complain or change these positions, and therefore, there is concern that these positions may result in peripheral neuropathy or the formation of pressure ulcers. Some types of body postures may put limitations on movements of the diaphragm and the rib cage and may affect respiratory functions. It is not uncommon that the skull is placed in anteflexion or greatly rotated, thus causing inhibition of venous return and increased intracranial pressure.

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Various attentions are necessary to avoid these problems that are characteristic in neurosurgical procedures.

26.2 General Characteristics of Body Positioning During Neurosurgery

26.2.1 The Necessity of Stable Fixation of the Skull

During neurosurgical procedures, the skull needs to be fixed in a stable manner. The Sugita frame (Mizuho Ikakogyo Co., Ltd., Tokyo, Japan), which is a rotating device that provides fixation of the skull with four pins, the three-point Mayfield skull fixation device (Integra LifeSciences Corporation, Plainsboro, NJ, USA), and supporting devices provide stable fixation of the skull, and the surgical procedure can be performed safely and easily. Stable fixation of the skull is essential in stereotactic brain surgery. Loosening of the support device during surgery is extremely dangerous, and thus, there is a need for full verification. When there is no strict need for fixation of the skull, a doughnut-shaped round mat or a horseshoe-shaped head support is used. Tracheal tubes that are safe to manage intraoperatively are used, and their depth is reconfirmed and fixed after the body's posture has been fixed.

26.2.2 Measures Against Peripheral Neuropathies, Pressure Ulcers, and Deep Vein Thrombosis

Areas that are loaded with weight or compressed need to be checked. It is therefore important that weight load and pressure are distributed and reduced by applying buffering objects, such as pads or pillows, in order to avoid compressing areas that peripheral nerves pass through and to prevent hyperextension of nerves traveling through joints and blood flow deficits in the extremities. Once peripheral neuropathy occurs, it takes a few months to achieve recovery; in some cases, irreversible handicaps may persist thereafter. Particularly, when patient conditions are associated with systemic diseases, such as diabetes, renal disease, or diseases of the spinal column, such as spinal canal stenosis or thoracic outlet syndrome, there is a high probability of the development of neuropathies. For these reasons, preoperative checkups are required.

As a preventive measure against deep vein thrombosis, the patient wears elastic stockings and uses an intermittent pneumatic compression device.

26.2.3 Considerations for Venous Return

Under general anesthesia, sympathetic-mediated vasomotor activities are inhibited. If a muscle relaxant is used, the muscle pump cannot be expected to be active, and thus, venous return to the heart is impaired. Particularly in neurosurgical and brain surgical procedures, it is not uncommon that the skull is placed in anteflexion or greatly rotated, thus causing further inhibition of venous return and increased intracranial pressure. A slight elevation of the skull at angles of 15–20° promotes venous return and reduces bleeding of venous origin in the operative field. However, caution is needed. If the head is elevated too high, the venous pressure becomes negative, and, as a result, air is likely to flow into the sinuses and veins and cause air embolisms.

26.3 Basic Positioning During Neurosurgical Procedures

26.3.1 Supine Position

26.3.1.1 Indications

The use of the supine position makes it possible to handle intracranial lesions, such as those in the frontal region, temporal region, anterior half of the parietal region, lateral ventricle, third ventricle, anterior part of the base of the skull, interior part of the base of the skull, and upper part of the posterior fossa, as well as pituitary lesions, lesions in the cervical spine, and carotid artery lesions.

26.3.1.2 Setting of the Body Posture

In the supine position, complications are less frequent than those found in other positions; however, caution is needed to avoid compression of the eyeballs or the supraorbital nerve by anesthesia masks or endotracheal tubes. In the supine position, the sites that are likely to be compressed and to develop pressure ulcers include the occipital region, sacral region, and heels. In addition, the use of a horseshoe or a round mat for long hours is likely to cause hair loss [3]; thus, fixation with pins is preferable in case the surgery lasts long hours. The upper extremities are placed in supination to prevent ulnar nerve paralysis, which is caused by compression of the elbow by the operating table. In addition, there is a need to consider the possibility of radial nerve palsy due to compression on the external side of the upper arm or brachial plexus palsy due to rotation of the head or hyperextension of the neck. When the head is rotated, excessive force should not be applied to the endotracheal tube. Particularly in obese patients, impairments in venous return due to torsion of the neck should be prevented with a suitable shoulder pillow. In the anteflexion

posture, caution should be used because of the possibility of one-lung ventilation due to bending or pushing of the endotracheal tube, and, inversely, in the retroflexion posture, one should be careful that the tube does not fall out.

26.3.1.3 Physiological Effects

The ventilatory volume is thought to decrease by about 10 % in the supine position. However, under general anesthesia, this has virtually no clinical impact. A slight elevation of the head promotes venous return and may potentially reduce venous hemorrhages. This also reduces the load on the back. Conversely, placing the head in a low position may lead to the congestion of veins in the brain and an increase in intracranial pressure. During a parietal craniotomy with head rotation to the left or right, an excessive lordotic position may cause venostasis. Due to muscle tension, pain, and reflexes that are associated with specific receptors, a subject who is awake is protected from compression and hyperextension. However, their effects disappear when a muscle relaxant is administered after the induction of anesthesia. Therefore, caution is needed.

26.3.2 Prone Position

26.3.2.1 Indications

The prone position is used in surgeries involving the posterior half of the skull, as well as in spinal and vertebral surgeries requiring a posterior approach.

This is applicable to intracranial diseases that affect the parietal lobe, occipital lobe, posterior half of the corpus callosum, pineal region, cerebellum, cerebellopontine angle, fourth ventricle, brainstem, and craniocervical junction.

26.3.2.2 Setting of the Body Posture

Before surgery, patients need to be asked to adopt the body posture and head position that are expected to be used during surgery to check whether there are symptoms of compression of the brain stem or cervical spinal cord, such as numbness of the extremities or respiratory depression. This is particularly important in surgeries involving the craniocervical junction. In addition, a confirmation of the safe range of motion for the neck needs to be performed, and, if necessary, the subjects should be instructed to wear a cervical orthosis.

Anesthesia is induced on a transportation stretcher, an airway is secured, an indwelling balloon catheter is put in place, and the arterial pressure is visually monitored, after which the body's posture is changed. At the time when the body's posture is changed, the anesthesiologist should perform the removal and installment

of the monitor in the right order and should consider minimizing the time interval during which the patient is without monitoring. Careful caution must always be exercised in regard to the complications of the prone position, namely, ischemia of the retina and blindness that is associated with an increase in intraocular pressure. The optic papilla is anatomically poor in terms of autoregulation and development of collateral circulation [4]. Hypotension, anemia, and venostasis that occur during surgery facilitate the development of ocular compression-induced disorders [5]. Thus, during surgery, it should be confirmed that the eyeballs are not subjected to increased pressure after movements of the neck and head. Considerable caution is also needed with regard to other pressure points, namely, the chest, axillary regions, iliac crests, femurs, genitals, and knees. A pad or a thick pillow is deployed on the chest and pelvis, and mobility is given to the abdominal wall to facilitate respiratory movements. The neck is placed in anteflexion, a pad is deployed underneath, the patient is placed in a reverse Trendelenburg position, the knees are bent, a pillow is placed at the ankle joint, and the lower thigh is lifted up (Fig. 26.1a, b).

In surgical procedures that involve the posterior part of the skull, the head must be placed at a higher elevation than the heart to maintain low intracranial venous pressure [6]. The backplate of the bed is tilted to ensure that the upper body is elevated by 10–30°. If the neck is fixed in further anteflexion to improve the visibility of the surgical field, the head will be in a lower position, and the upper body will need to be lifted up even further (Fig. 26.1c). However, if the angle

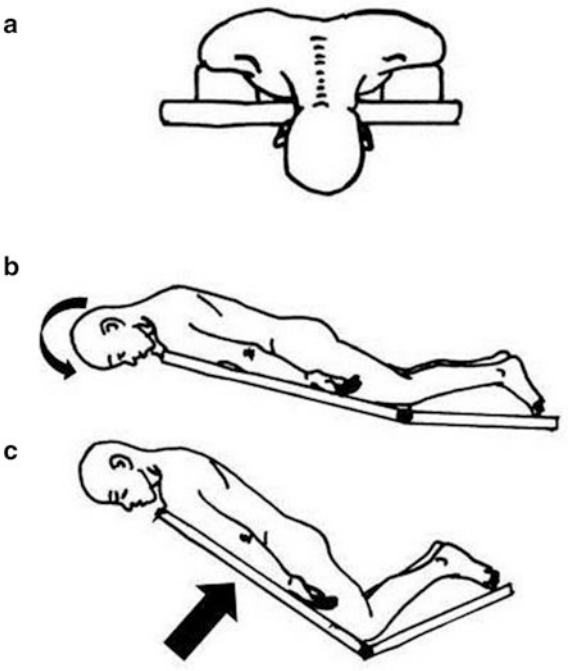

Fig. 26.1 (**a**) The schema showing a basic prone position in which the neck is placed in anteflexion. (**b**) The schema showing a basic prone position in which a pad is deployed underneath, the patient is placed in a reverse Trendelenburg position, the knees are bent, a pillow is placed at the ankle joint, and the lower thigh is lifted up. (**c**) If the neck is fixed in further anteflexion, the upper body needs to be lifted up

reaches 45° or more, there is a risk of the development of an air embolism. In addition, stronger anteflexion may cause a narrowing of the anteroposterior diameter of the hypopharynx, and, in surgical procedures that last long hours, caution is needed because ischemia may occur in association with compression of the tongue base by foreign objects, such as the endotracheal tube. Macroglossia due to reperfusion edema may occur after extubation, and it may rapidly cause airway obstruction [7].

In surgical procedures that involve the chest or lumbar spine, compression of the inferior vena cava needs to be reduced. Pressure in the epidural venous plexus may increase because of impairments of the venous backflow in the inferior vena cava. This may increase the amount of bleeding from a laminectomy. Therefore, during spinal surgery, spinal surgery frames such as the Relton-Hall type, Wilson type, and Andrews' improved type are effective in preventing compression of the inferior vena cava by managing abdominal pressure.

26.3.2.3 Physiological Effects

The decrease in ventilation volume is about 10 %. Unless suitable assistive devices are used, severe restrictive ventilator impairments may occur. In other words, there is restriction of the movements of the diaphragm due to the compression of internal abdominal organs, as well as a limitation of breathing movements due to anterior compression of the chest and abdomen. This results in the development of hypoventilation and hypoxemia due to a decrease in lung-thorax compliance. The decrease in ventilator volume can be maintained at about 10 % by reducing compression of the chest and abdomen through the use of rolls, spinal surgery frames, and direction indicators. In the circulatory system, a decrease in blood pressure and a decrease in venous pressure may develop as a result of a decrease in venous return due to compression of the femoral vein and abdominal vena cava.

26.3.3 Lateral Position

26.3.3.1 Indications

Compared with the prone and supine positions, the lateral position is more complex, includes many variations, and is often associated with positioning-related complications. The lateral position is used in surgical procedures, such as various approaches that use a temporal craniotomy (skull base surgery, including the infratemporal fossa approach, anterior transpetrosal approach, presigmoid transpetrosal approach, translabyrinthine approach, and transjugular approach) and in lateral approaches to the cervical spine, posterior cranial fossa, and cerebellopontine angle lesions that use the lateral suboccipital approach, as well as the transthoracic/retroperitoneal approach to the thoracic and lumbar spine.

Variants of the lateral position include the park-bench position [8], lateral oblique position [9], three-quarter prone position [10], and Janetta position (semilateral position) which is used in the treatment of trigeminal neuralgia and hemifacial spasm.

26.3.3.2 Setting of the Body Posture

A pillow is placed under the axillary cavity to reduce the load of the body weight on the shoulder on the lower side of the body and to prevent impairments of blood circulation in the lower extremities. The lower limb on the lower side of the body is placed in flexion, the other lower limb on the upper side of the body is placed in extension, and a pad is placed between the two lower limbs. A chest-and-waist support is used for the immobilization of the patient's body. On the ventral side, support is applied to the pubic bone and sternum. On the dorsal side, support is applied to the thoracic spine, pelvis, and buttocks. In the park-bench position, the lower limb on the lower side of the body is fixed with an arm rest that is placed between the operating table and the craniostat (Fig. 26.2). Measures are taken to prevent the shoulder joint on the lower side of the body from going into abduction, and the elbow is placed in a slight flexion. In addition, venous return from the lower extremities, as well as intracranial venous return, can be maintained by raising the patient's upper body and by putting it in a jack-knife position, which means it is bent at the waist. If the upper body is elevated higher than 30° in the lateral position, the pressure in the venous sinus will become negative, and an air embolism may occur as a result [11].

When performing an approach to the cerebellopontine angle, the shoulder on the upper side of the body may interfere with the visibility of the tentorial notch, and therefore, it is pulled to the caudal side. Under such circumstances, caution is needed because the use of excessive force to pull on the shoulder joint may cause brachial plexus paralysis. In the same way as in the prone position, the face of a patient in the lateral position is often turned toward the floor, and the endotracheal tube may easily come out as a result of the gravity of the tube itself and saliva. Thus, fixation needs to be ensured. Head fixation with rotation and flexion of the neck is likely to be accompanied by an increase in the cuff pressure of the endotracheal tube, and the persistence of excessive cuff pressure may result in recurrent nerve paralysis due to the endotracheal tube.

26.3.3.3 Physiological Effects

In the lateral position, the decrease in ventilator volume is about 10 %. In the lung on the upper side of the body, the ventilation volume increases due to an increase in compliance, whereas in the lung on the lower side of the body it decreases as a result of a decrease in compliance. Meanwhile, due to the influence of gravity, pulmonary blood flow increases in the lung on the lower side of the body and

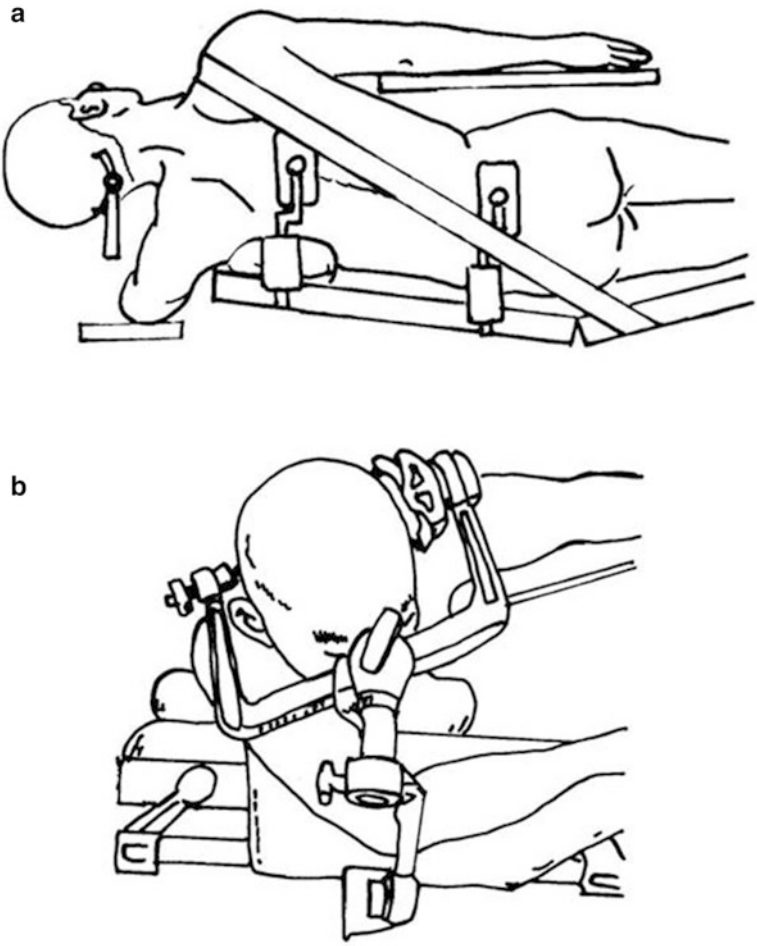

Fig. 26.2 (**a**) The schema showing a basic park-bench position in which the shoulder on the upper side of the body is pulled to the caudal side. (**b**) The schema showing a park-bench position in which the face of a patient is rotated to the floor, and the lower limb on the lower side of the body is fixed with an armrest that is placed between the operating table and the craniostat

decreases in the lung on the upper side. As a result, the dead-space effect increases in the lung on the upper side of the body, and a shunt-like effect increases in the lung on the lower side of the body. This is likely to cause an imbalance in the ventilation-perfusion ratio. A disorder that occurs in the lung on the lower side of the body facilitates the development of hypoxemia and hypercapnia. Setting the position of the body while monitoring percutaneous oxygen saturation (SpO_2) and end-tidal CO_2 ($ETCO_2$) has also been recommended [12]; however, partial pressure of carbon dioxide in arterial blood ($PaCO_2$) and $ETCO_2$ shows marked disparities in the lateral position.

26.3.4 Sitting Position

26.3.4.1 Indications

The sitting position is used in pineal tumor surgery, upper cervical spine surgery, and surgical procedures that involve the posterior cranial fossa (the floor of the fourth ventricle, the pontomedullary junction, and the cerebellar vermis). This position makes it easy to reach the midline region. However, it should be avoided in patients with low cardiac functional reserve, in postoperative patients who underwent ventriculoatrial shunt surgery, in patients with a defect in the atrioventricular septum, and in those who are likely to develop an air embolism. In addition, based on extensive experience in surgeries that have been conducted in the sitting position, the morbidity and mortality that are associated with the sitting position are said to be within an acceptable range [13–18]. However, the risks are considered to be higher if the procedures are performed by teams who have little opportunity to conduct surgeries under such conditions.

26.3.4.2 Setting of the Body Posture

In general, the half-seated position, which is closer to the resting posture, is used more often than the sitting position (Fig. 26.3). This is because this position allows for the fixation of the head at a lower position and for a reduction in the difference in the height between the surgical field and the heart. A three-point fixation of the head is performed in the supine position. The backplate is folded in such a way that the buttocks are placed low and the upper part of the body is raised up. The hands are placed on the abdomen and are fixed gently. A pillow is deployed under the knee, and the lower extremities are placed as high as possible in a horizontal position. To ensure that the procedure can be performed even when there is an urgent need for

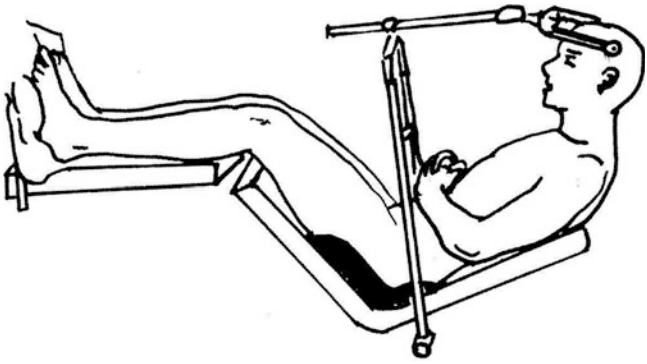

Fig. 26.3 The schema is showing the semi-sitting position which allows for the fixation of the head at a lower position and for a reduction of the difference in the height between the surgical field and the heart

the patient to be returned to the supine position, a U-shaped support head fixation device is fixed to the backplate to allow for the procedure to be performed immediately. The neck is positioned in slight anteflexion. A gap of about two fingerbreadths must be present between the sternum and the mandibular bone. For safety, in some cases, fixation of the body's position is conducted while monitoring the regional cerebral oxygen saturation (rSO_2) and somatosensory-evoked potentials [18]. When there is concern for hypotension, fluid is loaded by infusion, and the lower extremities are wrapped with elastic bandages beforehand. The use of G-suits for wrapping the lower extremities up to the pelvis, as well as the wearing of shock pants, should also be taken into consideration.

26.3.4.3 Physiological Effects

This may potentially promote venous return, decrease intracranial pressure, and reduce the amount of bleeding. At the time of the estimation of the cerebral perfusion pressure (CPP), the level of the external acoustic meatus is determined as a reference for the monitoring of the mean blood pressure and venous pressure in the surgical field. The CPP should be maintained at 60 mmHg or higher. Placing a patient in a sitting position while they are under anesthesia puts them at risk for developing a decrease in cardiovascular function and, particularly, hypotension. Vasopressors may also need to be administered in some cases. In a previous report, the mean arterial pressure was relatively unaffected, but the wedge pressure, stroke volume, and cardiac index decreased [19]. The absence of a change in mean arterial pressure, which is associated with a decrease in cardiac index, signifies an increase in systemic vascular resistance. In elderly people or patients with a history of valvular heart disease or coronary artery disease and those who are unable to tolerate an increase in vascular resistance, an indwelling pulmonary artery catheter should be put into place, and alternative body positions should be taken into consideration.

26.3.4.4 Complications Associated with the Sitting Position

An air embolism is the most feared potentially life-threatening complication of surgery in a sitting position. When dural venous sinuses in the posterior cranial fossa are left open after a surgical procedure that is performed in the sitting position, the fact that they adhere to the surrounding bones keeps them from collapsing even when the venous pressure becomes negative. As a result, leaving them open allows air to flow in. For the monitoring of venous pressure in the surgical field in the posterior cranial fossa, the catheter is inserted in a retrograde manner from the internal jugular vein or from a vein in the upper arm. Then, the catheter tip is pushed forward under fluoroscopic guidance up to the level of the external acoustic meatus. In the presence of a sudden decrease in SpO_2 or $ETCO_2$, an air/pulmonary embolism is suspected. Air inflow inside veins must be detected rapidly with cardiac

auscultation, Doppler ultrasound examinations of the chest wall, and transesophageal echocardiography. Monitors that are used for the detection of venous air embolisms should have high sensitivity, good specificity, and a hair trigger, allow for quantitative evaluations of venous air embolisms, and be indicative of the process of recovery from a venous air embolism. These requirements are met by $ETCO_2$ and chest wall ultrasonography/Doppler, which are currently the standard monitors. Transesophageal echocardiography is more sensitive than chest wall Doppler; however, its safety for long-term use has not yet been established. Once air flow is detected inside veins, the operator should be informed immediately, and the surgical field should be covered with gauze that has been soaked in physiological saline solution. The anesthesiologist should rotate the operating table toward the right and upward, stop the inhalation of nitrous oxide, and attempt to aspirate the air from the indwelling central venous catheter or pulmonary artery catheter that had initially been put in place.

Other complications of surgery in the sitting position include macroglossia, quadriplegia, pneumocephalus, and sciatic nerve paralysis. Macroglossia is due to an impairment of venous return, and it is caused by indwelling devices in the oral cavity or excessive anteflexion, like that found in the prone position. Transesophageal echography may also be listed among the causes. Quadriplegia is often due to impaired blood flow and spinal cord compression that is caused by latent spinal diseases. Caution is needed when there are indications of the presence of diseases of the cervical spine. Pneumocephalus may cause delayed awakening, and it should be prevented by filling the cavity with artificial cerebrospinal fluid or physiological saline solution after the suture of the dura mater has been completed. Sciatic nerve paralysis is particularly frequent in obese individuals, and therefore, caution is needed.

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Chapter 27
Fluid Management

Masashi Ishikawa and Atsuhiro Sakamoto

Abstract Fluid management of neurosurgical patients has been a difficult problem for anesthesiologists. Cerebral edema may become a crisis of life. Although restrictive fluid management has been used for a long time, excessive fluid restriction may result in hypotension which can reduce cerebral perfusion pressure and cerebral blood flow. The goals of fluid management for neurosurgical patients include maintaining intravascular volume, preserving cerebral perfusion pressure, and minimizing cerebral edema.

The blood–brain barrier prevents not only the movement of colloids but also small ions. Because there are so few protein molecules compared with the number of ions, the fluid movement is governed by crystalloid osmotic pressure rather than colloid oncotic pressure in the brain. Intraoperative fluid administration should be given at a rate sufficient to replace the urinary output, insensible losses, and blood loss, but a reduction of osmolality should be avoided. Fluid administration will not induce cerebral edema as long as normal serum osmolality and oncotic pressure are maintained, and cerebral hydrostatic pressures are not markedly increased.

Keywords Blood–brain barrier • Osmolality • Colloid oncotic pressure

27.1 Introduction

Fluid management in neurosurgical patients is a difficult problem for anesthesiologists. Many neurological diseases can result in cerebral edema, a condition which can be life-threatening. Therefore, fluid administration in the treatment of neurosurgical patients has tended to be kept to a minimum for fear of inducing this condition [1]. Excessive restriction of fluid (hypovolemia), however, may result in hypotension, which can reduce cerebral perfusion pressure (CPP) and cerebral blood flow, with devastating consequences [2]. Diuretics are often administered for cerebral edema in neurosurgical patients, so intravascular volume always tends to be depleted preoperatively. However, it may also be necessary to keep the

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intravenous volume high in order to maintain a perioperative hemodynamic stability and an adequate CPP. The goals of fluid management in neurosurgical patients include maintaining intravascular volume, preserving CPP, and minimizing cerebral edema [3]. Cerebral perfusion and hemodynamic stability are necessary for the maintenance of neuronal homeostasis; however, the optimal fluid choice for prevention of secondary injury is unknown. Moreover, it is difficult to define clear guidelines on fluid management in such patients due to a lack of data on which to base them. It is possible to examine some of the physical determinants of water movement between the intravascular space and the central nervous system, however. This article provides some reasonable recommendations based on the available evidence.

27.2 Fluid Movement

27.2.1 Osmolality

With fluid therapy, the three blood characters can be manipulated: osmolality (concentrations of large and small molecules), colloid oncotic pressure (COP; large molecules only), and hematocrit.

Osmolality is the hydrostatic force acting to equalize the concentration of water on both sides of a semipermeable membrane. Water will move along its concentration gradient until both osmolalities equalize. The method to measure serum osmolality is the delta-cryoscopic technique. However, it is not always possible to obtain an immediate measurement with this method. Osmolality can be calculated from the osmoles that are routinely measured, such as sodium (mmol/L), urea (mg/dL), and glucose (mg/dL):

$$\text{Calculated serum osmolality} = 2 \times (\text{Na}+) + \text{urea}/2.8 + \text{glucose}/18$$

Osmolality is determined by the total number of dissolved particles in a solution, regardless of their size. COP is the osmotic pressure generated by large molecules such as albumin. In biological systems, vascular membranes are often permeable to small ions, but not to large molecules. Normal COP is approximately 20 mmHg.

One common fact of fluid infusion is a reduction in hematocrit. This hemodilution is typically accompanied by an increase in cerebral blood flow (CBF) [4, 5] due to a compensatory response to a decrease in arterial oxygen content [6–8]. However, the normal CBF responses to hemodilution are attenuated, and these changes may contribute to secondary tissue damage in the face of brain injury [9]. Several animal studies have shown that regional oxygen delivery may be increased or maintained in the face of modest hemodilution (Hct approximately 30 %), with improvement in CBF and reduction in infarction volume. In spite of this, hemodilution has not been shown to improve survival or functional outcomes [10]. A hematocrit level of

30–33 % gives the optimal balance of viscosity and O_2 content and may improve neurological outcomes [1, 11, 12]. In contrast, marked hemodilution (Hct < 30 %) causes a pronounced reduction in oxygen delivery capacity [5] and can aggravate brain injury. Active attempts to lower hematocrit are probably not advisable at the present time.

27.2.2 The Starling Equation and the Blood–Brain Barrier

The major factors that control fluid movement between the intravascular and extravascular spaces are the transcapillary hydrostatic gradient and the osmotic and oncotic gradients. The Starling equation [13] that describes the force driving water across vascular membranes is as follows:

$$\mathrm{FM} = \mathrm{k}(\mathrm{Pc} + \mathrm{pi\text{-}Pi\text{-}\,pc})$$

FM is fluid movement, k is the filtration coefficient of the capillary wall, Pc is the hydrostatic pressure in the capillaries, Pi is the hydrostatic pressure in the interstitial space, and pi and pc are interstitial and capillary osmotic pressures, respectively.

In brief, fluid movement is proportional to the hydrostatic pressure gradient and the osmotic gradient across a vessel wall. The driving force of the osmotic gradient will depend on the relative permeability of the vessels to solutes. In the peripheral organ, the capillary endothelium has a pore size of 65 Å and is freely permeable to small molecules and ions, but not to large molecules such as albumin [14]. The movement of water is governed by the plasma COP. Therefore, pi and pc are defined only by COP. Fluid will move into the interstitial space whenever the hydrostatic gradient increases or the COP decreases in the peripheral organs. This is familiar to anesthesiologists, who have seen peripheral edema in patients given a large amount of crystalloid during surgery.

In contrast, the effective pore size of capillaries in the blood–brain barrier (BBB) is only 7–9 Å [14]. This small pore size of the BBB prevents not only the movement of colloids but also small ions (Fig. 27.1). The fluid movement across the BBB is governed by both of the large molecules and small ions. Because there are so few protein molecules compared with the number of ions, the COP is a low fraction of the total osmolality (crystalloid osmotic pressure ≈ 5,600 mmHg, COP ≈ 20 mmHg) and the influence of COP change is diminished in the brain. These differences explain why the reduction of COP by administration of large volumes of isotonic crystalloids results in peripheral edema but does not induce cerebral edema [4, 12, 15]. However, once plasma osmolality decreases, even small further reductions in plasma osmolality increase brain water content and ICP [4].

Fluid movement when the BBB is injured is different from the situation when the BBB is intact. Drummond et al. [16] reported that COP reduction has the potential to aggravate brain edema according to the nature and severity of the brain injury. Since brain injury is often heterogeneous, there may be brain areas where the

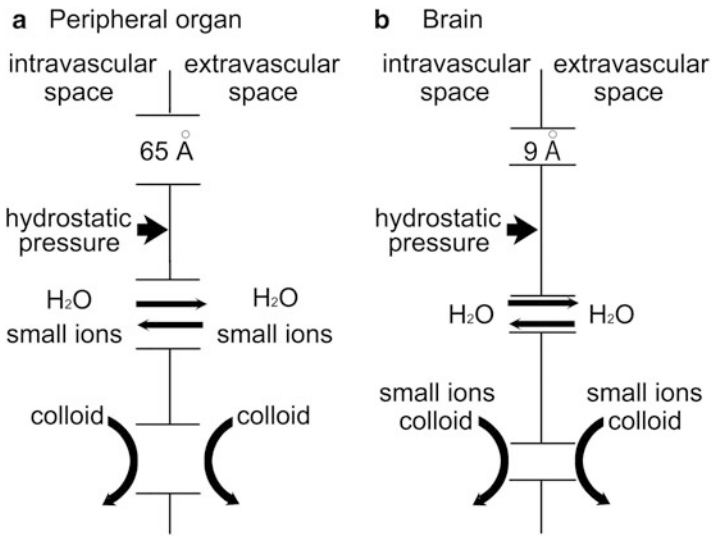

Fig. 27.1 Vascular permeability

osmotic/oncotic gradient is totally effective (normal BBB), areas where only the colloid oncotic gradient is effective (mild BBB injury), and areas where there is no osmotic/oncotic gradient (severe BBB injury). The presence of a functionally intact BBB is essential if osmotherapy is to be successful [17].

27.3 Fluid Formulations

27.3.1 Crystalloids

Crystalloids are the solutions that contain water and low molecular weight solutes, which may be charged (e.g., Na+ or Cl−) or uncharged (e.g., glucose or mannitol), and have an oncotic pressure of zero. Crystalloids may be categorized as hypo-osmolar, iso-osmolar, or hyperosmolar and may or may not contain glucose.

Hypo-osmolar fluid administration reduces plasma osmolality, drives water across the BBB, and increases cerebral water content and ICP [1, 4]. As a consequence, hypo-osmolar crystalloids (0.45 % NaCl or D5W) should be avoided in neurosurgical patients.

The volume administration will have no effect on cerebral edema as long as normal serum osmolality is maintained and as long as cerebral hydrostatic pressures are not markedly increased. Iso-osmolar solutions with an osmolality ≈ 300 mOsm/L, such as 0.9 % saline, do not change plasma osmolality and do not increase brain water content. This does not apply to solutions that are not truly iso-osmolar. The administration of large volumes of the commercially available lactated Ringer's

solution (calculated osmolarity ≈ 275 mOsm/L, measured osmolality ≈ 254 mOsm/kg) can reduce plasma osmolality and increase both brain water content and ICP [4, 18].

Crystalloids may be made hyperosmolar by the inclusion of electrolytes (e.g., Na+ and Cl−) or low molecular weight solutes such as mannitol or glucose. Hyperosmolar solutions exert their beneficial effects by osmotically shifting water from the nervous tissue (intracellular and interstitial spaces) to the intravascular space. The increased serum osmolality reduces the cerebrospinal fluid secretion rate, and this effect can contribute to improved intracranial compliance [19–21].

27.3.2 Colloids

Colloids contain high molecular weight molecules, such as natural (albumin) or synthetic molecules (hetastarch, dextran), and have an oncotic pressure similar to that of plasma. Although it is accepted that a reduction in serum osmolality will cause cerebral edema [4, 16], there is no consensus on the effect of COP reduction on cerebral edema [11, 15, 22–24].

27.4 The Recommendation for Perioperative Fluid Management

27.4.1 Intraoperative Fluid Management

Intraoperative fluid administration should be given at a rate sufficient to replace the urinary output, insensible losses, and blood loss, but a reduction of osmolality should be avoided. The available data indicate that fluid administration will not induce cerebral edema as long as normal serum osmolality and oncotic pressure are maintained and cerebral hydrostatic pressures are not markedly increased. Although commercially available lactated Ringer's solution (1–3 L) can be safely used, if large volumes are needed for blood loss, switching to a truly iso-osmolar fluid is probably advisable, and a combination of iso-osmolar crystalloids and colloids may be the best choice.

27.4.2 Postoperative Fluid Management

In the postoperative period, large fluid administration is not necessary. However, the cerebral blood volume (CBV) and serum sodium level decrease in the

postoperative period [25]. Hyponatremic hypovolemia may be induced by the shift of fluid and sodium to the interstitial space due to surgical stress. Periodic measurements of serum osmolality and fluid administration targeted to maintain normovolemia and normal osmolality are recommended. If cerebral edema does develop, specific treatment with diuretics that will increase osmolality appears to be reasonable unless this therapy results in hypovolemia.

27.5 Fluid Monitoring

Anesthesiologists want to know whether their patient is hypovolemic and the change cardiac output (CO) in response to intravascular volume expansion. Early hemodynamic assessment by ensuring appropriate CO is important for adequate cerebral perfusion and oxygen delivery in patients after aneurysmal subarachnoid hemorrhage (SAH) [26, 27]. Studies using transesophageal Doppler to optimize CO have shown the clinical benefits of this approach [28]; however, very few centers use transesophageal Doppler in their daily clinical management of neurosurgical patients. Insertion of a pulmonary artery catheter (PAC), an established method for measurement of CO, is also rarely performed due to the risk of cardiopulmonary complications. Mutoh and colleagues demonstrated that transpulmonary hemodynamic monitoring (PiCCO system) was useful for fluid management, and a good correlation was apparent between CO measured by PiCCO and PAC after SAH [29].

Respiratory variations in the arterial waveform and plethysmographic waveform have been shown to be related to a patient's fluid status. The FloTrac system, using the patient's own peripheral blood pressure waveform and individual patient demographic data, continuously tracks CO and stroke volume variation (SVV). The FloTrac-derived SVV is an acceptable preload indicator for SAH patients during the intraoperative period [29]. It has been shown that respiratory variations of the plethysmographic waveform amplitude are able to predict fluid responsiveness in mechanically ventilated patients [30]. Instead of invasive monitoring, plethysmographic indices that include the respiratory variation in pulse oximetry plethysmographic waveform amplitude and the plethysmographic variability index are reliable predictors of responsiveness to a fluid infusion [31]; however, these dynamic variables have several limitations. Patients are required to be sedated and their lungs mechanically ventilated. They must also be in sinus rhythm [32], the chest and pericardium must be closed [33], and the intra-abdominal pressure should be within a normal range [34]. However, these limitations rarely restrict the use of the noninvasive plethysmographic indices to monitor the response of neurosurgical patients to fluid infusion.

27.6 Conclusions

Hemodynamic stability and maintenance of cerebral perfusion are essential to the treatment of neurosurgical patients. It is important to pay attention to the influence of fluid therapy on the brain as well as the rest of the body based on cerebral pathophysiology and general status. However, fluid management has progressed rapidly. Important questions still remain concerning the complications of current fluid therapy and the comparative advantages of specific regimens and the choice of fluid formulations in a variety of clinical circumstances.

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Part VI
Anesthetic Management: Vascular Procedures

Chapter 28
Anesthesia for Intracranial Vascular Surgery

Yukihiko Ogihara

Abstract Subarachnoid hemorrhage (SAH) secondary to ruptured cerebral aneurysm carries a poor outcome and high mortality. There are various types of cerebral aneurysm and several risk factors for aneurysm development or rupture.

Preoperative grading scales, such as the Hunt and Hess scale, are useful to estimate prognosis. In addition to physical symptoms (sudden severe headache, nausea, or vomiting), SAH leads to systemic physiological responses in patients. Complications of SAH are not only intracranial but also extracranial (myocardial ischemia, arrhythmia, or neurological pulmonary edema). Recently, CT angiography has become essential to investigate ruptured aneurysms.

Preoperative management of cerebral vasospasm, arrhythmia, pulmonary edema, hypovolemia, and hyponatremia is required. Premedication differs according to the patient's grade. There are many monitoring systems (invasive and noninvasive) for the central nervous system. The induction of anesthesia and the hemodynamic response should be controlled adequately without compromising cerebral perfusion pressure. Total intravenous anesthesia is preferred particularly when motor evoked potential measurement is performed. Artificial ventilation is controlled to prevent hypercapnia which may increase intracranial pressure. Triple-H therapy may be a reliable method to prevent postoperative cerebral vasospasm. Adequate postoperative pain management is thought to inhibit hypertension or tachycardia, which may become worse in the patient.

Keywords Subarachnoid hemorrhage (SAH) from a cerebral aneurysm • Cerebral vasospasm • Anesthetic management

28.1 Introduction

Cerebral aneurysms are the most common cause of subarachnoid hemorrhage (SAH) excluding trauma. An SAH destroys cerebrovascular autoregulation and induces not only intracranial but also serious systemic complications, such as

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increasing intracranial pressure, cerebral vasospasm, or cardiopulmonary disturbance, with high mortality. Anesthesiologists should be familiar with the pathophysiology and treatment of SAH resulting from a cerebral aneurysm. At the beginning of this chapter, basic knowledge, clinical symptoms, and complications of cerebral aneurysm and SAH are reviewed, followed by a discussion of anesthetic management from the preoperative to postoperative period.

28.2 Pathophysiology of Cerebral Aneurysms

28.2.1 Epidemiology

SAH comprises only 1–7 % of all strokes; however, it has a relatively younger age of onset and poorer outcome than cerebral infarction [1]. The incidence of SAH secondary to ruptured cerebral aneurysm is 11–16 cases per 100,000 population per year [2, 3] and its mortality is 32–67 % [4], in agreement with previous reports. The incidence of unruptured aneurysm is 5 % [5], and if the size is < 10 mm and there is no history of subarachnoid hemorrhage, the incidence of rupture is 0.05 % per year [6].

28.2.2 Types and Location of Cerebral Aneurysms

28.2.2.1 Types

Saccular (berrylike) aneurysms are common and most are classified as small, being less than 12 mm in diameter. Giant aneurysms are more than 25 mm [7] and occasionally measure up to 10 cm. Fusiform aneurysms are often associated with severe atherosclerosis. Other types of aneurysms include dissecting, traumatic, and mycotic aneurysms.

28.2.2.2 Location

The most common locations are the anterior communicating artery (ACoA), internal carotid-posterior communicating artery (ICPCoA), and middle cerebral artery (MCA) bifurcation. The emergence of cross flow into the ACoA contributes to the formation of aneurysms [8]; therefore, hemodynamic stress may relate to the formation of cerebral aneurysms at a vessel's branching point, such as the ICPCoA or MCA bifurcation.

28.2.3 Risk Factors

28.2.3.1 Risk Factors for Developing Aneurysms

Risk factors for developing aneurysms include a family history of the disease (unruptured aneurysms or SAH), hypertension, smoking, atherosclerosis, previous infection, fibromuscular dysplasia, polycystic kidneys, coarctation or hypoplasia of the aorta, and connective tissue disorders (Ehlers-Danlos syndrome, Marfan syndrome, pseudoxanthoma elasticum).

28.2.3.2 Risk Factors for Ruptured Aneurysms

Risk factors for ruptured aneurysms depend on the size (more likely if > 6 mm [9]), morphology, location, and any previous history of SAH [10].

28.2.4 When an Aneurysm Ruptures

The pathophysiologic changes [10] include a sudden increase in intracranial pressure (ICP), decrease in cerebral blood flow (CBF) and cerebral perfusion pressure (CPP), loss of cerebrovascular autoregulation, spread of blood through the subarachnoid space causing inflammation and meningism, and cerebral vasoconstriction.

28.2.4.1 Treatment of Increased ICP

Treatments for increased ICP include maintaining a head-up position with sufficient fluid infusion, mild hyperventilation, intravenous infusion of osmotic diuretic agents, bolus or continuous administration of barbiturates, mild hypothermia, and external ventricular drainage of cerebrospinal fluid (CSF).

28.3 Preoperative Assessment

28.3.1 Preoperative Grading Scales

28.3.1.1 Neurological Symptom Grading Scales

The Hunt and Hess scale has been used widely as a preoperative neurological symptom grading scale (Table 28.1 [11]). As the World Federation of Neurological Surgeons (WFNS) grading scale is based on the Glasgow coma scale (GCS), the

Table 28.1 Hunt and Hess grading scale [11]

Grade	
I	Asymptomatic or minimal headache and slight nuchal rigidity
II	Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy
III	Drowsiness, confusion, or mild focal deficit
IV	Stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity, and vegetative disturbances
V	Deep coma, decerebrate rigidity, moribund appearance

Table 28.2 World Federation of Neurological Surgeons (WFNS) grading scale [12]

WFNS Grade	GCS score	Motor deficit
I	15	Absent
II	14–13	Absent
III	14–13	Present
IV	12–7	Present or absent
V	6–3	Present or absent

scale is designed more simply and clinically estimates the prognosis by combining the GCS with major focal neurological deficits (aphasia, hemiparesis, or hemiplegia) (Table 28.2 [12]).

28.3.1.2 Grading of Blood by Computed Tomography (CT)

Although it has been pointed out that the Fisher grading system (Table 28.3 [13]) is not adapted to current technically sophisticated CT imaging, there are good correlations between this scale and symptomatic cerebral vasospasm [14].

28.3.2 Clinical Symptoms of SAH

28.3.2.1 Physical Symptoms

Cerebral aneurysms are most frequently manifested as SAH together with a sudden severe (thunderclap) headache, neck pain, nausea, vomiting, focal neurological signs, depressed consciousness, and prolonged coma.

28.3.2.2 Physiological Symptoms

Additionally, SAH leads to a range of systemic physiological responses and occasionally results in a hazardous situation or even death.

Table 28.3 Fisher grading system [13]

Group	Blood on CT
1	No subarachnoid blood detected
2	Diffuse deposition or thin layer with all vertical layers of blood (interhemispheric fissure, insular cistern, ambient cistern) < 1 mm thick
3	Localized clots and/or vertical layers of blood ≥ 1 mm thick
4	Intracerebral or intraventricular clot with diffuse or no subarachnoid hemorrhage

An abnormal ECG after SAH can be recognized in 70–100 % of the patients and presents variable waves as follows: peaked P waves, short PR interval, prolonged QT interval, large U waves, peaked T waves, and rarely electrical transformations of subendocardial ischemia or infarction. An overstressing of the sympathetic nervous system from increased ICP brings about these changes and is also fraught with excessive increases in blood pressure (Cushing reflex). The changes are often accompanied by mild elevation of cardiac enzymes, but do not usually correlate with significant myocardial dysfunction.

Leukocytosis, in which the white blood cell count increases to more than 20,000 per mm^3 after SAH, presents a poor clinical grading scale value, and the mortality reaches 50 % [15].

Other physiological changes after SAH include electrolyte imbalances, particularly hyponatremia, and acid-base abnormalities.

Caution from Drake [16]

An incident occurred which shows that, once alerted, both physicians and the public can recognize a warning bleed. In London, Ontario, a first year resident in neurology was sued by a widow for missing a "warning leak" some 2 weeks before her husband's fatal hemorrhage. A large judgment was rendered against him by the court and the story was featured in detail in the newspapers. During the following week, eight patients were referred to an emergency department by their physician for lumbar puncture, and in five of them the fluid was bloody. Also of interest was that they thought they had had a hemorrhage.

28.3.3 Complications of SAH

28.3.3.1 Intercranial Complications Secondary to SAH

Rebleeding is a fatal complication of SAH, which may form intracerebral or intraventricular hematomas and increase mortality and morbidity. The incidence of rebleeding peaks within 24 h after SAH; during the first 12 h, 12 % of the patients suffer from rebleeding and most of them receive poor grading at the initial symptom

evaluation [17]. A giant cerebral aneurysm occurring in a patient under 40 years old shows a higher tendency of rebleeding than in an older patient [18].

Vasospasm is generally manifested clinically 3–5 days after SAH and may induce cerebral ischemia or infarction, which are foremost causes of morbidity and death. Early vasospasm observed within 48 h after rupture of a cerebral aneurysm is recognized in 10 % of the patients and suggests a worse prognosis, but there is no relationship between delayed cerebral vasoconstriction and prognosis [19].

Hydrocephalus occurs in 10 % of the patients after SAH. Once it occurs, any aneurysm treatment cannot affect the progression of hydrocephalus. Acute hydrocephalus is characterized by the onset of lethargy and coma within 24 h of SAH, whereas chronic hydrocephalus develops weeks after SAH in surviving patients. Symptoms of chronic hydrocephalus include impaired consciousness, dementia, gait disturbance, and incontinence.

Seizures are deleterious because of increasing CBF and cerebral metabolic rate for oxygen ($CMRO_2$). Patients who present with lobar intracerebral hemorrhage on CT scan have a high rate of seizures.

28.3.3.2 Extracranial Complications

Extracranial complications include myocardial ischemia and infarction, arrhythmia, hemodynamic derangements, neurological pulmonary edema, and gastric hemorrhage (Cushing ulcer).

28.3.4 Investigations of SAH

28.3.4.1 Digital Subtraction Angiography (DSA)

Digital subtraction angiography (DSA) is still useful for investigation of cerebral aneurysms. When the presence of an aneurysm is suspected, repeat DSA after a suitable interval is required.

28.3.4.2 CT Angiography

The role of contrast-enhanced CT angiography is essential to investigate ruptured aneurysms, because of its ability to obtain important information about intracerebral or intraventricular hemorrhage, cerebral infarction, brain edema, and hydrocephalus that may be difficult to obtain by the use of DSA. In addition, CT investigation is noninvasive and may be repeated sequentially. The pulsation of cerebral aneurysms can be seen by recently developed four-dimensional CT [20].

28.3.4.3 Magnetic Resonance Imaging (MRI)

The detection of SAH by magnetic resonance imaging (MRI) is 94 % within 4 days after SAH and 100 % after 4 days using T2-weighted imaging [21].

28.3.4.4 Other Investigations

Transcranial Doppler (TCD) and cerebral arteriography can detect cerebral vasospasm before clinical symptoms occur [22].

28.3.5 How Should We Treat Aneurysms?

28.3.5.1 Treatment of Aneurysms

The treatment of a ruptured aneurysm should be considered first and then the prevention of rebleeding and removal of the hematoma. An unruptured aneurysm requires consideration regarding the cure and prevention of bleeding. A giant aneurysm must be prevented from rupturing, and the reduction in the diameter of the aneurysm needs to be planned.

28.3.5.2 Which Surgical Treatment Is Better?

Although there are no universal guidelines to choose whether neurosurgery (clipping) or neuroendovascular therapy (coiling) should be used, the general criteria are as follows:

- Neuroendovascular coiling is recommended to treat an aneurysm of the internal carotid-ophthalmic artery.
- Neurosurgical clipping is suggested to treat an aneurysm of the MCA.
- There are no indications for endovascular therapy for giant cerebral aneurysms, fusiform aneurysms, and small (<3 mm) thromboembolic aneurysms.

28.4 Anesthetic Management

28.4.1 Preoperative Management

28.4.1.1 Cerebral Vasospasm

Vasospasm of the cerebral artery may induce cerebral ischemia or infarction; therefore, early treatment of vasospasm is very important. “Triple-H therapy (HHH therapy)” which stands for hypertensive, hypervolemic, and hemodilution,

consists of intravenous administration of fluids or inotropic drugs, or both [22], and improves cerebral perfusion with increased blood pressure and intravascular volume accompanied by lower blood viscosity. Thus, the combination of hypervolemia and isoproterenol may be a reasonable therapy for untreated cerebral aneurysms [23]. A central venous pressure (CVP) of 10 mmHg or a pulmonary artery wedge pressure (PAWP) of 12–16 mmHg, or both, is considered as an index of optimal volume expansion. A hematocrit value of about 30 % is an advantage for the cerebral microvasculature.

28.4.1.2 Changes in the ECG Wave Tracing

Changes in the ECG wave tracing after SAH are well known and are correlated with increased catecholamine levels in the blood. Clinically, 33 % of SAH patients show some cardiac complications, mostly arrhythmia and lung edema [24].

Usually, the antiarrhythmic agents which do not prolong the QT interval, such as propranolol, lidocaine, and phenytoin, are prescribed. Contraindicated agents include procainamide, quinidine, and disopyramide.

28.4.1.3 Neurogenic Pulmonary Edema

Neurogenic pulmonary edema is caused by systemic and lung vasoconstriction-induced massive adrenergic discharge [25]. To determine whether the lung edema is neurogenic, it has to be distinguished from iatrogenic lung edema caused by excessive infusion of crystalloid or transfusion of blood, edema resulting from heart or renal failure, and aspiration pneumonia. Treatments include airway management, oxygenation, positive end expiratory pressure (PEEP), administration of adrenocortical hormone, and diuretic drugs.

28.4.1.4 Hypovolemia

Hypovolemia emerges necessarily after SAH because of excessive decreases in red blood cell mass or total blood volume [26]; thus, intravascular expansion therapy for symptomatic cerebral vasospasm becomes necessary (hypervolemia is part of "triple-H therapy"). Although cerebral vasospasm occurs from a combination of cerebral vasoconstriction and a decrease in total blood volume, cerebral ischemia can occasionally emerge with normal blood volume, even if there is vasoconstriction [27].

28.4.1.5 Hyponatremia

Hyponatremia occurs commonly after SAH. It is regarded as being induced by the cerebral salt-wasting syndrome (CSWS) rather than by the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) [28]. CSWS brings about excessive natriuresis by means of atrial natriuretic peptide (ANP) from the hypothalamus, and therefore we must treat to replace the sodium deficit with salt, using either normal or hypertonic (3 %) saline. Recently, brain natriuretic peptide (BNP) [29] or dendroaspis natriuretic peptide (DNP) [30] has been suggested as giving rise to hyponatremia.

28.4.1.6 Cerebral Ischemia

Cerebral ischemia worsens the morbidity and leads to poor overall mortality. Hyperglycemia associated with cerebral ischemia accelerates intracellular acidosis; hence, blood sugar level should be controlled to within 80–120 mg/dL to prevent brain injury. Similarly, hyperthermia worsens cerebral damage; the treatment by moderate hypothermia (34–35 °C) is effective to protect the brain. Otherwise, the calcium antagonist nimodipine (but not nicardipine) administered p.o. decreases the risk of morbidity, ischemic neurological disturbances, cerebral infarction, and rebleeding and also reduces death from vasospasm. Intravenous injection of a calcium antagonist cannot be recommended because blood pressure depression is an adverse event [31].

28.4.1.7 Acute Hydrocephalus

Acute hydrocephalus may require external ventricular drainage to normalize ICP. Hydrocephalus drained within 24 h preoperatively shows rebleeding in 4.4 % of the patients; the value is similar to later drainage [32].

28.4.1.8 Early Seizures

Early seizures occur in 3 % of the patients, frequently before hospitalization; prophylactic therapy is therefore controversial.

28.4.2 Premedications

Preoperative medications such as anticonvulsants or steroids, if prescribed, are continued. Drugs for gastric conditions, either an H_2 antagonist or metoclopramide,

are given before the induction of anesthesia. Giving small doses of opioids or benzodiazepine, or both, may be effective in good-grade patients. Conversely, almost all poor-grade patients do not receive hypnotic premedication, but receive blood pressure control. If an endotracheal tube is in place, medication for sedation and muscle relaxation may be given. Because of the hypovolemia after SAH, hydration with isotonic crystalloid solution is required before induction.

28.4.3 Monitoring

28.4.3.1 Noninvasive Conventional Monitoring

The V_5 lead of a 12-lead ECG represents heart rate, rhythm, and cardiac ischemia.

Intermittent noninvasive blood pressure can indicate the risk of rebleeding.

Urine output may be an estimate of the intravascular volume and renal function intraoperatively. When excessive urine output occurs, hypovolemia and electrolyte imbalances may exist, and diabetes insipidus (DI), SIADH, or CSWS needs to be considered.

End-tidal CO_2 concentration (P_{ETCO2}) conveniently suggests the status of the cerebrovascular autoregulation of the brain, relaxed or tight. In addition, a sudden decrease in the P_{ETCO2} may enable early detection of an air embolism.

Percutaneous oxygen saturation (S_PO_2) measurement via the pulse oximeter is helpful to prevent hypoxemia.

Deep body temperature measured at the tympanic or nasopharyngeal region reflects brain temperature and is useful to help protect the brain from hyperthermia.

28.4.3.2 Invasive Monitoring

Invasive arterial blood pressure measurement, performed before induction, is essential to strictly control systemic blood pressure and to prevent rupture of aneurysms and cerebral ischemia caused by violent fluctuations in blood pressure. Moreover, several blood samples via the arterial route may be obtained for analyzing blood gas, measuring blood sugar level, or other clinical factors.

CVP (central venous pressure) for the monitoring of preload is of great importance for several indications, such as preoperative hypovolemia, severe heart disease, and excessive bleeding intraoperatively.

Transesophageal echocardiography (TEE) is performed to evaluate left cardiac system function and air embolism.

28.4.3.3 Monitoring of the Central Nerve System (CNS)

Monitoring of motor evoked potentials (MEP) outperforms other CNS monitoring, such as somatosensory evoked potentials (SSEP) or microvascular Doppler ultrasonography (MDU), in detecting subcortical ischemia in the brain, which brings about motor dysfunction [33].

Brain tissue O_2 ($PtiO_2$) may be valuable in detecting ischemia expression in the brain [34].

TCD (transcranial Doppler) can show the condition of the CBF and appearance of air embolism.

ICP monitoring is helpful to preserve the CPP.

Jugular bulb oxygen saturation ($SjvO_2$) can show the O_2 supply and demand in the brain.

28.4.4 Goals of Anesthetic Management

Neuroanesthesiologists should make plans for the anesthetic management before surgery (Table 28.4 [22]). The basic goals are as follows.

28.4.4.1 Blood Pressure

Avoid sudden increases or rapid decreases in arterial blood pressure, which would induce aneurysm rupture due to a steep change in transmural pressure of the aneurysm.

Table 28.4 Anesthetic management of patients with intracranial aneurysms [22]

Preoperative	Neurologic evaluation is performed to look for evidence of increased intracranial pressure and vasospasm
	Electrocardiogram changes frequently are present
	HHH therapy is indicated if vasospasm is present
	Calcium channel blockers
Induction	Avoid increases in systemic blood pressure
	Maintain cerebral perfusion pressure to avoid ischemia
Maintenance	Opioid plus propofol and/or volatile anesthetic is the recommended regimen
	Mannitol (0.25–1.0 g/kg IV) also can be given
	Maintain normal to increased systemic blood pressure to avoid ischemia during temporary clipping
Postoperative	Maintain normal to increased systemic blood pressure
	Early awakening is recommended to facilitate neurologic assessment
	HHH therapy is given as needed

HHH hypervolemia, hypertension, hemodilution

28.4.4.2 CPP and CBF

Maintaining the CPP and CBF to prevent hypoxemia is important, even during temporary vessel occlusion. It is equally important to remember that CBF depends on systemic blood pressure because cerebrovascular autoregulation is lost after SAH.

28.4.4.3 ICP

Controlling ICP appropriately and retaining "brain relaxation (not tight or bulging brain)" are necessary to prevent cerebral edema or vascular engorgement.

28.4.5 Induction of Anesthesia

The hemodynamic response evoked by direct laryngoscopy, tracheal intubation, and particularly the placement of head pins should be controlled adequately without compromising the CPP. After optimal head position is obtained, an opioid (fentanyl, 2–5 mcg/kg; morphine, 20–50 mcg/kg; remifentanil, 0.5 mcg/kg/min) and a hypnotic agent (propofol, 1–2 mg/kg; thiopental, 3–5 mg/kg; midazolam, 0.1–0.2 mg/kg) are administrated intravenously, followed by a muscle relaxant (rocuronium, $\geq$0.6 mg/kg; vecuronium, 0.1 mg/kg) to facilitate insertion of an endotracheal tube. Lidocaine (1.5 mg/kg) is given before laryngoscopy and intubation, if needed. All procedures are carried out with a 100 % oxygen mask and in some cases adding a low-dose inhalation anesthetic (0.5 MAC).

28.4.6 Maintenance of Anesthesia

28.4.6.1 Management of Anesthetic Agents

A volatile anesthetic (isoflurane, sevoflurane, or desflurane) can be chosen under conditions of normal ICP, but usually total intravenous anesthesia (TIVA) with propofol, narcotic, and muscle relaxant is suitable for cerebral aneurysm surgery, particularly in a patient with a high ICP. Although lurching or other movement while the patient's head is fixed is very dangerous, no addition of muscle relaxant after intubation is required when MEP measurement is performed.

28.4.6.2 Artificial Ventilation

Pulmonary ventilation is controlled to maintain the $PaCO_2$ between 30 and 35 mmHg, averting hypercapnia which may increase the ICP. Generally, the respiratory rate is raised to add minute volume, but simultaneously high airway pressure, which also may increase ICP, should be inhibited.

28.4.6.3 Blood Pressure

The systemic blood pressure, before coiling or clipping, is maintained within the patient's normal range or a mean arterial pressure (MAP) between 70 and 80 mmHg, thus optimizing the CPP ($\geq$50 mmHg). During temporary proximal occlusion, MAP is maintained in the high-normal range to facilitate perfusion through the collateral circulation and to prevent distal cerebral ischemia or infarction caused by regional hypotension. At this time, a vasopressor (phenylephrine, 0.1–0.2 mg IV; dopamine, 3–5 mcg/kg/min; norepinephrine, 0.1–0.2 mcg/kg/min) can be used to raise the MAP gently. The MAP after embolization with coiling need not change from the normal range. On the other hand, after placement of a cerebrovascular clip, as the aneurysm is isolated from the systemic circulation, a MAP as high as 110 mmHg is acceptable, which may be of value in preventing postoperative vasospasm.

28.4.6.4 Fluid Management

Some type of lactated or acetated Ringer's solution is preferred to normal saline. However, it may aggravate cerebral edema if an excessive amount of hypoosmotic crystalloid solution is infused; therefore, maintaining euvolemia is an important matter. Colloids (5 % albumin or 6 % hetastarch) are acceptable, although hetastarch (>500 mL) may interfere with hemostasis.

28.4.6.5 Cerebral Protection (See Sect. 28.4.1.6)

When collateral cerebral circulation cannot be maintained by systemic hypertension alone, some means of cerebral protection must be employed. Intermittent intravenous administration of thiopental (3–5 mg/kg) or propofol (1–2 mg/kg) is considered a promising treatment to prevent cerebral ischemia. Mild hypothermia (33 °C) or a calcium antagonist (e.g., nimodipine) is also effective. A solution of 20 % mannitol offers cerebral protection in addition to its diuretic action.

28.4.6.6 If Brain Swelling Occurs

If cerebral edema occurs, it is important to first discontinue the administration of volatile anesthetics. The infusion of crystalloid solution should cease and be replaced with hypertonic saline (1.8–7.5 %). Mannitol (0.5–1 g/kg), an osmotic diuretic, reduces cerebral volume beginning 5–10 min after infusion. Rapid administration or large doses of mannitol cause several side effects, including hypotension, hyponatremia, and hyperosmotic serum. Furosemide (0.5–1 mg/kg), a diuretic agent, is also effective in decreasing the ICP. Barbiturates, which suppress cerebral metabolism and reduce cerebral blood flow, can also be used to decrease the ICP. Thiopental, a 5 mg/kg bolus infusion followed by 2–5 mg/kg continuous infusion, may be a conventional prescription. Other treatments to decrease the ICP include maintaining a head-up position (15–30°) and augmenting hyperventilation ($PaCO_2$ of 25–30 mmHg).

28.4.7 Emergence from Anesthesia

On awakening from anesthesia, a gentle extubation is required to prevent coughing which may increase the possibility of hemorrhage. A bolus intravenous infusion of lidocaine (1.5 mg/kg) may inhibit the response.

28.4.8 Postoperative Anesthetic Management

28.4.8.1 Cerebral Vasospasm

Cerebrovascular vasoconstriction, following neurosurgical procedures for SAH treatment, is the most important issue in postoperative management. Treatment reduced serious vasospasm and improved long-term prognosis after the mechanism of cerebral vasospasm was unraveled and several valid therapies were established [35]. Triple-H therapy, composed of hypertension, hypervolemia, and hemodilution, may be easy to understand and be an unfailing method to treat postoperative cerebral vasospasm, in the same way as preoperatively. However, if triple-H therapy continues until unnatural hypervolemia occurs, the patient's cardiac function would closely approach the conditions of heart failure and, in particular, the observed tachycardiac arrhythmia.

28.4.8.2 Postoperative Polyuria

Postoperative polyuria occurs from several causes and induces electrolyte imbalances and therefore should be treated adequately in concordance with each

etiology. DI caused by a decrease in ADH secretion includes polyuria, hypernatremia, low specific gravity of urine, and dehydration. Treatments for DI are infusion of 0.45 % saline solution and intramuscular injection of vasopressin (5–10 U) [36]. Treatments for SIADH are water restriction and infusion of isotonic solution. Treatment for CSWS has been mentioned previously (see Sect. 28.4.1.5).

28.4.8.3 Postneurosurgical Pain Management

Adequate sedation and analgesia are important postoperatively, because of the stress resulting in hypertension or tachycardia which may become worse in the patient. After brain surgery, it is necessary to assess neurological findings, including consciousness level; therefore, oversedation must be avoided. Other than the use of appropriate opioids, such as the patient-controlled analgesia system, scalp nerve block or administration of acetaminophen is effective.

28.4.8.4 Other Postoperative Management

Meningitis may result from an indwelling intracranial drain. Some neurological changes, such as delayed return of consciousness or neurological deterioration, may be observed. An immediate CT scan or MRI should be performed to investigate this condition.

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Chapter 29
Anesthesia for Carotid Endarterectomy

Yuji Kadoi

Abstract Carotid endarterectomy (CEA) is a preventative procedure performed in the presence of well-defined indications. Although the impact of the type of anesthetic method on outcomes has been extensively studied, it remains unresolved whether regional or general anesthesia is superior in CEA. The use of a carotid shunt is based on neurological monitoring during clamping. Although various techniques have been used to monitor cerebral perfusion under general anesthesia and detect cerebral ischemia during carotid artery cross-clamping, none are completely reliable. Drastic hemodynamic changes may be observed during both the intraoperative and postoperative periods. It is essential to maintain adequate systemic and cerebral hemodynamics during the perioperative period.

Keywords Regional • General • Brain protection • Monitoring • Hemodynamics • Anesthetics

29.1 Introduction

Carotid endarterectomy (CEA), a prophylactic procedure used in vascular surgery, is performed in patients at risk of stroke from emboli arising from atheromatous plaque at the carotid bifurcation [1–3]. The aim of CEA is to decrease subsequent risk of fatal or disabling stroke in patients with significant carotid stenosis, but the benefits are only realized if perioperative morbidity and mortality are low.

Patients likely to benefit from this procedure may be divided into two groups: symptomatic, those with active plaques that enter the cerebral circulation and cause transient ischemic attacks (TIAs), and asymptomatic, those with significant carotid stenosis at the bifurcation, but with no history of TIAs or strokes.

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) [2] and the European Carotid Surgery Trial (ECST) [3] showed that CEA improves outcomes in symptomatic patients with >70 % stenosis compared with best medical treatment (reduction in arterial pressure, antiplatelet drugs, statins or diet to

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reduce serum cholesterol, smoking cessation, and reducing alcohol intake). In addition, the Asymptomatic Carotid Surgery Trial (ACST) [4] demonstrated that CEA improves outcomes in those with carotid stenosis >60 %, but no symptoms.

In this chapter, we discuss perioperative management in patients undergoing CEA.

29.2 Physiological Effects

Eighty to ninety percent of the cerebral blood supply is delivered from the two internal carotid arteries, and the remaining blood supply comes from the basilar arteries. The carotid and basilar arteries unite to form the circle of Willis at the base of the brain. Although the circle of Willis offers the brain protection against occlusion of any of the constituent vessels, its ring is incomplete in 15–20 % of healthy individuals.

29.3 Monitoring Cerebral Ischemia During CEA Surgery

Monitoring and maintaining cerebral perfusion pressure during CEA is extremely important, especially at the time of carotid artery cross-clamping. Performing CEA under regional anesthesia allows direct monitoring of the neurological status since the patient is awake [5]. This allows intraoperative detection of cerebral ischemic episodes. Patients who are awake, however, are susceptible to anxiety-related sympathetic responses, which have the potential to increase the risk of myocardial ischemia. In addition, not all surgeons can complete the procedure within the time afforded by regional anesthesia.

Various techniques have been used to monitor cerebral perfusion under general anesthesia and possibly detect cerebral ischemia during carotid artery cross-clamping, including (1) carotid artery stump pressure, (2) electroencephalography (EEG), (3) evoked potentials, and (4) near-infrared spectroscopy (NIRS). However, none of these are completely effective in detecting cerebral ischemia during carotid artery cross-clamping.

29.3.1 Carotid Artery Stump Pressure

When the ipsilateral common carotid artery is clamped, cerebral blood flow and pressure are maintained via the circle of Willis. During carotid cross-clamping, measurement of stump pressure, defined as the arterial pressure in the ipsilateral carotid artery distal (brain side) to the cross-clamp, is widely used as an indicator to monitor cerebral blood flow (CBF). Stump pressure reflects the pressure within the

circle of Willis and depends on the collateral circulation and systemic blood pressure. It is widely believed that a stump pressure of greater than 50 mmHg is an adequate cerebral perfusion pressure and is an indicator of the adequacy of collateral blood supply via the circle of Willis. However, there is a poor correlation between stump pressure and EEG, NIRS, and changes in evoked potential [6]. In addition, anesthetic agents can alter stump pressure by changing cerebral vascular resistance.

29.3.2 Electroencephalography

Electroencephalography is widely used to evaluate the adequacy of cerebral perfusion. Sundt et al. [6] examined the correlation between neurologic deficits and EEG changes during CEA and found that the EEG demonstrates excellent sensitivity in detecting cerebral ischemia intraoperatively, as compared to other monitoring modalities. However, EEG changes during cross-clamping do not always indicate development of new neurologic deficits after surgery. This discrepancy may be attributable to the fact that most cases of stroke after CEA are embolic in origin and may not be attributable to cerebral ischemia during cross-clamping. Rampil et al. [7] examined the relationship between intraoperative EEG changes and postoperative neurologic deficit. They found that although there is a good correlation between intraoperative ischemic EEG changes (a 50 % decrease in spectral edge frequency lasting for 10 min or more) and the incidence of postoperative neurologic deficits in patients with no preoperative neurologic deficits, intraoperative EEG changes were not predictive in patients with preoperative neurologic deficit.

29.3.3 Evoked Potentials

Somatosensory evoked potentials (SSEPs) reflect activity in the sensory cortex following peripheral nerve stimulation and are thought to be less sensitive than EEG in detecting changes in cortical function. In addition, inhaled anesthetics, such as isoflurane, sevoflurane, and desflurane, can reduce the amplitude and latency of SSEPs. Changes in SSEP latency and amplitude may be helpful in identifying patients with diminished cerebral perfusion pressure during cross-clamping.

29.3.4 Near-Infrared Spectroscopy

Near-infrared spectroscopy measures regional cerebral oxygenation (rSO_2), which is thought to be an indicator of the state of cerebral oxygenation and a composite

indicator of the status of cerebral arterial, venous, and capillary blood flow, being predominantly affected by venous blood. Although some studies have shown a higher predictive value for cerebral ischemia, other studies have shown poor specificity and a poor positive predictive value. There are some limitations to using NIRS during carotid surgery: the sensors are placed over the frontal lobes and are not ideally positioned for detecting reductions in middle cerebral artery blood flow; and in addition, the signals may be contaminated by blood flow in extracranial tissues.

29.4 Choice of Anesthetic Method in CEA: Regional Anesthesia or General Anesthesia?

Carotid endarterectomy can be performed under both regional and general anesthesia (Table 29.1). However, which anesthetic method is superior in regard to postoperative outcomes remains controversial. The impact of the type of anesthetic method on surgical outcomes has been extensively studied [8–12]. A recent study from a single institute showed that anesthesia technique failed to significantly influence outcome [10]. A meta-analysis by Guay [8] showed that regional anesthesia in CEA reduced the rate of development of new neurologic impairment (odds ratio = 0.60; 95 % confidence interval, 0.48–0.75; $p < 0.00001$), stroke (0.54 [0.43–0.68], $p < 0.00001$), stroke and/or death (0.62 [0.49–0.78], $p < 0.0001$), death (0.65 [0.48–0.87], $p = 0.004$), and myocardial infarction (0.50 [0.36–0.70], $p < 0.0001$). Another meta-analysis [9] concluded that although nonrandomized studies suggest potential benefits with the use of regional over general anesthesia in CEA, these studies may be biased, and the evidence from randomized trials is inconclusive. The recent GALA trial [11] was a multicenter, randomized controlled trial of 3,526 patients with symptomatic or asymptomatic carotid stenosis from 95 centers in 24 countries. In this trial, participants were randomly assigned to CEA under general ($n = 1{,}753$) or regional ($n = 1{,}773$) anesthesia between June 1999 and October 2007. The GALA trial did not show a definite difference in short-term (30 days after surgery) and long-term (1 year after surgery) outcomes (rates of stroke, myocardial infarction or death, quality of life, and length of hospital stay)

Table 29.1 Advantages and disadvantages of general anesthesia and regional anesthesia for CEA

	Advantages	Disadvantages
General anesthesia	Control of CO_2 levels	No solid direct neurological monitoring
	Attenuated stress response	Increased rate of shunt usage
	Immobility	Postoperative hypertension
Regional anesthesia	Direct assessment of patient's neurological status possible	Increased risk of myocardial ischemia due to surgical stress
	Reduced hospital stay	Risks associated with incomplete block

between general and regional anesthesia for carotid surgery. Thus, it is plausible that the choice of anesthetic method in CEA may have a limited influence on postoperative outcomes.

29.5 Regional Anesthesia

Carotid endarterectomy can be performed under regional anesthesia (deep and superficial cervical plexus block) if the patient is cooperative and an adequate block is established. Although CEA can be performed under cervical epidural anesthesia, this is not common because of the technical difficulties and high frequency of complications associated with this regional anesthetic procedure. In a series of 394 patients who underwent CEA under cervical epidural anesthesia, serious complications included dural puncture, venepuncture, and respiratory muscle paralysis [13].

The advantages of regional anesthesia are that it allows direct intraoperative monitoring of the patient's neurological status since the patient is awake or only lightly sedated, there is less postoperative hypertension, and cerebral autoregulation is relatively preserved. The disadvantages of regional anesthesia in CEA include the risk of complications related to the block itself and patient discomfort. In addition, patients must be cooperative and be able to lie flat and still, with their head turned to one side for 60 min or more. Furthermore, positioning of the drapes may be unpleasant for the patient and access to the airway is restricted, which may be a problem if conversion to general anesthesia is needed.

Peitzman et al. [5] retrospectively reviewed 314 carotid endarterectomies performed at the University Health Center of Pittsburgh to assess whether regional anesthesia was a safe technique for carotid endarterectomy and whether the neurologic complications that occurred were embolic or ischemic in origin. Overall, the incidence of neurologic complications was 3.1 %, and that of non-neurologic complications was 2.8 %. In their study, the duration of cross-clamping ranged from 30 s to 4 min. Furthermore, patients were closely observed for neurological status, including alertness, speech, motor ability, and two-point discrimination. If a new neurologic deficit was observed, a shunt was created. Observation of awake patients suggested that half of the neurologic deficits that occurred in this series were due to embolization rather than cerebral ischemia. In addition, a much higher rate of non-neurologic complications (myocardial infarction, pneumonia) occurred in patients receiving general anesthesia compared with regional anesthesia (12.8 % vs. 2.8 %). They concluded that CEA under regional block is a safe and reliable technique.

29.6 General Anesthesia

One of the advantages of general anesthesia over regional anesthesia in CEA is that the patient's ventilation can be controlled, allowing control of arterial carbon dioxide (CO_2) and oxygenation. If conversion from regional to general anesthesia is required intraoperatively, a laryngeal mask may be inserted. However, access to the airway during surgery is difficult, and as the patient's head is turned to one side, it is preferable to have an endotracheal tube in place rather than a laryngeal mask for adequate airway management. The disadvantage of general anesthesia is the need to use indirect methods for neurological monitoring. Most patients who undergo CEA have cardiovascular or ischemic heart diseases. Hence, abrupt hemodynamic changes should be avoided to prevent the occurrence of ischemic heart attacks under anesthesia.

To date, no data exist regarding the preferred anesthetic agents for CEA under general anesthesia [14]. Many in vitro and in vivo studies have shown that both volatile anesthetic agents such as isoflurane, sevoflurane, and desflurane and intravenous anesthetic agents such as propofol may have neuroprotective effects [14]. Michenfelder et al. [15] retrospectively studied 2,223 patients undergoing CEA at the Mayo Clinic and showed low incidences of EEG ischemic changes in patients receiving isoflurane compared with those receiving enflurane or halothane. Thus, isoflurane is thought to have neuroprotective effects, although some other studies failed to show any neuroprotective effects with isoflurane [1].

Barbiturates are believed to be the gold standard for pharmacologic cerebral protection, although several studies failed to show any neuroprotective effects of barbiturates [14]. Propofol is widely used for neurosurgical anesthesia because of its neuroprotective effects. Conti et al. [16] compared cerebrovascular reactivity and cerebral autoregulation between sevoflurane and propofol-remifentanil-based anesthetic regimens and showed that propofol-remifentanil anesthesia induced a dose-dependent low-flow state with preserved cerebral autoregulation, whereas sevoflurane at high doses provided a certain degree of luxury perfusion. McCulloch et al. [17] showed that ipsilateral internal carotid artery pressure (ICAP) and apparent zero-flow pressure (critical closing pressure) during carotid endarterectomy are both higher with propofol compared with sevoflurane, which was attributable to the fact that vasodilatation associated with sevoflurane anesthesia can cause cerebral steal. Godet et al. [18] suggested that maintenance of anesthesia predominantly with propofol and a low dose of remifentanil, both administered using target-controlled infusion (TCI), is associated with greater stability in perioperative hemodynamics than predominantly remifentanil-alone anesthesia.

29.7 How Do You Manage the Intraoperative Ischemic Changes Indicated by EEG?

Several proposed measures should be undertaken when ischemia is detected by EEG during cross-clamping, including (1) placement of a carotid shunt, (2) increase of blood pressure by 20–40 mmHg, and (3) pharmacological neuroprotection. To date, many proposed agents, including anesthetics, have been shown to possibly provide cerebral protection [14]. However, no agents have been proved to definitely and effectively provide cerebral protection [14]. If the above measures do not result in amelioration of the ischemic changes on EEG, additional cerebral protection can be achieved only by hypothermia.

Placement of a temporary artificial shunt has its own risks, including particulate or bubble embolization, arterial wall dissection, kinking of the shunt, and thrombus formation. The decision as to whether or not to perform a shunt is significantly difficult. Some surgeons always insert a shunt, while others only perform a shunt in patients with severe bilateral disease. Although a number of techniques and monitors are available to assist with this decision, none of the currently available monitors for detecting cerebral ischemia is perfect. Hence, surgeons must be aware of the benefits and risks of creating a shunt in these patients.

29.8 Hemodynamic and Respiratory Management During CEA

Most patients undergoing CEA suffer from many other complications, including cardiovascular and neurological diseases, hypertension, and diabetes mellitus. Cardiovascular instability in patients undergoing CEA is a well-documented problem. These patients are prone to episodes of hypotension and hypertension in the operative period, since their arterial pressure is often difficult to control. This perioperative hemodynamic instability influences morbidity and mortality. Furthermore, patients undergoing CEA often suffer from both cerebral and ischemic heart diseases, so that maintenance of adequate systemic perfusion (both cerebral and myocardial perfusions) is extremely essential during the perioperative period. It is recommended that their systolic arterial pressure be maintained at ± 20 % from preoperative baseline values in the perioperative period.

The choice of anesthetic agents for CEA does affect the intra- and postoperative hemodynamic profile. Anesthetic agents such as volatile anesthetics and propofol have dose-dependent cardiovascular depressant effects. Caution must be exerted when determining the anesthetic dosage in order to avoid dangerous hypotension during anesthesia induction.

Carotid cross-clamping is frequently associated with a marked increase in arterial pressure, whereas after restoration of carotid flow, it is preferable to avoid hypertension. Both postoperative hypertension and hypotension are often observed

after CEA. Baroreflex function is inevitably disturbed in patients undergoing CEA, which causes increased arterial pressure variability because of decreased vagal and sympathetic baroreflex sensitivity.

Postoperatively, hypertension is often observed in these patients. It is reported that the incidence of postoperative hypertension is as high as 70 %, with 50 % of patients requiring therapeutic intervention [1, 19, 20]. This predisposes the patients to wound hematoma and myocardial ischemia. In addition to the risk of airway narrowing solely due to the location of the surgical site in the neck, a wound hematoma can cause severe airway obstruction. Cerebral hyperperfusion syndrome occurs in 1–3 % of patients after CEA, presenting with symptoms such as severe headache, seizures, and neurologic deficits and leading to intracranial hemorrhage. This is caused by increased blood flow in dilated cerebral arterioles that were previously hypoperfused due to carotid stenosis, also known as ischemia-reperfusion injury. Important risk factors for hyperperfusion syndrome include recent ipsilateral ischemic stroke, severe ipsilateral or contralateral carotid disease, markedly increased cerebral perfusion after flow restoration, and severe postoperative hypertension. Prompt and adequate arterial pressure control after CEA may improve postoperative outcomes by reducing neurologic and wound complications. The recommendation of target arterial pressure of $<$160 mmHg or within 20 % of preoperative values is widely accepted. Although adequate arterial blood pressure control is important, this is associated with certain difficulties. Before carotid cross-clamping, a relatively high arterial pressure is required to supply adequate distal cerebral perfusion through the stenotic region to prevent watershed cerebral ischemia. Once blood flow has been restored and the stenosis relieved, the cerebral vessels previously protected by the stenosis are suddenly exposed to a relatively high pressure.

Postoperatively, hypotension may sometimes occur due to the residual effects of anesthetic agents or overuse of antihypertensive drugs. However, other possible factors, such as low cardiac output related to myocardial ischemia and hypovolemia due to hematoma, should not be ruled out.

In healthy patients, cerebral autoregulation maintains CBF within a narrow range between approximately 40 and 60 ml/100 g/min, despite mean arterial pressures between 50 and 150 mmHg. However, the lower limit of cerebral autoregulation is still unclear. Drummond [21] suggested that the lower limit of cerebral autoregulation is 70 mmHg, which is higher than the commonly accepted value of 50 mmHg. It is widely known that the cerebral autoregulation curve shifts rightward in patients with hypertension and that cerebral autoregulation in diabetic patients may be impaired. In addition, it has been shown that carotid atheroma itself reduces cerebral perfusion pressure and impairs cerebrovascular reactivity. Hence, the appropriate arterial blood pressure level required to maintain cerebral perfusion pressure during CEA is still unclear.

Hypercapnia and hypocapnia may also produce undesirable effects in patients with cerebral ischemia. In areas of ischemia, the cerebral vessels are maximally dilated and have lost their normal response to carbon dioxide, whereas vessels in the rest of the brain are still normally reactive. In this situation, hypercapnia may result

in a steal effect by inducing the vasodilation of normally reacting vessels, thus stealing blood from the ischemic areas. In contrast, hypocapnia induces vasoconstriction in normally reacting vessels, which may divert blood flow to ischemic areas. Hence, it is important to maintain normocapnia in patients undergoing CEA.

29.9 Summary

Carotid endarterectomy is offered to patients at risk of cerebral ischemia due to atherosclerotic lesions in the carotid artery. Although the impact of the type of anesthetic method on outcomes has been extensively studied, it remains unresolved as to whether regional or general anesthesia is superior in CEA. Although various techniques have been used to monitor cerebral perfusion under general anesthesia and detect cerebral ischemia during carotid artery cross-clamping, none are completely reliable. Furthermore, cardiovascular instability in patients undergoing CEA is a well-documented problem that requires prompt and adequate arterial blood pressure control postoperatively to improve outcomes by reducing neurologic and wound complications.

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Chapter 30
Anesthesia for Adult Brain Arteriovenous Malformations and Moyamoya Disease

Kimito Minami, Kenji Yoshitani, and Yoshihiko Ohnishi

Abstract Moyamoya disease and brain arteriovenous malformations are representative cerebrovascular diseases. Patients with these diseases often need surgical intervention, and high-quality perioperative management would improve mortality and morbidity such cases. This article reviews evidence-based preoperative, anesthetic, and postoperative management of patients with these diseases.

Keywords Moyamoya disease • Brain arteriovenous malformations • Preoperative management • Anesthesia • Postoperative management

30.1 Introduction

Moyamoya disease and brain arteriovenous malformations are representative cerebrovascular diseases. Patients with these diseases often need surgical intervention, and high-quality perioperative management would improve mortality and morbidity such cases. This article reviews evidence-based preoperative, anesthetic, and postoperative management of patients with these diseases.

30.2 Moyamoya Disease

30.2.1 Introduction

Moyamoya disease (MMD) is a chronic progressive cerebrovascular disease characterized by bilateral stenosis or occlusion of the intracranial internal carotid arteries and their proximal branches. The prevalence of the disease varies by race and is found frequently in Japan and other Asian countries. The presenting symptoms of MMD differ by age. Transient ischemic attack (TIA) and ischemic stroke

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are more common in children, while intraparenchymal and intraventricular hemorrhage are more frequent in adults. This chapter will review preoperative, intraoperative, and postoperative management in patients with MMD.

30.2.2 Preoperative Considerations

Moyamoya is a progressive cerebrovascular disease in which repeated ischemic stroke and hemorrhage worsen the patient's neurological functioning. Long-term follow-up data from Japan and Korea suggest that neurological dysfunction occurs in 50–66 % of patients if untreated [1–3]. A Korean observational study suggested that children less than 3 years old tended to have significantly worse outcomes than older children, mainly because of preoperative infarction [4]. For patients with symptomatic MMD, surgical revascularization is considered to prevent further ischemic events. However, there are no randomized controlled studies comparing the clinical benefits of surgery with those of conservative therapy for MMD. Two large Japanese survey studies resulted in conflicting findings: that published in 1997 found no significant differences in outcome between surgical revascularization and conservative therapy [5], whereas that published in 2000 demonstrated better outcomes in children who received surgery as primary therapy [6].

Preoperative angiography with bilateral injection of the internal carotid, external carotid, and vertebral arteries is recommended to evaluate sites of occlusion and collateral circulation. Disease severity is classified into one of six progressive stages defined by Suzuki et al. (Table 30.1: Suzuki grading system) [7]. In patients with occlusive cerebral arterial disease, measurement of cerebral blood volume (CBV), CBV/cerebral blood flow (CBF) ratio, and oxygen extraction fraction (OEF) allows quantitative determination of the degree of hemodynamic compromise [8]. Increases in CBV and CBV/CBF ratio occur as a result of autoregulatory vasodilation and prolongation of mean transit time for maintaining CBF when cerebral perfusion pressure decreases (stage I). When cerebral perfusion pressure decreases further and vasodilation is maximal, CBF begins to decrease, but a compensatory increase in OEF maintains constant cerebral oxygen metabolism (stage II). Stage II patients are thought to be good candidates for surgical

Table 30.1 Suzuki grading system

Grade	Definition
I	Narrowing of ICA apex
II	Initiation of moyamoya collaterals
III	Progressive ICA stenosis with intensification of moyamoya-associated collaterals
IV	Development of ECA collaterals
V	Intensification of ECA collaterals and reduction in moyamoya-associated vessels
VI	Total occlusion of ICA and disappearance of moyamoya-associated collaterals

"ICA" denotes internal carotid artery and "ECA" external carotid artery

revascularization. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) with acetazolamide are used for evaluating cerebral hemodynamic reserves [9]. SPECT can provide preoperative identification of the location of a proper recipient artery in patients with MMD who need revascularization surgery [10].

Surgical treatment approaches include direct and indirect techniques, as well as their combinations [11–13]. The most common direct technique is superficial temporal artery to middle cerebral artery bypass (STA-MCA bypass) [14], and indirect techniques include encephaloduroarteriosynangiosis, encephalomyosynangiosis, and encephaloarteriosynangiosis [15, 16]. Direct techniques are preferred in adult patients, while indirect techniques are preferred in children because of the small size of the anastomosing vessels. It takes approximately 2–3 months for the development of cerebral neovascularization after indirect surgery [17].

30.2.3 Anesthetic Management

The goal of anesthetic management in patients with MMD is to preserve CBF and avoid inducing ischemic complications during the perioperative state. During hospitalization, precautions to minimize crying and hyperventilation in children reduce the risk of ischemia [12]. Midazolam is a commonly used premedication [18], but in Japan syrup-formed oral midazolam is not commercially available. Diazepam syrup and triclofos syrup are alternative choices.

The choice of anesthetics may affect perioperative morbidity. Volatile anesthetics cause cerebral vasodilation and an increase in CBF. Consequently, the use of volatile anesthetics in patients with MMD may cause the intracerebral steal phenomenon in the maximally dilated vessels of ischemic regions. The results of a study investigating the effect of inhalation anesthesia and total intravenous anesthesia (TIVA) with propofol and opioids on regional cortical blood flow (rCoBF) suggested that rCoBF may be decreased with inhalation anesthesia and may induce intracerebral steal [19]. rCoBF was not decreased with TIVA [19]. Further, one study comparing the effect of sevoflurane and propofol on intracranial pressure (ICP) and rCoBF measured with a laser Doppler concluded that rCoBF was significantly higher and ICP was significantly lower with propofol [20]. Therefore, we recommend TIVA with propofol for patients with MMD.

The partial pressure of arterial carbon dioxide is an important determinant of CBF. Hypocapnia induces cerebrovascular vasoconstriction and decreases in CBF, and hypercapnia induces vasodilatation and increases in CBF. In patients with MMD, cerebrovascular reactivity to carbon dioxide is preserved during hypocapnia [21]. We should avoid hyperventilation during anesthesia because hypocapnia-induced decreases in CBF may increase the risk of cerebral ischemia [22], as might hypercapnia. In patients with MMD, diseased vessels are maximally dilated in order to increase blood supply. Hypercapnia dilates non-diseased vessels but

diseased vessels no longer dilate, so blood flow to regions supplied by diseased vessels decreases. A study measuring rCoBF using laser Doppler flowmetry concluded that in patients with MMD, not only hypocapnia but also hypercapnia decreased rCoBF [23]. We recommend maintaining a normal partial pressure of arterial carbon dioxide during anesthesia.

Blood pressure should be maintained at or above preoperative baseline levels. A fall in mean arterial blood pressure will result in a decrease in CBF and consequently an increased risk of ischemia and infarction. Adults may tolerate reductions in CBF better than children because the cerebral metabolic oxygen consumption rate decreases with age [24]. To avoid hypotension, it is recommended that preoperative cessation of drinking be kept to a minimum to avoid dehydration and that adequate volume replacement be maintained during surgery. Ephedrine, phenylephrine, and dopamine are common vasopressors for the treatment of hypotension [18, 25, 26]. Anesthetics should be carefully titrated because almost all intravenous and volatile anesthetic agents have the potential to decrease blood pressure.

Body temperature should be maintained within the normal range perioperatively. Hyperthermia increases cerebral metabolic rate, which causes an increase in oxygen consumption and possible cerebral ischemia [27]. Mild hypothermia is theoretically beneficial during revascularization surgery for patients with MMD, but few studies have examined this issue, and none have used a randomized controlled design.

30.2.4 Postoperative Management

Patients undergoing revascularization procedures should be cared for in the intensive care unit postoperatively, and blood pressure, urine output, respiratory rate, oxygen saturation, and hemoglobin concentration should be closely monitored. Since hypotension may cause ischemic events and graft thrombosis, mean blood pressure should be maintained within 80–100 mmHg in adults [28]. Intravenous hydration with isotonic fluids at 1–1.5 times the normal maintenance rate is recommended [29]. Hypertension should also be avoided because it exacerbates postoperative bleeding and may cause cerebral hyperperfusion syndrome. In MMD patients, the occurrence of this syndrome after revascularization results from a rapid increase in CBF in the chronically ischemic brain. Previous studies have shown that the incidence of temporary neurological deterioration due to hyperperfusion after STA-MCA anastomosis is as high as about 40 % in adults [30–32]. Adult-onset disease, hemorrhage-onset disease, surgery on the dominant hemisphere, and increased postoperative white blood cell count are reported risk factors for postoperative cerebral hyperperfusion syndrome [32, 33]. A recent study reported that prophylactic systemic blood pressure lowering (systolic blood pressure $<$130 mmHg) prevented symptomatic cerebral hyperperfusion after STA-MCA bypass in patients with MMD [34].

Pain management in patients with MMD is very important. Adequate pain control may reduce the risk of stroke and the length of hospitalization [24, 29]. Examples of approaches used include periprocedural sedation, intravenous opioid infusion with careful attention to respiratory depression, and regional anesthesia (e.g., cervical plexus block). Painless wound handling with the use of absorbable surgical suture, sterile adhesive strips, and soft paraffin gauze is recommended. The use of local anesthetics when placing intravenous lines is also recommended.

Key Points
- *Maintain* normocapnia; *Avoid* hypocapnia and hypercapnia.
- *Maintain* normotension, normovolemia, and normothermia during surgery.
- *Avoid* hypertension and hypotension during postoperative care.
- Pain management is very important.

30.3 Arteriovenous Malformations

30.3.1 Introduction

Arteriovenous malformations (AVMs) in the brain are congenital focal vascular malformations in which the lack of a capillary bed results in abnormal arteriovenous shunting. The most common symptom of brain AVMs is intracranial hemorrhage [35–39]. Patients between 20 and 40 years of age are at highest risk of hemorrhage [35–37]. Reports concerning the peak age of hemorrhage are conflicting, with studies reporting highest risk in older patients [40] or in younger patients [41], a bimodal distribution [35], or a constant risk across age [38]. Other symptoms of AVMs are seizures, mass effect due to direct compression or swelling, and ischemic presentation of the regions around AVMs. Seizures are more likely to occur in patients with AVMs with superficial drainage [42]. The prevalence of brain AVMs is estimated at 0.01 % of the general population [43]. Arteriovenous malformations are not considered to be an inherited disease, but genetic variation may influence their development [44, 45]. Patients with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) may have cerebral and spinal cord involvement, including brain AVMs [46]. This chapter will review the preoperative, intraoperative, and postoperative management of patients with AVM.

30.3.2 Preoperative Considerations

Methods of AVM treatment include surgical resection, catheter embolization, and radiosurgery. Surgical resection immediately eliminates the risk of AVM rupture,

but carries risks associated with surgery, including permanent paralysis, aphasia, hemianopsia, and death [47–50]. Catheter embolization can be a definitive treatment for lesions less than 1 cm in size that are fed by a single feeding artery [51, 52]. Catheter embolization is an effective adjunctive method for reducing the nidus size of large AVMs and reducing surgical blood loss [53]. Radiosurgery is often recommended when AVMs are less than 3 cm in size and are located in areas where surgery is likely to induce neurological complications [43]. It takes approximately 1–3 years from the time radiosurgery is begun to completely obliterate AVMs, and the risk of hemorrhage is present throughout this time. Complications of radiosurgery include seizures, nausea, vomiting, headaches, hemorrhage, radionecrosis, progressive edema, and venous congestion. The reported rates of transient neurological deterioration and permanent neurological deficits are 5.2 % and 1.4 %, respectively [54]. Staged radiosurgery, which targets different AVM components during different sessions, gives good results [55].

There have been no randomized trials directly comparing conservative management and invasive treatment, including surgery, radiosurgery, and catheter embolization. A systematic review and meta-analysis of observational studies showed that complications leading to permanent neurological deficits or death occurred in a median of 7.4 % of patients after surgery, in 5.1 % after radiosurgery and in 6.6 % after catheter embolization [56]. Thus, weighing the risks of invasive treatments against the benefits is important. A simple risk prediction formula for AVM hemorrhage has been presented: (lifetime risk of hemorrhage) = 105 − (patient age in years) [57, 58]. The risk of surgery is commonly estimated with the Spetzler-Martin grading scale, which incorporates lesion size, location, and venous drainage pattern (Table 30.2: Spetzler-Martin grading scale) [59]. The reported incidence of surgery-related neurological morbidity in patients with grade I, II, or III lesions is low. In contrast, patients with grade IV and V lesions had surgery-related neurological morbidity rates of 31.2 % and 50 %, respectively [48]. Consequently, it is recommended that patients with grade I or II legions undergo surgical treatment and that patients with grade III legions undergo surgical treatment after

Table 30.2 Spetzler-Martin grading scale

Feature	Score
Maximum diameter	
<3 cm	1
3–6 cm	2
>6 cm	3
Location	
Non-eloquent cortex tissue	0
In or adjacent to eloquent cortex tissue	1
Venous drainage	
Superficial only	0
Deep	1

The sum of the scores is equal to the grade

catheter embolization. Treatment of patients with grade IV or V legions requires a multidisciplinary approach [50].

Aneurysms are found in about 60 % of patients with brain AVMs [60]. Their management depends on their location and size. Conflicting results have been obtained regarding the status of feeding artery aneurysms less than 5 mm in size following AVM treatment, with one study observing their regression [61] and another reporting their rupture [62]. Microsurgical clipping or endovascular coiling of feeding artery aneurysms is recommended if their size is greater than 7 mm [63]. Aneurysms located at a distance from AVMs are managed similarly to intracranial aneurysms in patients without brain AVMs [43].

30.3.3 Anesthetic Management

No randomized controlled trials have been conducted to determine the optimal anesthetic agent during surgical removal of AVMs. Theoretically, volatile anesthetics induce cerebral vasodilation. Sevoflurane induces less vasodilation than desflurane or isoflurane [64]. These volatile anesthetics have the potential risk of increasing ICP, although none of these three agents were found to induce clinically relevant increases in ICP in patients without intracranial hypertension [65]. Propofol has no vasodilatory effect, and anesthesia with propofol has been associated with lower ICP and cerebral edema than that with volatile anesthetics in patients with brain tumors [66]. Therefore, we recommend propofol anesthesia in patients with intracranial hypertension.

Intraoperative monitoring includes electrocardiography and pulse oximetry, as well as measurement of blood pressure with arterial cannulation, body temperature, and end-tidal carbon dioxide. Neurophysiological monitoring, including motor evoked potentials, somatosensory evoked potentials, and brain stem auditory evoked potentials, has been shown to be beneficial in preventing permanent neurological deficits [67–69].

There is no strong clinical evidence regarding the optimal blood pressure range that should be maintained during AVM removal surgery. Physiologically, AVMs are high-flow and low-resistance shunts and have fixed vascular resistance. Arteriovenous malformation vessels do not autoregulate in response to changes in blood pressure or partial pressures of carbon dioxide [70]. The mean blood pressure in AVMs is approximately 45–60 % of systemic blood pressure [70–72], and there seems to be no relationship between chronic hypertension and AVM rupture [73]. Thus, ventilation seems not to affect AVM flow, and perioperative transient hypertension does not apparently induce intracranial hemorrhage, except in cases of comorbid intracranial aneurysm. Induced hypotension may facilitate surgical hemostasis by reducing blood loss from small and deep feeding arteries, but the outcome of deliberate hypotension needs to be analyzed by randomized trials [74].

30.3.4 Postoperative Management

After undergoing surgery or catheter embolization, patients should remain in the intensive care unit for at least 24 h. Mental status, invasive blood pressure, urine output, respiratory rate, oxygen saturation, and hemoglobin concentration should be closely monitored. Mean blood pressure should also be closely monitored, and postoperative hypertension should be avoided. One report showed that in patients with AVMs of grade II or higher and more than 3.5 cm in size, aggressive postoperative blood pressure control that maintained the mean blood pressure under 70 mmHg significantly decreased the incidence of delayed hemorrhage from 4.4 to 1 % [75].

Body temperature should be maintained within the normal range postoperatively in the intensive care unit. Hyperthermia increases cerebral oxygen demand [76], and hypothermia-induced shivering also increases oxygen demand [77]. Increase in oxygen demand results in neurologic deterioration.

Key Points
- Weigh the risks of invasive treatments against the benefits.
- *Maintain* normothermia.
- *Avoid* postoperative hypertension.

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Part VII
Anesthetic Management: Neuroanesthesia for Tumor Surgery

Chapter 31
Anesthesia for Posterior Fossa Tumor Surgery

Kenichi Sekimoto and Tomonori Takazawa

Abstract Posterior fossa surgery is associated with higher rates of morbidity and mortality and a wider variety of complications than surgery in the supratentorial compartment. Indeed, this type of surgery presents difficult challenges due to the anatomical and physiological peculiarities of the area involved, which also require the patient to be placed in a specific position preoperatively. Moreover, it presents special problems related to cranial nerve dysfunction and prevention of and monitoring for venous air embolism. These complications may be avoided by careful perioperative planning and the judicious management of general anesthesia. In this regard, certain aspects of general anesthesia require close attention. This chapter discusses pre- and postoperative considerations, intraoperative positioning and monitoring, choice of anesthetic technique, methods of preventing venous air embolisms, and the effects of surgery on the cardiovascular and respiratory centers.

Keywords Intracranial pressure • Venous air embolism • Brainstem

31.1 Introduction

Among tumors of the posterior fossa, those of the cerebellum and brainstem are the most common. Preoperative considerations and the induction and maintenance of anesthesia in posterior fossa tumor surgery are similar to that for other types of intracranial tumor. However, anesthesiologists need to pay special attention to the potential risks associated with posterior fossa tumor surgery, as it may induce various complications, including accidental brainstem compression, brainstem stimulation, cranial nerve dysfunction, increased intracranial pressure (ICP), pneumocephalus, and venous air embolism. Moreover, depending on the intraoperative body position, a number of complications may develop during surgery, including hypotension and quadriplegia. This chapter reviews how general anesthesia can be managed in such a way as to avoid these problems arising.

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31.2 Preoperative Considerations

31.2.1 Anatomy and Physiology

The posterior fossa is circumscribed by the cerebellar tentorium superiorly, the foramen magnum inferiorly, the clivus anteriorly, and the occiput posteriorly. It contains vital nerve structures such as the majority of the brainstem (lower midbrain, pons, and upper medulla), the cerebellum, and the fourth ventricle. Even a small amount of swelling and edema can induce major neurological signs and symptoms, because the brainstem is a crucially important area containing the nuclei for cranial nerves III to XII, the vital vascular and respiratory centers, and many efferent and afferent fiber tracts connecting the brain to the rest of the body. Hydrocephalus due to obstruction of ventricular outflow is a common cause of increased ICP with posterior fossa lesions. This poses challenges for the anesthesiologist, whose intraoperative goals are to facilitate surgical access, minimize nervous tissue trauma, and maintain respiratory and cardiovascular stability.

31.2.2 Signs and Symptoms

Signs and symptoms due to space-occupying lesions in the posterior fossa result from increased ICP caused by obstruction of cerebrospinal fluid outflow. Intracranial hypertension syndrome is one of the first possibilities to consider in diagnosing posterior fossa neurological disorders. Primary nonspecific symptoms consist of headache, vomiting, vertigo, and fatigue, as in supratentorial lesions. Signs of developing cerebellar and brainstem interference include dysmetria, respiratory irregularities, bradycardia, hypertension, visual disturbances (due to papilledema), hemiparesis, and cranial nerve deficits (dysphasia, laryngeal dysfunction). More specific clinical syndromes include acoustic neuromas, other tumors of the cerebellopontine (CP) angle, brainstem gliomas, and carotid body tumors (Table 31.1). Multiple cranial nerve impairments are common, including bulbar palsies.

31.2.3 Pathology

In this area, acoustic neuromas and meningiomas are common. However, consideration must also be given to malignant and benign tumors and vascular diseases.

Table 31.1 Signs and symptoms in relation to lesion location

CP angle	Cerebellum	Midline and forth ventricle
Trigeminal neuralgia	Vertigo	Truncal ataxia
Trigeminal dysesthesia	Vomiting	Wide-based gait
Facial palsy	Hemiparesis	Nystagmus
Deafness	Hypotonia	Extraocular movement abnormalities
Vertigo	Intention tremor	Truncal titubation
Bruns nystagmus	Limb ataxia	Hydrocephalus
	Dysmetria	Papilledema
	Dysdiadochokinesia	
	Dysarthria	
	Equilibrium disturbance	

Malignant tumors

Hemangioblastomas, astrocytomas (in children), and metastases

Benign tumors

Acoustic tumors, meningiomas, subependymomas, and choroid plexus papillomas

Vascular diseases

Arteriovenous malformations and aneurysms

31.2.4 Preoperative Evaluations

A complete medical history is ascertained, especially for seizure disorders, sensory or motor dysfunction, and cardiac and pulmonary dysfunction. Medications that may cause hemodynamic changes during surgery are reviewed, such as steroids, mannitol and diuretics, antidepressants, antihypertensives, L-dopa, and benzodiazepines. The American Society of Anesthesiologists Physical Status should be carefully evaluated as an important factor in determining the position of the patient during posterior fossa surgery, particularly in reference to cardiovascular and pulmonary stability and airway manageability.

Assessment of the signs and symptoms of increased ICP is also important in preoperative evaluations. Anesthesiologists should check the level of consciousness and presence of headache and vomiting, together with the responses of these symptoms to steroids. When preoperative evaluation using CT or MRI suggests increased ICP in severe cases, the patient can be treated by ventricular drainage, endoscopic third ventriculostomy, or hypertonic osmotherapy with mannitol and furosemide administered either pre- or intraoperatively.

Anesthesiologists should check for possible hypovolemia due to vomiting, poor intake, or treatment with hypertonic osmotherapy. In addition, patients should also be checked for abnormalities in electrolyte and hormone levels, as these can be associated with brain tumor and brain tumor treatment, such as steroid administration. For example, neurogenic diabetes insipidus induces abnormalities in electrolyte levels.

31.3 Positioning

Posterior fossa surgery requires unusual positioning of the patient. The prone, lateral (park bench), and sitting positions are the most commonly used. Irrespective of the position selected, however, care in positioning is of extreme importance, because most problems seem to be avoidable with careful positioning and padding of vulnerable areas.

31.3.1 Sitting Position

The sitting position for posterior fossa surgery has both benefits and disadvantages [1] (Table 31.2).

Issues requiring particular attention in positioning are as follows:

- Patient's head is fastened in a three-pin head holder (Mayfield-type head pins). Infiltration of the scalp and periosteum at the pin site reduces hypertensive response [2].
- Legs are kept as high as possible to promote venous return.
- Legs are placed in thigh-high compression stockings to limit pooling of blood.

Table 31.2 Benefits and disadvantages of the sitting position

Benefits
Good surgical access, with less tissue retraction and less cranial nerve damage
Good cerebrospinal fluid and venous drainage, with decreases in ICP and intraoperative bleeding
Easier access to airways
Lower airway pressure
Disadvantages
Hemodynamic instability
Risk of air embolism
Quadriplegia with cervical spinal ischemia
Pneumocephalus

- A minimum gap of 1 in. should be maintained between the chin and suprasternal notch. Avoid excessive head flexion, which can cause jugular compression, macroglossia, swelling of the face, and cervical cord ischemia.
- For similar reasons, avoid excessive neck rotation.
- Elbows are held up by pillows to avoid contact with the table and prevent extension of the brachial plexus.
- Legs are freed of pressure at the level of the common peroneal nerve just distal and lateral to the head of the fibula.

The contraindications for the sitting position are severe hypovolemia, severe hydrocephalus, extreme age, and impaired cardiac function. The main contraindication to the use of the sitting position, however, is the presence of a right-to-left intracardiac or pulmonary shunt, which would facilitate systemic embolization of air.

31.3.1.1 Air Embolism

Venous air embolism (VAE) can occur whenever the operation site and open veins are above the level of the heart. It is thus a specific complication when using a sitting position, but also occurs, although not as frequently, in patients operated on in a lateral or prone position. The danger is increased with posterior fossa surgery, as cut veins in the bone may be held open by surrounding structures. While a massive air embolism will cause sudden and catastrophic hemodynamic changes, small quantities of air may have little clinical significance. When an air embolism occurs, pulmonary vascular resistance and pulmonary artery and right atrial pressures increase, cardiac output decreases, and abnormalities are seen on electroencephalography. Increases in physiological dead space impair gas exchange by causing a V/Q mismatch. As a result, CO_2 excretion decreases.

31.3.2 Prone Position

The prone position is the most commonly used position in posterior fossa surgery. The head is raised to decrease venous bleeding. Keeping the head elevated and the shoulders at or above the edge of the operating table prevents the development of necrotic lesions in the areas around the face. The advantages of the prone position are the low risk of air embolism and good hemodynamic stability with minimal risk of hypotension. The disadvantages, compared to sitting, include reduced clarity of the surgical field, increased blood loss, difficult access to the airway, ischemia, and the risk of retinal bleeding due to compression in the orbital area.

31.3.3 Lateral or Park Bench Position

This position can be used for laterally placed lesions, including tumors in the CP angle and aneurysms of the vertebral and basilar arteries. There is a risk of brachial plexus injury if the uppermost arm is pulled caudally to gain access to the retromastoid area. Stretching and damage to the brachial plexus due to excessive neck rotation should be avoided. Extreme neck flexion is associated with the risk of quadriplegia.

31.4 Monitoring

The goals of monitoring are to ensure adequate perfusion of the central nervous system and to maintain cardiovascular stability. As a result, routine operative monitoring suffices for most posterior fossa cases, usually with the addition of an intra-arterial catheter for blood pressure monitoring.

31.4.1 Brainstem Monitoring

In operations involving the CP angle and lower brainstem, the risk of cranial nerve injury is significant. Hence, intraoperative stimulation and recordings from cranial nerves V, VII, VIII, XI, and XII are often employed. The main modalities employed are somatosensory evoked potentials (SSEPs), motor evoked potentials (MEPs), brainstem auditory evoked potentials (BAEPs), and spontaneous and evoked electromyography (EMG). Muscle relaxants impair the interpretation of MEPs and EMG, while nitrous oxide (N_2O) and high-dose volatile anesthesia may interfere with SSEPs and MEPs [3]. Although BAEPs are robust, many common anesthetic agents decrease the amplitude and increase the latency of evoked responses. Volatile agents should be kept at less than 0.5 minimum alveolar concentrations, and N_2O should not be used [4]. The anesthetic plan will often depend on opioids. Propofol and dexmedetomidine infusions are also often incorporated.

31.4.2 Monitoring for Venous Air Embolism

For sitting cases, monitoring to detect VAE is necessary. Several monitoring options are clinically available (Table 31.3). In general, precordial Doppler ultrasonography and end-tidal CO_2 ($EtCO_2$) monitoring are the minimum requirements for detection of VAE. Precordial Doppler is more sensitive than any other type of monitoring apart from transesophageal echocardiography [5]. However, problems

Table 31.3 Monitoring to detect and treat VAE

$EtCO_2$ monitoring
Precordial
Stethoscope
Precordial Doppler ultrasonography
Central venous catheter (central venous and pulmonary artery pressure)
Transesophageal echocardiography

include positioning the probe, ultrasonic interference, and the need for continuous monitoring by a trained person. Monitoring of $EtCO_2$ is generally regarded as the most useful option, offering intermediate sensitivity and a qualitative estimate of the size of the VAE [6]. In general, the larger the volume of the air embolus, the greater the decrease in $EtCO_2$ will be.

31.5 Choice of Anesthetic Technique

There is no evidence to suggest that any one anesthetic drug or technique is superior to another for posterior fossa surgery. Moreover, the hemodynamic changes associated with the assumption of a sitting position are minor, regardless of the anesthetic technique employed.

31.5.1 Use of Nitrous Oxide

The use of N_2O remains controversial [7, 8]. This controversy extends to the effect of N_2O on pneumocephalus [9]. No study has demonstrated any effect of N_2O on venous air embolism. Combining these controversies with the potentially deleterious effects of N_2O on neuroprotection outlined earlier, we see no role for N_2O in posterior fossa craniotomy, given the ready availability of viable alternatives in anesthetic management.

31.5.2 Airway Maintenance

The airway requires special attention. With posterior fossa cases, substantial neck flexion is often required for optimal surgical exposure. Such flexion, however, may result in the tip of the endotracheal tube penetrating the main bronchus or kinking of the endotracheal tube in the posterior pharynx.

Some clinicians use a wire-reinforced tube, while others prefer nasotracheal intubation. We use neither routinely, but emphasize that careful assessment of tube patency and position is of utmost importance, because access to the airway is quite limited. This assessment should be conducted after positioning the patient, but before making the skin incision. Palpation of the cuff above the sternal notch is useful in confirming the position of the tube. If the anesthesiologist observes evidence of partial obstruction of the tube (e.g., high airway pressure or slow upstroke of the $EtCO_2$ trace), they should confirm that a suction catheter can pass freely through the endotracheal tube and insist on repositioning of the head and neck if it cannot.

31.5.3 Ventilation

In most cases, controlled mild hyperventilation is desirable in improving surgical exposure and reducing retraction pressure on the brain. However, changes in respiration may be more sensitive to brainstem manipulation than hemodynamic changes. Therefore, use of spontaneous ventilation may be appropriate in rare circumstances, when manipulation or ischemia of the respiratory center is likely. This should only be undertaken after discussion with the surgeon, however, since the hypoventilation that occurs with spontaneous ventilation during general anesthesia may cause brain engorgement and make surgical exposure more difficult.

31.6 Prevention of Venous Air Embolism

The most effective means of preventing VAE derives from the choice of surgical technique and the tolerance of the surgeon for lower head positions. In addition to monitoring for VAE (31.3.2), however, the anesthesiologist can contribute by ensuring adequate hydration and avoiding drugs that dilate the venous capacitance vessels such as nitroglycerin.

31.6.1 Volume Loading

Volume loading is helpful in reducing the risk of a fall in blood pressure when the patient is in a sitting position. Moreover, this approach may assist in raising venous pressure and reducing the risk of VAE.

31.6.2 Positive End-Expiratory Pressure

Positive end-expiratory pressure (PEEP) does not reduce the incidence of VAE [10], but does impair surgical conditions through reducing venous return and increasing the chance of paradoxical air embolus in patients with a patent foramen ovale. This method should therefore not be used in craniotomies in the absence of a strong rationale based on respiratory pathology. The release of PEEP represents a period of elevated risk of VAE [6].

31.6.3 Deliberate Hypoventilation

While some studies have suggested that moderate hypoventilation may reduce the risk of VAE [10], hypoventilation also increases cerebral blood flow volume, which may impair surgical exposure. Mild hyperventilation is likely to remain the more common practice until any benefits of hypoventilation can be clearly confirmed.

31.6.4 Central Venous Pressure Catheters

In addition to allowing measurement of the effectiveness of attempts to raise venous pressure and reduce the hydrostatic gradient, central venous pressure catheters can be used to aspirate air that has entered the circulation. For optimum recovery, the tip of the catheter should be close to where the superior vena cava enters the right atrium, and catheters with multiple orifices have been shown to be more effective. Such a catheter enables significant volumes of air to be rapidly extracted from the right atrium, breaking the "air lock" that causes the loss of cardiac output.

31.7 Effects on the Cardiovascular and Respiratory Centers

31.7.1 Cardiovascular Center

Operations on or near the brainstem (e.g., during acoustic schwannoma surgery) can produce abrupt, often profound, cardiovascular responses that may signal potential damage to the brainstem. Stimulation of the floor of the fourth ventricle, medullary reticular formation, or trigeminal nerve results in hypertension, usually in association with bradycardia. Bradycardia also results from stimulation of the vagus nerve. If such changes occur, the surgeon should be alerted immediately so that the manipulation provoking such responses can be avoided. Masking such

changes with pharmacological treatment is undesirable unless the changes prove both recurrent and severe. Hypertensive responses are typically so abrupt and transient that by the time a drug is administered, the stimulus has gone and treatment becomes unnecessary.

31.7.2 Respiratory Center

Spontaneous ventilation was once advocated for procedures that entailed the risk of damage to the respiratory center. Spontaneous ventilation is now rarely used, as the proximity of the cardiomotor areas to the respiratory center should permit cardiovascular signs to serve as an indicator of impending damage to the latter. Respiratory pattern is more likely to be a relevant parameter for monitoring when the threat to the brainstem is a result of vessel occlusion [11] than when that threat is attributable to direct mechanical damage caused by retraction of or dissection in the brainstem.

31.8 Emergence from Anesthesia

Providing early neurological assessment is one of the most valuable contributions of the anesthesiologist to outcomes in neurosurgical patients. It is therefore imperative to have patients emerge quickly, even when surgery has been prolonged. At the same time, emergence from anesthesia involves substantial changes in pressure, $PaCO_2$, cerebral blood flow, and autonomic activity, and careful planning is thus indispensable.

Failure to emerge can represent a neurological event resulting from the surgery such as intracranial bleeding, vessel occlusion, an embolic event, or seizure. In such cases, the interval until diagnosis represents a critical determinant of outcome. The anesthesiologist must be able to state with confidence that the delayed emergence is unlikely to be pharmacological. The usual approach is to immediately perform CT; the operating room should be left available in the event that an emergent return is required.

31.8.1 Preventing Elevation of Intracranial Pressure

Adrenergic blocking agents should be administered to attenuate the sympathetic effects often seen during and following emergence in patients with hypertension. Nicardipine can be considered if the patient exhibits refractory hypertension or hyperreactivity. Antiemetic therapy should be aggressive, because the elevation in ICP caused by retching and vomiting is particularly undesirable in craniotomy patients. Coughing or “bucking” during emergence causes dramatic spikes in ICP

and must be avoided. Several approaches can be used to achieve this goal, including the use of intravenous lidocaine, an opioid-based anesthetic, or deep extubation. In the case of deep extubation, the risk of an intraoperative neurological event causing delayed or failed emergence must be kept in mind.

31.8.2 Postoperative Swelling

In some posterior fossa procedures, particularly those involving activity near the brainstem, postoperative swelling can lead to an anticipated worsening of neurological status before subsequent improvement on the first or second postoperative day, necessitating prolonged intubation. The small anatomical space, the tendency of the cerebellum to swell following prolonged retraction, and bleeding all add to the threat. In addition, reduced respiration may result from, and in turn contribute to, such swelling. Sedative and respiratory depressant drugs must be used with great caution.

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Chapter 32
Anesthesia for Supratentorial Tumor Surgery

Kenji Ito and Toshiyasu Suzuki

Abstract Clinical approaches to the surgical removal of brain tumors are diverse and depend on the site of development and type and progression of the tumor. Anesthesia involves not only the planning for circulatory and respiratory management but also the maintenance of appropriate posture and intracranial pressure, with the necessity of taking each individual patient's condition into account. Intracranial pressure management is essential in preparing a favorable surgical field to avoid secondary injury. Therefore, careful consideration of drugs used, carbon dioxide reactivity, and cerebral blood flow is critical.

This chapter focuses on the basic knowledge and classification of supratentorial tumors and management of general anesthesia, including premedication. Intracranial pressure management is explained with regard to planning, preparation, maintenance, awakening, postoperative management, and complications during neurosurgical procedures.

Keywords Supratentorial brain tumor • Intracranial pressure elevation • Anesthetic management

32.1 Introduction

Central nervous system tumors arise from the brain, spinal cord, and surrounding tissues such as the meninx. These tumors often cause cerebral compression due to mass formation, inflammation, and fluid accumulation, which increases the intracranial pressure. The extent of intracranial pressure elevation varies depending on the site of development and type of tumor. Thus, anesthesia should be planned based on the condition of each patient.

This chapter focuses on the basic knowledge and classification of supratentorial tumors and management of general anesthesia including premedication. Intracranial pressure management is explained with regard to planning, preparation,

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maintenance, awakening, postoperative management, and complications during neurosurgical procedures.

32.2 What Is a Brain Tumor?

Central nervous system tumors, including blastomas, which are highly metastatic, originate from the parenchyma of the brain and tissue surrounding the spinal cord such as the meninx. They also often include congenital remnant tumor tissue, inflammation-induced granuloma, and masses which are formed by fluid retention in cystic lesions which cause brain compression. Of these, a true brain tumor in the narrow sense represents a neoplasm arising from the intracranial tissue, i.e., primary brain tumors which originate not only from the brain parenchyma but also from the meninx, pituitary, and cranial nerves and metastatic brain tumors developing in these regions.

32.3 Brain Tumor Classification

Various classifications of brain tumors have been attempted based on the development bed. The WHO classification was established by the Classification Committee of the World Health Organization in 1979. In the 2007 revision, brain tumors were classified into brain parenchymal (neuroepithelial), nerve sheath, meningeal, and blood vessel-derived tumors, goblet cell tumor, pituitary tumor, and metastatic tumor. Congenital tumors, tumorlike lesions, and vascular malformations are also classified [1, 2] (Table 32.1).

32.4 Brain Tumor Location

Brain tumors frequently develop in certain regions depending on the histologic type and age. Meningioma is the most frequent, accounting for about 22 % of all cases. It develops in the fornix in 25.7 % of cases, followed by the cerebral falx in 11.6 % of cases. Brain tumors, excluding meningioma, develop in the optic chiasm in 23.1 % of cases, frontal lobe in 13.6 %, cerebellopontine angle in 14.1 %, temporal lobe in 7.4 %, cerebellum in 5.8 %, parietal lobe in 5.4 %, and pineal body in 3 %.

Table 32.1 WHO classification of brain tumors

1. Neuroepithelial tumors
Astrocytoma
Anaplastic (malignant) astrocytoma
Glioblastoma
Oligodendroglioma
Ependymoma
Medulloblastoma
Choroid plexus papilloma
Pineocytoma
Neuronal and mixed neuronal-glial tumor
2. Nerve sheath cell tumor
Schwannoma
3. Meningioma
4. Malignant lymphoma
5. Hemangioblastoma
6. Goblet cell tumor, germ cell tumor
Germinoma
Teratoma
Mixed germ cell tumors
Embryonal carcinoma
Choriocarcinoma
7. Congenital tumor
Craniopharyngioma
Epidermoid cyst
Dermoid cyst
Lipoma
8. Pituitary adenoma
Functional adenoma
Nonfunctional adenoma
9. Advancement of peripheral tumor
Glomus jugulare tumor
Chordoma
Chondrosarcoma
10. Metastatic tumor

32.5 Brain Tumor Symptoms

Brain tumor symptoms are roughly divided into two types. The first are general symptoms associated with an intracranial pressure (ICP) elevation caused by tumor enlargement, cerebral edema, venous perfusion disorder, and circulatory disorder of the cerebrospinal fluid. The second type of symptoms are local (focal symptoms) caused by tumor compression and injury of the brain tissue.

32.5.1 General Symptoms (Symptoms of ICP Elevation)

Headache, nausea, and choked disk have been designated as a characteristic triad of brain tumor symptoms, but all of these symptoms represent ICP elevation. Not all of these symptoms develop, although once the patient is symptomatic, these conditions slowly become characteristically aggravated. For example, a headache may be severe in the morning. However, progression of ICP elevation may result in brain herniation. In uncal herniation, anisocoria associated with oculomotor paralysis, hemiplegia associated with midbrain disorder, disturbance of consciousness, and decerebrate rigidity are manifest. In cerebellar tonsil herniation, the medulla oblongata is compressed, leading to respiratory disorder and consequent death when left untreated.

32.5.2 Local Symptoms (Focal Symptoms)

Tumors compress, invade, and destroy the brain, inducing symptoms of local cerebral functional deficiency or symptoms of irritability. Local symptoms may include hemiplegia, disturbance of sensation, and convulsive attack. These may develop due to lesions near the central sulcus such as those in the motor area in the frontal lobe and sensory area in the parietal lobe. Pituitary lesions cause visual field defects and higher brain dysfunction in the dominant hemisphere such as impairment of speech and calculation proficiency.

32.6 Evaluation Before General Anesthesia

32.6.1 Physical Findings

Attention should be paid to the usual activities of daily living and presence of hemiplegia. When paralysis is present, venous and arterial routes and cuff attachment for indirect blood pressure measurement are limited. When disturbances of consciousness and memory are present, anesthesia should be explained after obtaining the necessary information and consent from the patient's family.

32.6.2 ICP Elevation

One factor that induces ICP elevation is massive occupation, although this depends on the tumor development site, size, and properties. Alterations in the levels of consciousness, diameter, and laterality of the pupil and light reflex are observed.

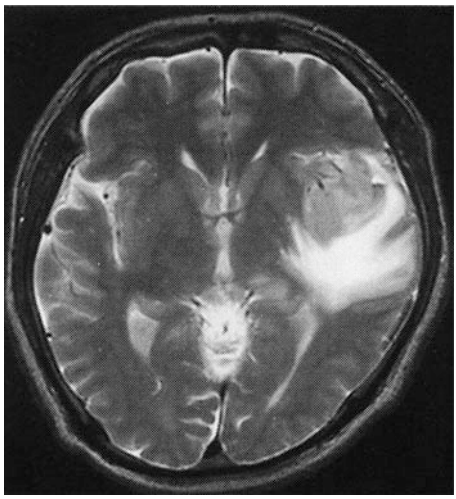

Fig. 32.1 T2-weighted MRI of glioblastoma. Edema is observed around the tumor

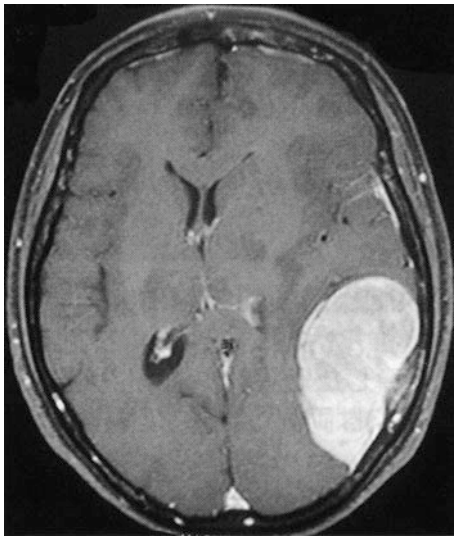

Fig. 32.2 MRI of fornix meningioma. Midline shift and narrowing of the left cerebral ventricle are observed here

Patient consultation following episodes of aspiration is also important for patients with ICP elevation because nausea and vomiting are often prevalent. Upon imaging, midline shift, loss of the cerebral ventricle (Fig. 32.1), and edema around the tumor (Fig. 32.2) feature prominently in ICP elevation.

32.6.3 Changes in Electrocardiography

Electrocardiographic abnormalities are observed in many patients undergoing neurosurgery. Cardiovascular and circulatory abnormalities should be examined before surgery. ST segment elevation or depression, conduction disturbance, and arrhythmia may be observed prior to surgery. Electrolyte abnormalities may occur and appear as electrocardiographic changes in functional tumors. Hyponatremia and hypokalemia are also often observed.

32.6.4 Blood Tests

Hemoglobin level, platelet count, coagulation system, and electrolytes should be checked.

32.6.5 Preoperative Tumor Vascular Embolization

Embolization of the tumor-feeding blood vessel is performed to prevent intraoperative hemorrhage in many cases of meningioma. The route for vascular treatment of this type should be confirmed beforehand.

32.7 Preanesthetic Medication and Premedication

32.7.1 Preanesthetic Medication

In patients in whom ICP elevation is predicted and in those with a disturbance of consciousness, respiration may be excessively inhibited by only a small amount of sedatives, which promotes ICP elevation through an increase in the partial carbon dioxide pressure in the arterial blood.

However, the use of a sedative at a low dose may be considered depending on the situation, because excess stress increases the cerebral perfusion pressure, blood flow, and metabolism.

Since H2 blockers elevate the pH of gastric juice, these are effective for patients with a past medical history of vomiting and aspiration. For patients with difficulty in ingestion, it is administered intravenously. H2 blockers also reduce ICP.

32.7.2 Premedication

The administration of a calcium antagonist to prevent cerebrovascular spasm and vasopressor administration to maintain cerebral perfusion are also advised.

Steroid and anticonvulsant administration should also be continued. Patients being treated with anticoagulants have been increasing with an increase in elderly patients. When difficulty in intraoperative hemostasis is expected, withdrawal of anticoagulants should be considered, but sufficient investigation is necessary because it may increase the risk of myocardial and cerebral infarction.

32.8 Preparation for Anesthesia

32.8.1 Vascular Route

32.8.1.1 Venous Route

For craniotomy, two venous routes with a large diameter are prepared because unexpected hemorrhage and difficulty in hemostasis may occur. When there is a risk of air embolism, when a cardiovascular agent is continuously administered and when the circulating blood volume is to be estimated, a central venous route should be secured. The internal jugular, femoral, and basilic veins are preferred for the insertion site. When the jugular vein is selected, attention should be paid to hematoma formation at insertion and promotion of ICP elevation by the Trendelenburg position.

When tumor vascular embolization procedure is applied before surgery, the insertion site may be limited.

32.8.1.2 Arterial Route

Since circulatory dynamics continuously change, an arterial line is useful because the blood pressure can be monitored in real time. It is also essential to measure the partial pressures of oxygen and carbon dioxide in the arterial blood, blood glucose, and electrolytes, which should be performed at the ear level because zeroing of a transducer is performed at the circle of Willis level.

32.8.2 Monitoring

32.8.2.1 Conventional Monitoring

The following means of monitoring are advised: electrocardiography; indirect blood pressure measurement; percutaneous oxygen saturation, partial pressure of end-tidal carbon dioxide, and muscle relaxation monitoring; direct arterial blood pressure measurement; and central venous blood pressure, urine volume, body temperature, and BIS monitoring, if coordination is possible.

32.8.2.2 Surveillance of Air Embolism

Neurosurgery may be performed in Fowler's or a sitting position, aiming at securing the visual field and reducing blood loss. When an open blood vessel is present, the occurrence of an air embolism should always be assumed. Clinically, an air embolism is considered unlikely to occur when the surgical field is present at a level lower than 20 cm from the heart.

For the monitoring of an air embolism, suprasternal Doppler and transesophageal ultrasonography are useful. A rapid decrease in the partial pressure of end-tidal carbon dioxide suggests pulmonary arterial embolism.

32.8.2.3 Evoked Potentials

Evoked potentials represent transient potential changes in the brain and spinal cord in response to the stimulation of sensory receptors and peripheral sensory nerves, including somatosensory evoked potentials (SEPs), motor evoked potentials (MEPs), visual evoked potentials (VEPs), and brainstem auditory evoked potentials (BAEPs). BAEPs are also termed auditory brainstem responses (ARBs). SEPs and MEPs are actually used widely in surgery. Abnormal evoked potentials are judged based on prolongation of the latency (time of appearance of potential after stimulation), reduction in the amplitude, and change and loss of waveform. These reportedly react sensitively with intraoperative cerebral ischemia.

32.9 Induction of Anesthesia to Awakening

32.9.1 Induction of Anesthesia

After initiation of oxygen inhalation, 1–2 μg/kg fentanyl is administered once or remifentanil is continuously administered at 0.25–0.5 μg/kg/min, followed by single administration of propofol at 1–1.5 mg/kg or target control infusion (TCI),

setting the target concentration in the effective region at about 3–3.5 μg/ml to induce sleep. When thiopental is used, it is administered once at 3–6 mg/kg. After falling asleep, a non-depolarizing muscle relaxant is administered. In patients being treated with anticonvulsants such as carbamazepine and phenytoin, drug interference occurs, for which an increase in the dose of non-depolarizing muscle relaxant is necessary. Attention should be paid to thiopental because it reacts with vecuronium and rocuronium and crystallizes. Suxamethonium should be cautiously used because it elevates the intracranial pressure. After sufficient muscle relaxation is obtained, tracheal intubation is performed. To prevent esophageal stimulation, spraying a local anesthetic in the trachea is effective.

32.9.2 Posture Fixation

Insertion of securing pins is the most nociceptive procedure. Sufficient pain relief or local anesthesia of the insertion site is administered. When fentanyl and remifentanil are used, bolus administration at 2–3 and 0.25–0.5 μg/kg, respectively, is necessary. When pressure reduction is insufficient, the pressure is reduced by administering 0.5 mg/kg esmolol. Since the intubation tube cannot be visually confirmed due to the surgical drape in many cases of neurosurgery, fixation should be applied while paying attention to accidental extubation. When the patient is placed in an irregular position such as the lateral or prone position, fixation should be performed very carefully. Attention should also be paid to brachial paralysis caused by abduction of the neck.

Tape fixation is applied to prevent disinfectant from entering the eyes during disinfection of the surgical field.

32.9.3 Maintenance of Anesthesia

The main objectives of anesthesia maintenance are to maintain sufficient cerebral perfusion pressure and oxygenation, prevent marked changes in ICP, prepare a favorable surgical field, and obtain a smooth awakening.

32.9.3.1 Inhalation Anesthesia

Sevoflurane and desflurane should be used for inhalation anesthesia. These are superior in adjustability and awakening is early. These reduce the cerebral metabolic rate, but increase the cerebral blood flow by vasodilation. Carbon dioxide reactivity and autoregulation are maintained when the minimum alveolar concentration is 1 or lower (sevoflurane, 1.7 %; desflurane, about 6 %). Concomitant nitrous oxide promotes ICP elevation [3].

32.9.3.2 Intravenous Anesthesia

Intravenous anesthesia is performed by continuous administration of propofol. This reduces the cerebral metabolic rate, cerebral blood flow, and volume [4]. Thus, ICP is secondarily reduced. Propofol also maintains autoregulation. When TCI is employed for maintenance, intraoperative awakening is prevented by adjusting the concentration at a level slightly higher than the sleep-inducing blood level (about 0.5–1 μg/ml).

32.9.3.3 Opioids

Fentanyl and remifentanil should be used for opiate administration. These do not influence the cerebral blood flow or metabolic rate [3]. They can be safely used even in patients with ICP elevation. When a highly invasive procedure is applied such as securing a pin insertion and skin or dural incisions, a single administration or dose elevation is performed beforehand.

32.9.3.4 Muscle Relaxant

Body movement or the cough reflex may cause a serious accident during neurosurgery. To prevent these, a muscle relaxant is administered over time. Rocuronium can be continuously administered in this case [5].

The muscle relaxation level to inhibit the cough reflex is a posttetanic count of 1–4.

When MEPs are monitored during surgery, additional muscle relaxant administration is to be avoided. MEPs are reduced in inhalation anesthesia when the anesthetic concentration is high.

32.9.3.5 Cerebral Perfusion Pressure (CPP)

CPP is calculated from the mean blood pressure.

CPP = MAP-ICP; ICP ≒ central venous pressure (CVP); normally, CVP is slightly higher.

The following relationship is present between the cerebral blood flow (CBF) and CPP:

CBF = CPP/cerebral vascular resistance.

When the ICP is normal, the mean blood pressure is maintained at 70 mmHg or higher to maintain CPP. When the ICP is elevated, the treatment to reduce the ICP is performed to maintain CPP and prepare a favorable surgical field.

(a) Hyperosmotic diuretics

Diuretics are used perioperatively for intracranial pressure control, on the assumption that treatment to prevent dehydration and sufficient transfusion volume for circulatory maintenance are administered preoperatively. A report of a study of patients with head injury demonstrated that a water deficit of 594 ml or more would aggravate the prognosis with no reference to ICP, mean arterial pressure, or cerebral perfusion pressure [9].

Mannitol is mainly used as a diuretic. The recommended dose is 0.25–2 g/kg. When the administration rate is high (1 g/kg or higher), hypotension is observed in the early phase, but transient intracranial pressure elevation may occur due to a subsequent increase in the circulating blood volume. This intracranial pressure elevation can be prevented by hyperventilation and slowing the administration rate. Furosemide may be concomitantly administered. Although the ICP-reducing mechanism of furosemide is unclear, transient intracranial pressure elevation can be prevented by concomitant administration of furosemide. The intracranial pressure-reducing effect of mannitol reaches the maximum at 30–45 min after the initiation of administration. While administration of a diuretic may decrease ICP or improve cerebral edema, sodium load should be considered when the effects of a diuretic are insufficient. Hypertonic saline increases the plasma crystalloid osmotic pressure and facilitates the transfer of water from the cerebral parenchyma to the plasma.

(b) Spinal cord drainage

Spinal cord or cerebral ventricular drainage reduces ICP by reducing the cerebrospinal fluid volume [6]. However, rapid ICP reduction by drainage of a large volume causes brain hemorrhage, reflex hypertension, bradycardia, and cardiac arrest due to the collapse of the bridging vein. Moreover, it is contraindicated in patients with severe ICP elevation because of the risk of brainstem herniation.

Spinal cord drainage reduces postoperative cerebrospinal fluid leakage.

32.9.3.6 Body Temperature Management

The body temperature is measured at two or more sites such as the rectum, tympanum, and esophagus. Since body temperature elevation increases the cerebral metabolic rate and oxygen extraction ratio, mild hypothermia at about 33–35° was previously induced, but no difference was noted in the postoperative course between the normal and low body temperature groups in a clinical study of aneurysm surgery, and the infection risk increased in the low body temperature group [7, 8]. Moreover, an increase in blood loss and delayed awakening were problematic. Therefore, it is now accepted that hypothermic management does not necessarily improve the prognosis.

32.9.3.7 Fluid Management

The blood–brain barrier is a semipermeable membrane that only allows water to penetrate freely in and out of the brain. Since water moves only when the osmotic pressure changes, the brain itself may work as an accurate osmometer. Decreases in plasma osmotic pressure of approximately 5 % could increase ICP and cause cerebral edema. Therefore, isotonic or slightly hyperisotonic levels should be maintained by appropriately controlling the circulatory blood volume with isotonic solutions during surgery. When the osmotic pressure is lowered, cerebral edema will become aggravated, while the increase in the pressure will require treatment. Commercially available crystalloid solutions are isotonic or slightly hypotonic, and thus excessive administration of these solutions may decrease the plasma osmotic pressure. The target of the circulating blood volume is set at about 30 % Hct, the blood glucose level is set at a normal level, and the osmotic pressure (320 mOsm/kg) is set at a slightly high level. For hyponatremia, physiological or hypertonic saline is transfused.

32.9.4 Awakening from Anesthesia

32.9.4.1 Early and Late Awakening

Early awakening after surgery is advantageous for neurological examination. On the other hand, late awakening is selected for patients with unstable circulatory dynamics due to preoperative ICP elevation and massive hemorrhage to continue systemic management. For patients in whom the brainstem is compressed by a certain cause, attention should be paid to the aggravation of a respiratory condition.

32.9.4.2 Extubation

When anesthesia is maintained with sevoflurane, desflurane, propofol, and remifentanil, response to verbal commands and eye-opening can be confirmed at about 10–20 min after the completion of administration. When these are markedly delayed, a cause other than anesthesia (such as cerebral edema, spasm, intracranial hematoma, and cerebral ischemia) is to be investigated.

When spontaneous respiration resumes and eye-opening and response to verbal commands are confirmed, extubation can be considered. Since neurosurgery requires deep muscular relaxation, muscle relaxants may remain. The criterion to perform extubation is judged using the train of four (TOF). A TOF value of 90 % or higher is the requirement for extubation.

32.9.4.3 After Extubation

Circulatory variation persists for about 10–25 min due to catecholamine release and nociceptive stimulation. The oxygen consumption increases up to about five times due to shivering. Oxygen is administered and a monitor is attached when the patient is transferred.

32.10 Postoperative Complication

32.10.1 Surgical Complication

Brain hemorrhage, intra- and extradural hemorrhage, and edema-induced ICP elevation may occur as surgical complications. Consciousness, respiratory conditions, and the presence or absence of paralysis must be carefully observed. Monitoring for a specific period is essential. When an abnormality is observed, neurological examination, imaging, and diagnosis should be immediately performed.

32.10.2 Thromboembolism

Thromboembolism is likely to develop because many neurosurgery patients are elderly, whereby recumbence for a prolonged period is necessary and dehydration readily occurs. The risk classification and treatment policies are shown in Table 32.2.

Table 32.2 Prevention of venous thromboembolism in neurosurgery

Risk level	Surgery and preventive method
Low risk	Neurosurgery other than craniotomy; early ambulation and active exercise
Medium risk	Craniotomy other than that for brain tumor; elastic stocking or intermittent pneumatic compression
High risk	Craniotomy for brain tumor; intermittent pneumatic compression or low-dose heparin
Maximum risk	Past medical history of venous thrombosis and craniotomy for brain tumor with thrombotic predisposition; low-dose heparin and elastic stocking or intermittent pneumatic compression

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Chapter 33
Anesthesia in Awake Craniotomy

Takashi Ishida and Mikito Kawamata

Abstract Awake craniotomy was introduced for surgical treatment of epilepsy a long time ago and has subsequently been used in patients undergoing surgical management of supratentorial tumors, arteriovenous malformations, and deep brain stimulation (Pasquet, Curr Res Anesth Analg 33(3):156–164, 1957). Awake craniotomy aims to maximize lesion resection while sparing important foci, particularly the so-called eloquent areas such as the motor, somatosensory, short-term memory, and language areas (July et al. Surg Neurol 71:621–625, 2009). Several new techniques have recently been developed for anesthetic management in awake craniotomy.

Keyword Awake craniotomy • Anesthesia • Local anesthetic • Propofol • Target-controlled infusion

33.1 Introduction

Awake craniotomy was introduced for surgical treatment of epilepsy and has subsequently been used in patients undergoing surgical management of supratentorial tumors, arteriovenous malformations, and deep brain stimulation [1]. Awake craniotomy aims to maximize lesion resection while sparing important foci, particularly the so-called eloquent areas such as the motor, somatosensory, short-term memory, and language areas [2]. The development of long-acting local and short-acting general anesthetics facilitated awake craniotomy. Various anesthetic techniques have been developed for awake craniotomy. This chapter reviews the presurgical evaluation of anesthetic techniques (asleep-awake-asleep techniques) for and complications involved in awake craniotomy.

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33.2 Presurgical Evaluation

Before resection, a provocation test (the Wada procedure) is performed to determine the dominant hemisphere using cerebral angiography [3]. The Wada test involves selectively anesthetizing the cerebral hemispheres, usually by injection of thiopental sodium or propofol into the carotid artery. Since speech is an issue when the posterolateral portions of the temporal lobe are involved and memory when it is the medial portions of the temporal lobe, this allows localization of the eloquent areas that control speech and confirms whether there is bilateral representation for short-term memory or both.

33.2.1 Preanesthetic Evaluation and Preparation

There are several important preoperative checkpoints to be evaluated (Table 33.1) [4, 5]. Preoperative evaluation is essential in predicting difficulty in managing the airway intraoperatively. Sleep apnea syndrome should be considered as an exclusion criterion for awake craniotomy. Evaluation of brain swelling is also important, since it is much more difficult to control intracranial pressure during spontaneous breathing than during mechanical ventilation. Epileptic patients should also be carefully evaluated, as uncontrollable seizures represent exclusion criteria for awake craniotomy. Finally, the patient's complete cooperation and participation are critical, and awake craniotomy should not be performed in patients with mental confusion or profound dysphasia.

Table 33.1 Preoperative checkpoints in awake craniotomy

Upper airway	Prediction of difficult tracheal intubation
	Obstructive apnea risk
Epilepsy	Pharmacotherapy
	Antiepileptic drug serum concentration
	Type and frequency of seizures
Nausea and vomiting	Past anesthesia
	Kinetosis
Intracranial pressure	Type of lesion
	Radiological and clinical signs
Hemorrhagic risk	Type and localization of lesion
	Therapy (antiplatelet drugs)
	Medical history
Patient cooperation	Anxiety
	Pain tolerance
	Neurological deficits

Prior to surgery, the patient must be informed about potential risks, safety measures, stages of the procedure, and what will occur while he/she is in the operating room. A visit to the operating room before surgery may help familiarize the patient with the environment they will encounter.

33.3 Anesthetic Techniques

The techniques employed in awake craniotomy range from minimal to deep sedation, the so-called asleep-awake-asleep techniques [4]. During the awake phase, patients are kept under spontaneous ventilation with an unprotected airway. During the asleep phase, airway management is achieved with a laryngeal mask airway (LMA), sometimes with positive-pressure ventilation. In this chapter, we will focus on the asleep-awake-asleep techniques.

33.3.1 Premedication

During awake craniotomy, it is important for the patient to be sufficiently alert to perform language and motor tasks that yield reliable results, based on which the extent of resection is determined. Therefore, as a matter of principle, drugs that could affect emergence should not be administered. If sedatives have to be administered, benzodiazepines are recommended, as antagonists are available. Since the patient's condition needs to be considered, anticonvulsants should only be administered preoperatively after discussion with the attending physician. H_2 blockers are administered for gastric protection and reducing the risk of aspiration pneumonia if vomiting should occur.

33.3.2 Intraoperative Monitoring

Intraoperative monitoring typically includes an electrocardiogram, invasive and noninvasive blood pressure measurement, pulse oximetry, respiratory rate, end-tidal carbon dioxide using capnography, and body temperature. End-tidal carbon dioxide is measured via the devices involved in the anesthetic technique (nasopharyngeal cannula, LMA, and facial mask). Normally, a urinary catheter is also inserted and urine volume measured. A bispectral index monitor is useful during the sedation/anesthesia period and also in evaluating the level of responsiveness during awake cortical mapping [6].

33.3.3 Anesthetic Drugs

Propofol should be used as a hypnotic agent. Propofol is an intravenous anesthetic drug that permits faster and clearer emergence than inhalation anesthetics, which affect the electroencephalogram (EEG) and sometimes induce excitement at emergence from sedation. Administration of propofol is useful in preventing perioperative nausea and vomiting. A target-controlled infusion (TCI) system [7] is used for propofol in order to maintain the optimal hypnotic level by adjusting the effect-site concentration of the agent, which determines its sedative effect. Infusion of propofol should be discontinued at least 15 min before EEG recording.

Opioids are used for sedation and analgesia, but exert some residual effects on the consciousness level after emergence. Remifentanil is therefore suitable in the management of strong surgical stimulation before emergence [8], as its effect rapidly disappears. It is also reasonable to administer a small dose of fentanyl repeatedly, expecting only a slight residual analgesic effect. The use of remifentanil at a low dose (0.1 μg/kg/min) appears not to interfere with EEG. Opioids should be used with careful attention to respiratory depression, which causes hypercapnia and brain swelling.

Dexmedetomidine is a highly selective α2-agonist with dose-dependent sedative, anxiolytic, and analgesic effects without ventilation suppression. Several studies have reported the successful use of dexmedetomidine during the awake period [9]. However, other studies have noted that this can result in poor emergence, necessitating a decrease in the dose or discontinuation of administration.

33.3.4 Local Anesthetics

The key to anesthetic management in awake craniotomy is to achieve a "pain-free" state with multimodal pain management. Since intravenous anesthetics affect the state of consciousness and respiration, local anesthetics are essential for assured analgesia. The local anesthetic must assure an 8-h duration of block. This is achieved with the use of long-acting local anesthetics such as ropivacaine or levobupivacaine or the combination of lidocaine and epinephrine. Problems such as local anesthetic toxicity did not occur, even at a mean ropivacaine dose of 3.6 mg/kg in a study on blood concentrations of local anesthetics in awake craniotomy [10].

A "scalp block" is performed to include seven nerves (Fig. 33.1) [4–6]. These nerve blocks are usually performed on the surgical scalp side. In addition to these nerve blocks, ring blockage of the scalp is performed. Additional infiltration is usually performed at the three head holder pin sites and along the skin incision line. Gauze soaked with a local anesthetic can be pressed against the wound. Since direct contact of a local anesthetic with the brain parenchyma can cause central nervous

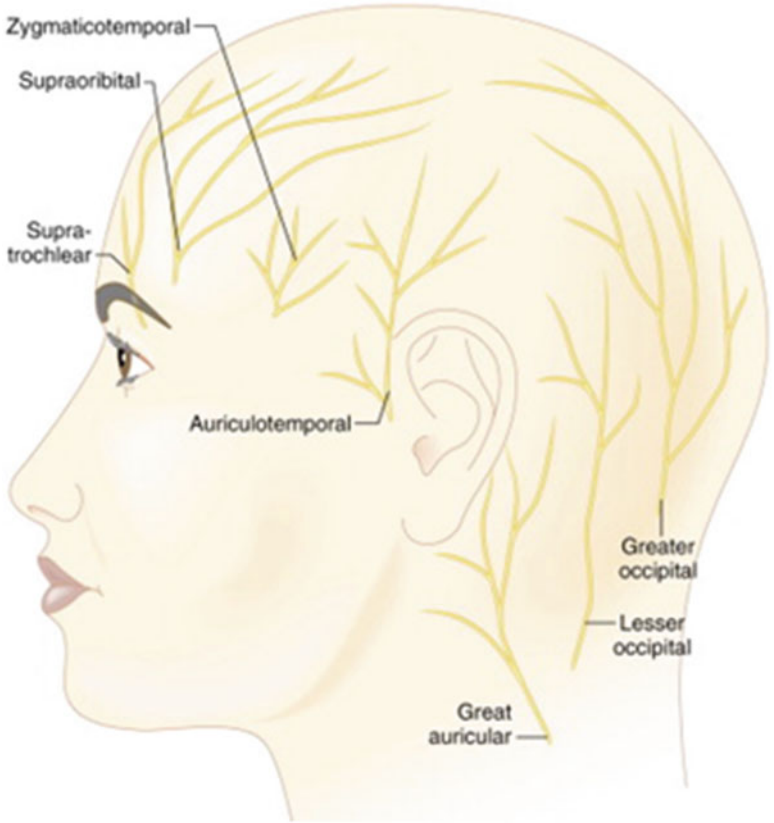

Fig. 33.1 Innervation of the scalp and nerves to be blocked in a "scalp block"

system symptoms such as convulsions, administration of a local anesthetic after dural incision should be performed carefully.

33.3.5 Airway Management

Maintenance of the airway during awake craniotomy is achieved by one of the two methods: by depending on spontaneous respiration, using no devices, or by using a device such as an LMA [11]. If a device is used, we can rely on spontaneous respiration and, if necessary, provide respiratory support or we can actively perform ventilation. Tracheal intubation is not recommended since it is likely to interfere with an awake study due to complications caused by emergence-induced coughing and depressed laryngeal function, including hoarseness. A tracheal tube can be placed in the pharynx via the nose for respiratory support, if necessary, or emergency intubation can be done with a bronchoscope. Nasal bleeding can become a

problem, however. If management is performed by spontaneous respiration without use of a device, hypercapnia may become a problem. This can usually be dealt with by TCI, however, avoiding the need to resort to narcotics or major craniotomy. Partly to decrease the dose of narcotics, it is important to perform sufficient local anesthesia as described in the next section.

The airway before emergence is usually managed with a face mask or an LMA. Airway management under assisted/controlled ventilation and spontaneous respiration can be performed safely with an LMA, although it is generally difficult to extubate safely and smoothly at awakening. Muscle weakness in a conscious state is rare with an LMA, since muscle relaxants are not necessary for LMA insertion.

33.4 Complications in the Awake Period

Many types of complications, including airway problems, hypoxemia, changes in blood pressure, changes in heart rate, seizures, nausea, poor cooperation, brain swelling, and toxicity of local anesthetics, can occur during the awake period (Table 33.2) [12–15]. The incidences of these complications may vary depending on the sedatives and analgesics used.

33.4.1 Pain

Generally, during the awake period, no systemic sedatives or analgesics should be used in order to minimize interference with functional mapping or the identification of epileptic foci. Pain may arise from poorly anesthetized areas (often in the temporal area) or the dura mater and brain vessels. In such cases, additional local anesthetic infiltration is indicated. Since this type of procedure is very long, posture-related pain may occur and is managed by allowing the patient small movements and administering drugs such as acetaminophen and diclofenac.

33.4.2 Nausea and Vomiting

Although the incidence of nausea and vomiting during awake surgery varies among reports, it has been reported to be approximately 0–10 % when anesthetic management is primarily done with propofol [12, 13]. Nausea and vomiting, in addition to causing discomfort for the patient, increases the risk of respiratory complications due to aspiration, and body movement and increased brain swelling associated with nausea/vomiting may make the surgical procedure more difficult. Nausea and vomiting may be induced by the surgical procedure itself or by the use of narcotics. At onset, the surgical procedure should be immediately discontinued and

Table 33.2 Complication incidences (%) in asleep-awake-asleep techniques in the literature

Airway Problems	Hypoxemia	Hypertension	Hypotension	Bradycardia	Seizures	Nausea	Poor cooperation	Brain swelling	LA toxicity	References
2	2	11	56	0.3	3	0.9	2	0.6	0	Skucas et al. [12]
13	nr	nr	nr	nr	19	13	nr	0	nr	Herrick et al. [13]
4	nr	4	0	0	8	0	4	0	nr	Berkenstadt et al. [14]
0.4	nr	nr	0.8	nr	8	0.8	nr	0	nr	Blanshard et al. [15]

All values are expressed as percentage
nr not reported; *LA* local anesthetic

metoclopramide or a serotonin receptor antagonist administered. If the symptoms are severe and do not improve, sedation with propofol and discontinuation of the awake craniotomy should be considered. Metoclopramide (10 mg), ondansetron (4–8 mg), droperidol (0.625–2.5 mg), and dexamethasone are useful in preventing nausea and vomiting.

33.4.3 Convulsions

The incidence of convulsions during awake craniotomy depends on the underlying disease and has been reported to be approximately 0–24 % [14, 15]. Convulsions are more likely to develop during electrical stimulation for brain functional mapping. If convulsions occur, electrical stimulation should be discontinued and the brain cooled with cold Ringer's solution or saline. If an EEG is being monitored, the procedure should be discontinued at the onset of a spike. Most convulsions cease with discontinuation of the surgical procedure and cooling of the brain. If these measures are ineffective, propofol or phenytoin should be administered at a sleeping dose. If convulsions do not cease with additional propofol, midazolam, or thiopental, awake craniotomy should be discontinued. During awake craniotomy, it is necessary to be prepared for emergency transition to airway management or general anesthesia at any time.

33.5 Re-induction and Completion of Craniotomy

Propofol is generally used as the anesthetic at the end of craniotomy, as it is during craniotomy. A decision as to whether tumor resection will be performed in the awake state or under sedation with propofol is made with consideration of the conditions at each institution and of each patient. Some surgeons want patients to be reawakened after tumor resection to check for neurological symptoms.

Insertion of an LMA should be done via a lateral caudal approach and requires some degree of proficiency when the head is fixed with pins. There is a risk of difficulty with airway establishment or vomiting, and it is recommended that at least two anesthesiologists should be involved in the insertion of the LMA. After establishment of the airway with an LMA, management can be achieved by controlled respiration with remifentanil or fentanyl. If establishment of the airway takes a long time, tracheal intubation can be considered. If an airway is not established, further local anesthetic should be given to allow surgery to be continued. Preparations should be made to allow for establishment of the airway with an LMA immediately after a sudden change in the patient's state, such as the onset of convulsions. If analgesia is insufficient, a small dose of fentanyl may be added. Caution is required with regard to the use of remifentanil with spontaneous respiration during craniotomy, as in emergence.

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Part VIII
Anesthetic Management: Neuroanesthesia for Traumatic Brain and Spinal Injury

Chapter 34
Anesthetic Management of Severe Head Injury

Yasuhiro Kuroda, Kenya Kawakita, and Toru Hifumi

Abstract Traumatic brain injury (TBI) is a major public health concern. Emergency surgery for TBI is performed frequently. A multidisciplinary approach may be needed, as TBI can often be just one element of polytrauma. Secondary cerebral injuries are also common after TBI and are caused by post-insult physiologic derangements. The main goals of the anesthetic management of TBI are to facilitate early decompression, provide adequate analgesia and anesthesia, maintain adequate cerebral perfusion, treat intracranial hypertension, provide optimal surgical conditions, and prevent secondary insults such as hypoxemia, hyper- and hypocarbia, and hypo- and hyperglycemia. Resuscitation of polytrauma including hemostasis by transcatheter arterial embolization and/or surgical hemostasis must be considered. The perioperative period is a critical window of opportunity in which anesthesiologists can prevent and reduce the burden of secondary brain injury after TBI. The choice of anesthetic strategy is guided by the influence of anesthetic agents and interventions on the pathophysiologic processes provoked by TBI.

Keywords Secondary injury • Traumatic brain injury • Anesthesia • Perioperative management • Outcomes

34.1 Introduction

The avoidance or correction of hypoxia and arterial hypotension is critically important in the prevention of secondary injury after traumatic brain injury (TBI). These goals are fundamental to the routine clinical practice of anesthesia and will be familiar to all anesthesiologists.

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34.2 Indications for Surgical Intervention After Traumatic Brain Injury

TBI is classified by the appearances on brain imaging (Fig. 34.1, Table 34.1). Patients who have sustained a TBI should undergo a full clinical assessment that includes an estimation of the conscious level (Table 34.2) and examination of the pupils, which together with imaging findings can then inform conservative or surgical treatment strategies (Table 34.3). In the presence of a mass lesion, indications for surgical evacuation are predicated on these clinical and radiological

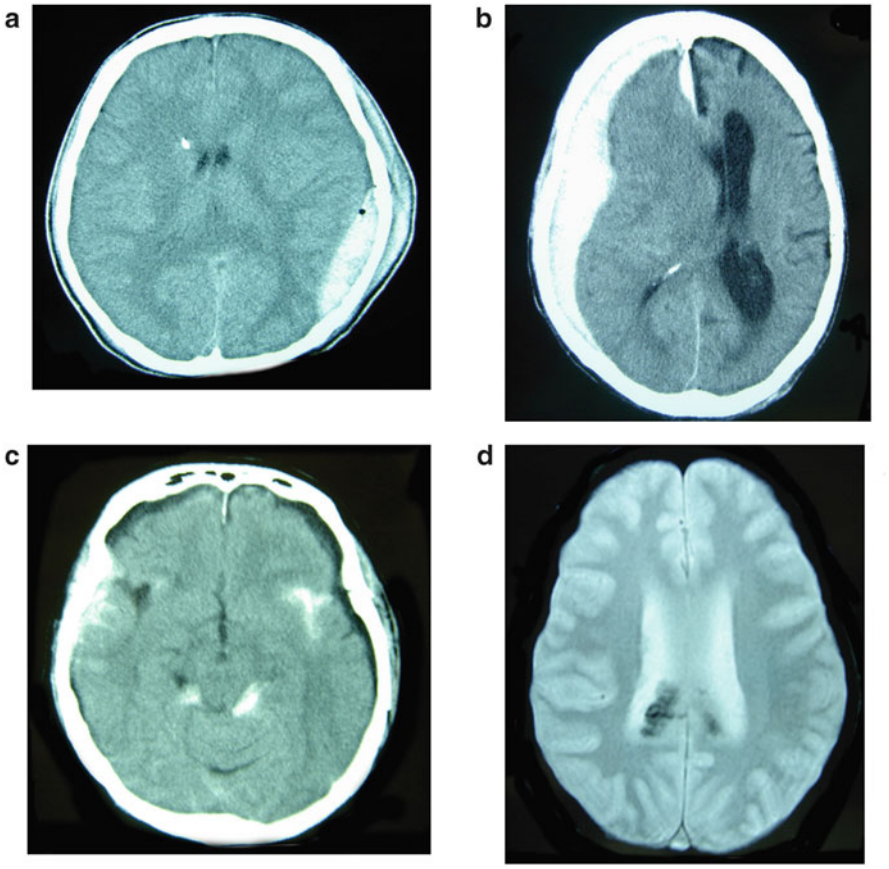

Fig. 34.1 Representative brain imaging of the various primary injuries that may be seen after traumatic brain injury. (**a**) Left epidural hematoma; (**b**) right subdural hematoma with mass effect, effacement of the right lateral ventricle, and right to left midline shift; (**c**) traumatic subarachnoid hemorrhage; (**d**) punctate foci of lesions (*black spots*) consistent with diffuse brain injury. Images (**a**) to (**c**) acquired by non-contrast axial computed tomography; image (**d**) acquired by axial gradient echo sequence magnetic resonance imaging

Table 34.1 Marshall CT classification of TBI

Category	Definition
Diffuse injury I (no visible pathology)	No visible intracranial pathology seen on CT scan
Diffuse injury II	Cisterns are present with midline shift of 0–5 mm; no high- or mixed-density lesion >25 cm^3 may include bone fragments and foreign bodies
Diffuse injury III (swelling)	Cisterns compressed or absent with midline shift 0–5 mm; no high- or mixed-density lesion >25 cm^3
Diffuse injury IV (shift)	Midline shift >5 mm; no high- or mixed-density lesion >25 cm^3
Evacuated mass lesion V	Any lesion surgically evacuated
Non-evacuated mass lesion VI	High- or mixed-density lesion >25 cm^3; not surgically evacuated
	Marshall et al. [60]

findings [1–5]. After diffuse TBI, decompressive craniectomy for the treatment of refractory elevated intracranial pressure (ICP) may also be warranted [6].

34.3 Pathophysiology of Traumatic Brain Injury (Table 34.4)

Primary brain injury is caused by the initial mechanical insult that may result in skull fracture, brain contusion, and vascular and parenchymal injury, which in turn can cause intracranial bleeding and increased ICP [7]. This is followed by an inflammatory response, edema formation, and excitotoxicity, resulting in further increases in ICP and reduction in cerebral perfusion pressure (CPP) [7]. The severity of primary injury is the major factor determining the outcome of patients with TBI.

Secondary brain injury is caused by subsequent physiological disturbance and further contributes to the worsening of outcomes [7]. The most important factors are hypotension (systolic blood pressure [SBP] <90 mmHg in adults) and hypoxemia (arterial partial pressure of oxygen, $PaO_2 < 60$ mmHg) [8], which are independently associated with increased morbidity and mortality [9]. Other common secondary insults include hypoglycemia, hyperglycemia, hypercarbia, hypocarbia, and raised ICP [10, 11]. The anesthesiologist must strive to maintain these physiological variables within their normal ranges in the emergency room, operating room, and the neurocritical care unit.

Table 34.2 Glasgow Coma Scale

Category	Scale
Eye-opening	
Spontaneous	4
To voice	3
To pain	2
None	1
Verbal response	
Oriented	5
Confused	4
Inappropriate	3
Incomprehensible	2
None	1
Motor response	
Obeys commands	6
Localizes to pain	5
Withdraws from pain	4
Flexion posturing to pain	3
Extensor posturing to pain	2
None	1

The Glasgow Coma Scale (GCS) score is widely used for the initial and serial neurological assessment of the TBI patients. Eye-opening, verbal responses, and motor responses are each scored as above. The sum of the scores in each category is added for the total GCS score. The total GCS score may range from 3 (most severely injured) to 15 (least severely injured). Patients with endotracheal or tracheostomy tubes are often assigned a verbal score of "1T"
Teasdale and Jennett [58]

34.4 Preoperative Assessment

Preoperative assessment must be undertaken quickly as the need for surgery after acute TBI is urgent, and management will have begun in the prehospital setting and emergency room. The anesthesiologist must often rely on limited and indirect information about the patient's premorbid medical and anesthetic history from relatives, friends, or carers. Eliciting a recent history of drug use is important, as some drugs may impair cardiovascular and central nervous system functions. Laboratory examination of the urine may be indicated to detect drugs or other intoxicants. Details of all investigations performed and treatments undertaken should be available to the anesthesiologist.

The anesthesiologist must undertake a rapid but comprehensive assessment of the cardiovascular, respiratory, and musculoskeletal systems in the context of possible other traumatic injuries and personally review all investigations, including imaging, in detail. Otherwise, complicating factors may persist or remain undetected as the patient is transferred to the operating room, even though early

Table 34.3 Surgical indication of TBI

Acute subdural hematoma	Hematoma thickness >10 mm (CT scan)
	Midline shift >5 mm (CT scan)
Acute epidural hematoma	Hematoma volume >30 cm^3 (CT scan)
	GCS score <9 with anisocoria
Parenchymal mass	Signs of progressive neurological deterioration referable to the lesion medically refractory intracranial hypertension mass effect (CT scan)
	GCS score (6–8) with frontal or temporal contusions (>20 cm^3) with midline shift >5 mm and/or cisternal compression (CT scan)
	Lesion volume >50 cm^3
Posterior fossa	Mass effect (CT scan)
	Distortion, dislocation, or obliteration of the fourth ventricle
	Compression or loss of visualization of the basal cisterns
	Presence of obstructive hydrocephalus
	Neurological dysfunction or deterioration referable to the lesion
Depressed skull fractures	Open (compound) cranial fractures depressed greater than the thickness of the cranium

GCS Glasgow Coma Scale, *CT* computed tomography

resuscitation is in progress. The perioperative period provides an opportunity to continue and refine an ongoing resuscitation and to address coexisting primary or secondary injuries. Surgery and anesthesia may also provoke new secondary insults, which may contribute to poor outcomes.

34.5 Initial Resuscitation

The most important aspects of management are early resuscitation and optimization of physiological variables. A brief neurological assessment should be performed using the Glasgow Coma Scale (GCS; Table 34.2) and an assessment made of pupillary responses. Surgical evacuation of an intracerebral hematoma should only be undertaken if the SBP can be maintained above 90 mmHg and the peripheral oxygen saturation (SpO_2) above 90 %. Associated thoracic, abdominal, spinal, and long bone injuries may be stable but can evolve during the perioperative period and must be considered in the differential diagnosis of new-onset hypotension, anemia, hemodynamic instability, or hypoxemia during anesthesia and surgery. Broken teeth, pneumocephalus, rib fracture, and pneumothorax may also be overlooked.

As part of the initial resuscitation, adequate intravenous access should be obtained, especially if blood loss from other injuries or during surgery is anticipated, and the anesthesiologist should check that blood is readily available for transfusion. Adequate patient monitoring should begin preoperatively. A peripheral arterial catheter should be sited, central venous access obtained for monitoring and drug administration, and a urinary catheter inserted.

Table 34.4 BTF G 3rd edition, 2007

System	Sequelae	Managements	Guideline recommendations	Level
Airway	Apnea	Early endotracheal intubation	Pneumonia prophylaxis	2
	Obstruction		Early tracheostomy when feasible	2
	Injury			
	Aspiration			
Pulmonary	ARDS	Supportive	Prophylactic hyperventilation not recommended	2
	Neurogenic pulmonary edema	Mechanical ventilation	Temporary hyperventilation for worsening ICP	3
	Contusion	High FIO_2	Avoid hypoxia (Pao2 <60 mmHg or Spo2 <90 %)	3
	Pneumothorax	Consider PEEP	Avoid jugular venous saturation <50 % or brain tissue oxygen tension <15 mmHg	3
		Thoracostomy		
Cardiovascular	Hypovolemia	Maintain normal to high-normal BP	Avoid hypotension (systolic blood pressure <90 mmHg)	2
	Arrhythmia	Replace intravascular volume	Avoid aggressively maintaining CPP >70 mmHg due to ARDS risk	2
	Contusion	Avoid hypotonic solution	Avoid low CPP (<50 mmHg)	3
	Tamponade	Avoid glucose-containing solution		
		Vasopressors		
		Pericardial window		
Brain	Primary injury	Monitor and control ICP	Monitor ICP via ventricular catheter connected to an external strain gauge	
	Secondary injury	Present secondary injury	Monitor ICP on all salvageable patients with a severe TBI (GCS score 3–8 after resuscitation) and an abnormal CT scan	2
	ICP increase	Decreased $CMRo_2$	Avoid ICP >20 mmHg	2
	CPP decrease	Hypothermia	Prophylactic barbiturate coma not recommended: barbiturate coma recommended for elevated ICP refractory to the maximum standard medical and surgical treatment	2

(continued)

Table 34.4 (continued)

System	Sequelae	Managements	Guideline recommendations	Level
		Hyperventilation	Prophylactic phenytoin or valproate not recommended for preventing late posttraumatic seizures (PTS): anticonvulsants indicated to decrease the incidence of early PTS (within 7 days of injury)	2
		Hyperosmolar therapy	Restrict mannitol use prior to ICP monitoring to patients with signs of transtentorial herniation or progressive neurologic deterioration not attributable to extracranial causes	3
		CSF drainage		
		Surgical decompression		
		Barbiturate coma		
		IV anesthetic agents		
		Avoid inhalational agents		
	Fever		Temperature management is still a matter of controversy	
Blood and homeostasis	Acute hemorrhage	Packed RBC: keep Ht > 30	Graduated compression stockings or intermittent pneumatic compression (IPC) stockings are recommended and should be combined with LMWH or low-dose unfractionated heparin for DVT prophylaxis; however, there is an increased risk for expansion of intracerebral hemorrhage	3
	Coagulopathy	FFP and factor VIIa		
	DIC	DIC treatment		
	Thrombocytopenia	Platelet		
	DVT	Prophylaxis		
	Hyponatremia	NS or 3 % NS slowly		
	Hypomagnesemia	Magnesium replacement		

(continued)

Table 34.4 (continued)

System	Sequelae	Managements	Guideline recommendations	Level
Endocrine	Hyperglycemia	Insulin: keep blood glucose <200 mg/dl	The use of steroids is not recommended for improving outcome or reducing ICP in patients with moderate and severe TBI; high-dose methylprednisolone is associated with increased mortality and is contraindicated	1
	SIADH	Water restriction		
	Cerebral salt-wasting syndrome	Sodium replacement		
	Diabetes insipidus	DDAVP		

Based on "Guidelines for the Management of Severe Traumatic Brain Injury. 3rd Edition. Journal of Neurotrauma. 2007.24 (Supplement 1)," level I recommendations are based on the strongest evidence for effectiveness and represent principles of patient management that reflect a high degree of clinical certainty. Level II recommendations reflect a moderate degree of clinical certainty. For level III recommendations, the degree of clinical certainty is not established

34.6 Standard Monitoring

The electrocardiogram is an essential means of detecting dysrhythmias and myocardial ischemia. Pulse oximetry is mandatory but may be unreliable in hypoperfusion, hypotension, or hypothermia. Capnography should be initiated to confirm that the endotracheal tube is correctly placed and that mechanical ventilation is optimal and can also provide a guide to changes in cardiac output. Large alveolar–arterial gradients in the partial pressure of CO_2 may arise, especially in patients with traumatic chest injuries, and end-tidal CO_2 concentration should be calibrated regularly against arterial measurements. Arterial catheterization also allows continuous arterial pressure monitoring, determination of CPP, and blood glucose sampling in patients who require surgical intervention. Central venous pressure measurement is a high priority, but it is advisable not to delay surgical evacuation of an expanding intracranial hematoma for the institution of invasive monitoring.

34.7 Multimodal Neuromonitoring

ICP monitoring is recommended in patients with severe TBI (GCS <9) with computed tomography (CT) imaging that shows a mass effect (caused, e.g., by hematomas, contusions, swelling, herniation, or compression of the basal cistern) and in patients with severe TBI with a normal CT scan if two or more of the

following features are present: age >40 years, unilateral/bilateral motor posturing, or SBP <90 mmHg [12].

Jugular venous oxygen saturation (SjO_2) is a useful means of assessing the adequacy of global cerebral oxygenation [13]. The indications are generally the same as those for ICP monitoring, and $SjO_2 < 50$ % may indicate the need to optimize ventilation and the systemic hemodynamic status or institute ICP-lowering measures [13].

Brain tissue oxygen tension ($PbtO_2$) monitoring has the advantage of identifying the focal areas of ischemia that may not be detected by changes in SjO_2, which more closely reflect global cerebral oxygenation [13]; $PbtO_2 < 15$ mmHg indicates ischemia [13].

Near-infrared spectroscopy offers the capacity to conveniently and noninvasively monitor cerebral oxygenation [13].

Transcranial Doppler (TCD) ultrasonography is a noninvasive technique that does not require ionizing radiation and can provide useful instantaneous cerebrovascular assessment of changes in cerebral blood flow (CBF) velocity, vasospasm, and autoregulation [14]. However, it is of greatest value in a neurocritical care setting rather than in the operating room, where it is rarely practical.

Cerebral biochemistry, including markers of neuronal ischemia and injury (the concentrations of lactate, pyruvate, glycerol, glutamate, and glucose), may be measured regionally by cerebral microdialysis.

The monitoring of cerebral oxygenation (global or focal), CBF, and metabolic parameters may be helpful in guiding important treatment decisions [15]. Combining these monitors in a multimodal approach refines the clinician's approach to goal-directed cerebral resuscitation, which can be tailored to individual patients' unique neurological and systemic pathophysiological status.

34.8 Induction of Anesthesia

The main goal of the induction of anesthesia is to achieve sufficiently deep anesthesia and optimal muscle relaxation to rapidly and safely control the airway and mechanically ventilate the patient without further perturbing intracranial dynamics. These goals must be achieved even in a patient who may have a full stomach, be hypovolemic, or have other injuries or medical problems.

The drug used for induction may cause cardiovascular depression leading to arterial hypotension, especially in the context of hypovolemia or concomitant cardiovascular disease. The dose of the hypnotic should be reduced in the face of hemorrhage, and occasionally none is used in patients with severe hypovolemia. Adequate intravenous access should be obtained to allow rapid infusion of fluid. Hypovolemia should be corrected before or, if surgery is urgent, during the induction of anesthesia by fluid replacement, guided by central venous pressure monitoring (if available). The anesthesiologist must be prepared to treat hypotension promptly and aggressively. Vasopressors should be prepared and ready for use. Leg

elevation can be helpful when treating anesthesia-related hypotension rather than the Trendelenburg position, which may do little to improve CPP.

34.9 Choice of Anesthetic Drug for Induction

An induction dose of sodium thiopental (3–6 mg/kg) or propofol (2–3 mg/kg) will provide a rapid onset of anesthesia while at the same time reducing CBF, cerebral blood volume (CBV), and ICP by cerebral vasoconstriction [16]. Both drugs decrease the cerebral metabolic rate for oxygen ($CMRO_2$) and attenuate increases in ICP with intubation. Depending on the dose used, propofol and thiopental may not suppress the cardiovascular responses to laryngoscopy and intubation [17], and so adjunctive drugs or repeated smaller doses of induction agents may be necessary.

Fentanyl (5 μg/kg) may be used, but to be effective it should be given at least 3–5 min before intubation; during this period there are risks of loss of airway protection and muscle rigidity that can compromise oxygenation. The combination of an opioid such as fentanyl with small doses of midazolam or sodium thiopental may avoid profound arterial hypotension.

Ketamine, which causes limited cardiovascular compromise, has been associated with increased CBF and increased ICP and may be relatively contraindicated for intubating patients with preexisting elevated ICP [18]. However, it has recently been reported that ketamine may exert beneficial neurological effects in anesthetized, mechanically ventilated patients with an increased ICP without causing adverse changes in cerebral hemodynamics [19]. Ketamine is not advocated in patients with TBI who are not mechanically ventilated.

Scopolamine or midazolam can be considered in order to inhibit memory formation in situations where very small doses of rapid offset anesthetics are being administered.

The choice of muscle relaxant for rapid sequence induction is generally between rocuronium and succinylcholine [20].

34.10 Airway Management (Fig. 34.2)

Many patients arrive at the hospital or operating room already intubated, but if they are not, securing a potentially compromised airway should be the anesthesiologist's first priority. In-line manual cervical stabilization is the standard of care mandated by the Acute Trauma Life Support (ATLS) curriculum for an unstable or uncleared cervical spine. If difficulty in securing the airway is anticipated in an uncooperative patient, it is prudent to sedate the patient to an appropriate level while maintaining spontaneous breathing, as performing an awake intubation is often counterproductive in a combative patient, and rendering the patient apneic carries many risks. Alternative means of securing the airway when endotracheal intubation is

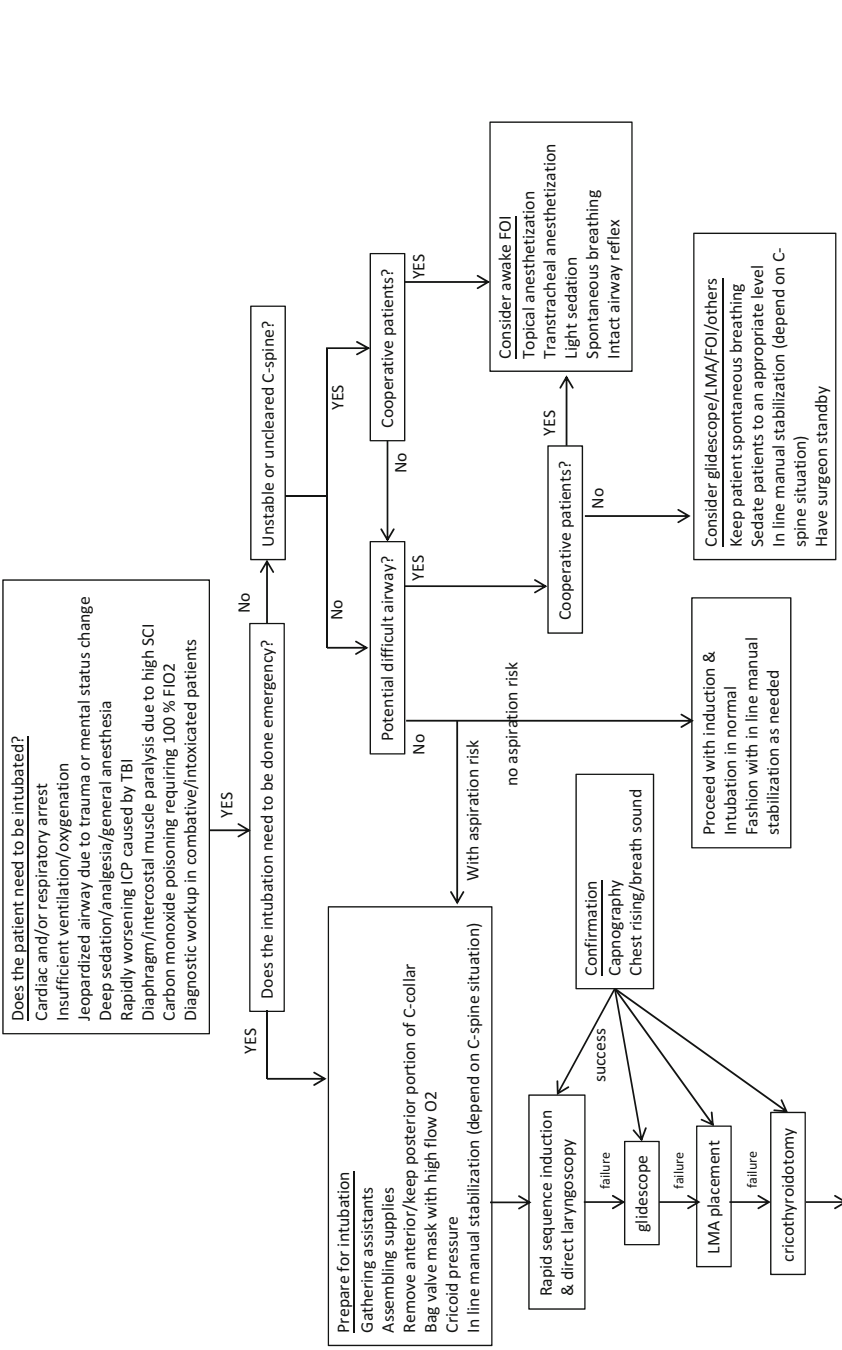

Fig. 34.2 Airway management algorithm for patients with traumatic brain injury. Abbreviations: *ICP* intracranial pressure, *FOI* fiber-optic intubation, *LMA* laryngeal mask airway, FiO_2 fraction of inspired oxygen (Modified from Meng L. chapter 9. Traumatic brain injury: Risk Assessment and perioperative management. Brambrink and Kirsch [59])

challenging include adjuncts such as the GlideScope, laryngeal mask airway, and fiber-optic bronchoscope, and anesthesiologists should have a low threshold for requesting a surgical airway. Capnography should be initiated to confirm the correct placement of the endotracheal tube and can subsequently be used to guide ventilation strategies to ensure normocapnia and detect a low-cardiac output state.

Airway management in TBI may be complicated by a number of factors, including preexisting or worsening hypoxia, uncertainty about the status of the patient's cervical spine, the presence of blood, vomitus or debris in the oral cavity and airway due to laryngeal or pharyngeal injury or skull base fracture, the risk of aspiration of stomach contents, unrecognized intracranial hypertension, and uncertain intravascular volume status.

Concomitant cervical spine injury is present in 10–20 % of patients with severe TBI [21]. It is generally considered that oral endotracheal intubation with head immobilization (rather than in-line immobilization) is a safe technique and does not compromise the cervical spinal cord [22]. Oral endotracheal intubation allows the airway to be secured rapidly and is less traumatic than nasal intubation. The choice of technique for tracheal intubation is determined by urgency, the anesthesiologist's expertise, and the resources available and generally incorporates rapid sequence intubation with cricoid pressure while the neck is immobilized [23]. The anterior part of the cervical collar may be removed when manual in-line stabilization has been established, to allow greater mouth opening and facilitate laryngoscopy. Newer airway devices, particularly videolaryngoscopes, have gained popularity for use in anesthesia for trauma patients and may be useful in difficult airway scenarios [24].

Nasal intubation should be avoided in the presence of a basal skull fracture or major maxillary trauma, as it runs the risk that the endotracheal tube may pass out of the airway or even into the cranium.

It is advisable to have a backup plan ready in case of difficult intubation, given the significant risk of intracranial hypertension resulting from increased CBV because of hypoxemia and hypercarbia.

Careful attention should be paid to patient positioning during surgery. A head-up posture (15–20°) is recommended, as it improves ICP without impairing CPP or CBF [25]. Finally, venous drainage from the head should not be obstructed by an overtight endotracheal tube tie or other equipment.

34.11 Maintenance of Anesthesia

There is little outcome-based evidence that any particular neuroanesthetic technique is superior. This is in part a result of the inherent difficulties of outcome-based studies in anesthesia [26] as well as of the difficulties in performing well-controlled trials in TBI. In TBI, CBF may be elevated, normal, or impaired, and no single anesthetic technique is ideal for all situations.

Propofol, which reduces CBF, may be an excellent choice for a patient who is normotensive or hypertensive and may have cerebral hyperemia. A technique that combines the use of an opioid and benzodiazepine may be preferred when postoperative mechanical ventilation is anticipated. Opioids have no direct effects on cerebral hemodynamics when ventilation is controlled.

All volatile anesthetic agents (e.g., isoflurane, sevoflurane, and desflurane) decrease $CMRO_2$ but may cause cerebral vasodilation, resulting in elevated ICP. Consequently, it has been recommended that the use of volatile agents should be avoided, owing to the risk of adversely affecting CPP. However, at less than 1 minimum alveolar concentration (MAC) concentration, their cerebral vasodilating effects are minimal, and hence low concentrations can be used in patients with TBI [27]. Nitrous oxide should be avoided as it increases $CMRO_2$ and causes cerebral vasodilation and increased ICP.

34.12 Oxygenation and Ventilation

Maintaining adequate and sustained oxygen delivery is fundamental to avoiding secondary hypoxic injury. A study of the Traumatic Coma Data Bank, a large prospectively collected dataset, demonstrated a significant and independent association between hypoxemia and increased morbidity and mortality [8]. Similarly, in patients with $SpO_2 < 60$ % without coexisting arterial hypotension, mortality was 50 % compared with 14 % in patients without hypoxemia [28]. Monitoring of arterial oxygenation is strongly recommended, and hypoxemia ($PaO_2 < 60$ mmHg or peripheral O_2 saturation <90 %) should be addressed without delay.

Mechanical ventilation should be adjusted to ensure normocarbia ($PaCO_2$, 35–45 mmHg). Hypercarbia ($PaCO_2 > 45$ mmHg) should be avoided, because it induces increases in CBF that further elevate ICP [29].

Hyperventilation results in blood and cerebrospinal fluid (CSF) alkalosis, which leads to cerebral vasoconstriction, reduced CBV, and therefore a lower ICP. Temporary hyperventilation may be vitally important for the rapid control of raised ICP and to facilitate surgical exposure during craniotomy. Hyperventilation is only a temporary measure, however, as resetting of CBF occurs within hours; CSF pH returns toward normal and rebound increases in CBF and ICP may occur when normocarbia is resumed [30]. During surgery, normocarbia should be restored before closure of the dura. In emergency situations (e.g., acute tonsillar herniation), if CPP is critically compromised by raised ICP, brief periods of hyperventilation may allow time for other measures, such as surgical evacuation of a hematoma or osmotic or barbiturate therapy, to be instituted. Excessive and prolonged hyperventilation may cause cerebral vasoconstriction, leading to worsening ischemia, and is not recommended as a routine therapy. During hyperventilation, it is preferable to monitor cerebral oxygenation and CBF by SjO_2, $PbtO_2$, or TCD ultrasonography [15].

Hyperventilation may be the least effective means of controlling elevated ICP in very severe TBI, when CO_2 reactivity may be impaired [31]. Cerebral injury is heterogeneous and, in some areas of the injured brain, critical falls in CBF may be induced by hyperventilation [32]. Hypocarbia may lower MAP and CPP, particularly if there is concomitant hypovolemia, and it may induce cardiac dysrhythmias. Hyperventilation has been associated with increased morbidity after TBI [33].

34.13 Arterial Blood Pressure

The Brain Trauma Foundation guidelines for the management of TBI recommend avoiding hypotension (SBP <90 mmHg) and maintaining CPP between 50 and 70 mmHg [34, 35]. There is a compelling evidence that hypotension causes secondary brain injury: a single episode of hypotension is strongly associated with poor outcome, independent of age, admission GCS, and pupillary function. A single episode of hypotension is associated with a twofold increase in mortality compared with matched controls without hypotension [8, 36].

Failure of cerebral autoregulation is common after TBI, but the extent to which it is impaired is variable and unpredictable. This impairment is prominent early after injury, but recovery is common within 2 weeks. Hypotension has been associated with increased morbidity and mortality [37] whether or not autoregulation is compromised. In the presence of impaired cerebral autoregulation, any degree of hypotension will produce a decrease in CBF and, although ICP may also decrease, cerebral ischemia may result. Animal models suggest that while either hypotension or acute head injury alone does not impair CBF, it may nonetheless fall significantly when both occur together [38]. Cerebral ischemia may still occur following hypotension and head injury even if autoregulation is preserved [31]. Cerebrovascular resistance will fall in response to a fall in MAP, producing an increase in CBV, a rise in ICP, and a net fall in CPP. The presence of multiple lesions on CT, subdural hematoma, maximum thickness of CT lesion, and longer duration of anesthesia increase the risk of intraoperative hypotension [39]. Hypotension during craniotomy contributes to adverse outcomes and is frequently encountered when the dura is opened [40]. This “decompression hypotension” may be predicted by low preoperative GCS, absence of mesencephalic cisterns on CT imaging, and bilateral dilated pupils [40]. Perioperative hypotension should be treated promptly.

Arterial hypertension may or may not be detrimental. It may increase CBF and CPP and reduce ischemia due, for example, to cerebral vasospasm following traumatic subarachnoid hemorrhage [41]. However, in the presence of impaired autoregulation and hyperemia, it may increase CBF, ICP, and cerebral edema and thus ultimately worsen cerebral ischemia. Both hypoperfusion and hyperperfusion must be avoided, but there may be no “ideal” MAP.

There is no evidence to support the superiority of one vasopressor over any other in the context of achieving cerebral perfusion targets. A single-center retrospective study of patients with severe TBI who received phenylephrine, norepinephrine, or

dopamine reported that phenylephrine afforded the greatest increase in MAP and CPP from baseline without altering ICP [42]. Limited data indicate that the effects of norepinephrine and dopamine on CBF velocity [43] and cerebral oxygenation or metabolism [44] are similar but that norepinephrine produces a more predictable and consistent effect [43] while dopamine may lead to higher ICP [45].

34.14 Fluid Resuscitation

Where possible, fluid resuscitation should be instituted before or during the induction of anesthesia. A greater appreciation of the dangers of hypotension and cerebral hypoperfusion has led to an emphasis on maintaining normovolemia, guided by invasive monitoring techniques including central venous pressure. Fluid overload caused by aggressive fluid therapy should also be avoided, as this may increase ICP and reduce CPP.

Warm, non-glucose-containing isotonic crystalloid solution is preferable for intravenous administration. Hypertonic saline may be beneficial because it increases intravascular fluid volume, decreases ICP, increases CPP, and reduces cerebral edema. However, a double-blind randomized controlled trial comparing hypertonic saline with standard fluid resuscitation protocols in the prehospital resuscitation of hypotensive TBI patients found no difference in neurological outcomes at 6 months [46]. The role of isotonic crystalloid solutions, however, is controversial. A post hoc analysis of Saline versus Albumin Fluid Evaluation (SAFE) study data found that resuscitation with albumin was associated with higher mortality and unfavorable neurological outcome at 24 months [47]. Hypotonic solutions should be avoided since they will reduce plasma osmotic pressure and may worsen cerebral edema.

Hematocrit should be measured regularly and maintained between 30 and 35 %, which likely gives the optimal balance between reduced blood viscosity and adequate oxygen-carrying capacity.

34.15 Hyperosmolar Therapy

Mannitol is commonly used for hyperosmolar therapy. A bolus of 0.25–1 g/kg of a 20 % solution is usually administered. Great care should be taken to avoid intravascular volume depletion and hypotension, which are deleterious to the patient with severe TBI. It is recommended that mannitol should only be administered in the presence of signs of transtentorial herniation or progressive neurological deterioration not attributable to extracranial causes [48]. In the situation of elevated ICP refractory to mannitol treatment, 7.5 % hypertonic saline administered as second-tier therapy can increase cerebral oxygenation and improve the cerebral and systemic hemodynamic status [49]. Glycerol is also routinely used to prevent intracranial hypertension and can cross the blood–brain barrier (BBB).

34.16 Targeted Temperature Management

Fever is consistently associated with worse clinical outcomes across a variety of severe brain injuries. It is a routine practice to treat fever with antipyretic drugs, surface cooling devices, or intravascular cooling devices. Nonetheless, the impact of fever control on outcome has yet to be determined. Shivering is an early response to hypothermia and can increase arterial blood pressure, ICP, respiratory effort, and oxygen consumption; it should be avoided in severe TBI. Therefore, if hypothermia is induced intraoperatively, muscle relaxation should be used and temperature corrected before relaxation is reversed. Muscle relaxation may be continued postoperatively if ongoing artificial ventilation is planned. While hypothermia may be beneficial, hyperthermia after trauma induced by loss of cerebral temperature homeostasis, drugs, or infection has a detrimental effect on outcome. In experimental models, hyperthermia increases neurological damage following cerebral ischemia. Hyperthermia should therefore be treated aggressively.

Hypothermia reduces cerebral metabolism during physiological stress, reduces excitatory neurotransmitter release, attenuates BBB permeability, and has been used for neuroprotection in TBI. Clinical evidence in terms of mortality and functional outcomes is still inconclusive. A meta-analysis reported a statistically insignificant reduction in mortality and increased favorable neurological outcome with hypothermia in TBI [50]. The benefits of hypothermia were greater when cooling was maintained for more than 48 h, but the potential benefits of hypothermia may likely be offset by a significant increase in the risk of pneumonia [50]. These observations support the previous findings that hypothermic therapy constitutes a beneficial treatment for TBI in specific circumstances. Accordingly, the Brain Trauma Foundation/American Association of Neurological Surgeons guidelines task force has issued a level 3 recommendation for an optional and cautious use of hypothermia for adults with TBI [51]. Although very early induction of hypothermia did not appear to be beneficial [52], achieving a core temperature of 35 °C before or soon after craniotomy with maintenance at 33 °C for 48 h thereafter may improve outcome in patients with intracranial hematomas [53].

34.17 Intracranial Pressure and Cerebral Perfusion Pressure

A uniform approach of maintaining ICP <20 mmHg and CPP between 50 and 70 mmHg for all patients may be overly simplistic. The Brain Trauma Foundation recommends initiating treatment when ICP exceeds 20 mmHg. While intracranial hypertension (ICP >20 mmHg) is associated with increased mortality and worse outcome, it is not clear that lowering ICP improves outcome. Indeed, ICP monitoring has not been shown to improve outcome. In 2012, a multicenter randomized trial of 324 patients with TBI conducted in Ecuador and Bolivia found that therapy

targeted to maintain ICP <20 mmHg measured using an invasive monitor was not superior to therapy based on clinical examination alone [54]. Whether these results are generalizable to more developed countries is unclear.

Numerous interventions that are routinely used to reduce ICP, such as craniectomy, hypothermia, and pharmacological coma, have not been shown to improve outcome in clinical trials. Initial therapeutic measures include elevation of the head of the bed, maintenance of the neck in a neutral position, avoidance of neck vein obstruction by endotracheal tube ties, prevention of hypercarbia, and adequate treatment of pain, agitation, fever, and seizures. A reduction in $CMRO_2$ leads to a reduction in CBF, which lowers CBV and hence ICP. In the face of decreased fuel delivery, a reduction in $CMRO_2$ might preserve the brain tissue. Reduction in $CMRO_2$ may be accomplished by induction of either a pharmacological coma or hypothermia.

If cerebral autoregulation is disturbed after TBI, then CPP will largely dictate CBF. Therefore, an attempt should be made to keep CPP within a range that prevents cerebral ischemia. The Brain Trauma Foundation currently recommends maintaining CPP between 50 and 70 mmHg. Elevating CPP above 70 mmHg with intravenous fluids and vasopressors should be avoided because of the risk of lung injury. Although lowering CPP below a critical threshold appears deleterious, raising it further does not appear to be advantageous. Optimization of CPP in the normotensive patient should begin with lowering ICP.

34.18 Management of Blood Glucose Concentration

The brain is an obligate consumer of glucose and hypoglycemia is injurious. Furthermore, hyperglycemia may be associated with a worsening of intracerebral acidosis and has been linked to poor neurological outcome after TBI. Avoidance of both hyper- and hypoglycemia is strongly recommended. Hyperglycemia can provoke or worsen secondary brain injury, leading to increased glycolysis evidenced by increased lactate to pyruvate ratio, further resulting in metabolic acidosis within the brain parenchyma, overproduction of reactive oxygen species, and ultimately neuronal cell death [55]. Tight glucose control with intensive insulin therapy remains a controversial strategy as clinical trials have not shown any benefit in terms of mortality, and there is a recognized risk of hypoglycemia [56]. Intraoperative hyperglycemia is common in adults undergoing urgent or emergent craniotomy for TBI, with up to 15 % of patients experiencing new-onset hyperglycemia, particularly those who have sustained severe TBI, have a subdural hematoma, had preoperative hyperglycemia, or are 65 years of age or older. Given the current evidence for the benefit of glucose control for TBI in the perioperative period, a reasonable target blood glucose concentration range is considered to be 80–180 mg/dl.

34.19 Coagulopathy

Brain injury leads to the release of tissue factor. Later, procoagulant factors are activated, resulting in thrombin formation and conversion of fibrinogen to fibrin. Disseminated intravascular coagulation inhibits antithrombotic mechanisms, causing imbalance of coagulation and fibrinolysis. Patients with GCS $\leq$8, Injury Severity Score $\geq$16, associated cerebral edema, subarachnoid hemorrhage, and midline shift are likely to have coagulopathy [57]. There are no guidelines for the management of coagulopathy in patients with TBI.

34.20 Summary

The multisystem sequelae of TBI and their management are summarized in Table 34.4. The perioperative period is critical for preventing secondary injuries after TBI.

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Chapter 35
Anesthetic Management of Spinal Cord Injury (Unstable Cervical Spine)

Akibumi Omi and Kazuaki Satomi

Abstract Spinal cord injury (SCI) often presents difficult anesthesia management problems. The goals of the perioperative management of SCI are to prevent further spinal cord damage and fatal complications. However, knowledge of the best treatment for neurological injury is limited. In the early management of acute injuries, it is most important to prevent secondary injury by spinal immobilization during transport, airway manipulation, and correct positioning. In addition to spinal immobilization, the current standard of anesthetic management includes support of adequate arterial oxygenation, blood pressure and spinal cord perfusion.

Keywords Spinal cord injury • Spinal immobilization • Manual in-line stabilization • Spinal cord perfusion pressure • Methylprednisolone

35.1 Introduction

Approximately 5,000 spinal cord injuries (SCIs) occur each year in Japan. These injuries affect both the young and the old, with most occurring in the 20s and 60s age groups. Injuries result from both traumatic and nontraumatic causes. Motor vehicle accidents are the most common causes of traumatic injuries. In the older group, falls are most frequently the cause, and the mortality is high, which is likely related to the patient's age and associated medical problems. Over the past 20 years, early mortality of SCI patients has decreased substantially [1–4]. At present, about 93 % of patients with cervical SCI survive the initial hospitalization [5]. This substantial reduction in mortality is due to improvement in many fields, including prehospital care, imaging of the injury, and treatment of other complications such as respiratory insufficiency, as well as the development of technology to minimize

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certain complications such as deep venous thrombosis [6, 7]. Additionally, the development of improved techniques of spine stabilization and aggressive rehabilitation programs has greatly contributed to hasten the mobilization of SCI patients. In this chapter, we review the known management methods of SCI [8, 9] and discuss anesthesia management problems.

35.2 Pathophysiology

The spinal cord can be traumatically injured by excessive flexion, extension, rotation, or axial loading [10]. Most SCIs are found in the lower cervical spine, just above the thorax, or in the upper lumbar region, just below the thorax, because the spinal cord is particularly susceptible to injury at the transition zones between the lordotic and kyphotic regions. Fracture-dislocation is the most common cause of cervical SCI. Current concepts suggest that two separate stages, initial or primary injury and, later, secondary injury, contribute to the final neurological damage of acute SCI. The primary injury occurs at the time of the traumatic insult. The secondary injury begins within minutes following the initial injury and appears to consist of a series of autodestructive processes, variably lasting for hours or days, which destabilize the neuronal membrane of surviving axons with a resultant progressive and irreversible pattern of spinal cord cystic degeneration and neurolysis. Traumatic SCI occurs upon direct force transduction to the spinal cord and initiation of the injury cascade. Subsequent to impact injury, the persistence of compression has been implied as the primary mediator of SCI. Conversely, the reversal of this compression has been a point of significant surgical controversy regarding application and timing [11]. Numerous animal models have demonstrated that decompression of the spinal cord improves recovery after SCI with recovery substantially depending on the time of decompression. In the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS) published in 2012, decompressive surgery within 24 h after the SCI was performed safely and was associated with improved neurological outcome [12].

35.3 Anesthetic Considerations

35.3.1 Preoperative Management

35.3.1.1 Spinal Immobilization

Extrication of the patient without additional injury is possible only when cervical spine immobilization is achieved. A combination of a rigid cervical collar with supportive blocks on a rigid backboard with straps and tape to immobilize the entire body is sufficient for achieving safe, effective spinal immobilization for transport

[13]. Although the application of Gardner-Wells tongs is considered the most effective technique, it is rarely a practical solution in the acute setting. As spinal immobilization devices are effective but their use can result in patient morbidity, they should be removed as soon as a definitive evaluation of the SCI and its management are accomplished.

35.3.1.2 Airway Management

Establishing and maintaining an airway is always the first priority. Supplemental oxygen should be provided once an airway is established. Lesions of the cervical spine may involve the phrenic nerves (C3-C5). Accordingly, the injuries above this level cause apnea and require patients to receive ventilator support. Loss of intercostal muscle function limits pulmonary reserve and the ability to cough. If acute respiratory insufficiency and inability to handle oropharyngeal secretions occur, immediate tracheal intubation or tracheostomy is necessary. Great care must be taken to prevent further injury during intubation. During airway maneuvers, the greatest motion of the cervical spine has been shown to occur at the atlantooccipital junction followed by the junction of the first two cervical vertebrae [14]. Before initiating intubation, the neck must be stabilized, preferably in Gardner-Wells tongs or a body jacket; if these are unavailable, a rigid cervical collar will substitute. This stabilization is carried out so as not to flex or extend the head or move it laterally during the course of tracheal intubation. If laryngoscopy and intubation are urgently indicated, the collar should be removed, and manual in-line stabilization (MILS) should be applied instead. This involves an assistant placing his or her hands on either side of the head, holding down the occiput and preventing any head rotation (Fig. 35.1). Previous reports of spinal cord damage following direct laryngoscopy in patients with unstable cervical spine injuries were based on weak coincidental evidence [15]. Therefore, direct laryngoscopy with MILS is now accepted as a safe technique for managing the airway in patients with potential cervical spine injuries. MILS may be effective, but it also makes direct laryngoscopy more difficult. The gum elastic bougie is a useful adjunct for direct laryngoscopy. Rigid indirect videolaryngoscopy may substitute for direct laryngoscopy. Supraglottic devices are extremely useful in cases of failed or difficult intubation. Some clinicians prefer awake fiber-optic intubation (nasotracheal or orotracheal); however, this requires topicalization of the airway, which causes coughing and potential injury to the spinal cord and high incidences of epistaxis, pulmonary aspiration, and laryngospasm. There are several intubation techniques, but no one technique has proved to be superior to the others. Clearly, the expertise and preferences of individual clinicians affect the choice of technique, together with the suitability of the technique and its risks of complications in a given patient.

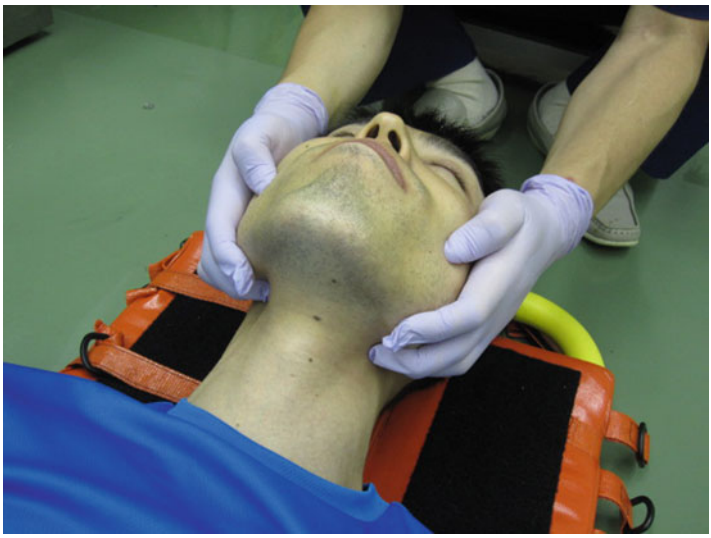

Fig. 35.1 Manual in-line stabilization

35.3.1.3 Fluid Resuscitation

Acute injury of the upper spinal cord can cause spinal shock, typically lasting 1–3 weeks, which is a condition characterized by the loss of sympathetic tone in the capacitance and resistance vessels below the level of the lesion, resulting in hypotension, bradycardia, areflexia, and gastrointestinal atony. Hypotension in these patients requires aggressive fluid therapy. However, fluid infusion alone should not be used to correct the hypotension associated with spinal shock because the volumes required are usually large and will usually aggravate any associated pulmonary compromise. Since such attempts usually result in fluid overload, careful administration of vasopressors is more preferable for restoring vasomotor tone and subsequently blood pressure.

35.3.1.4 Neurological Examination

The degree of physiological derangement following SCI is proportional to the spinal level of the lesion. SCI at the T1 level may be paraplegic to some degree, whereas fractures above C5 may result in quadriplegia and loss of phrenic nerve function. Injuries between these two levels result in variable loss of motor and sensory functions in the upper extremities. The American Spinal Injury Association (ASIA) has recently provided a standardized classification system of SCI in terms of spinal level (right and left, motor and sensory) and functional grade (Fig. 35.2). This system classifies the level of injury into five grades, A–E, with E indicating

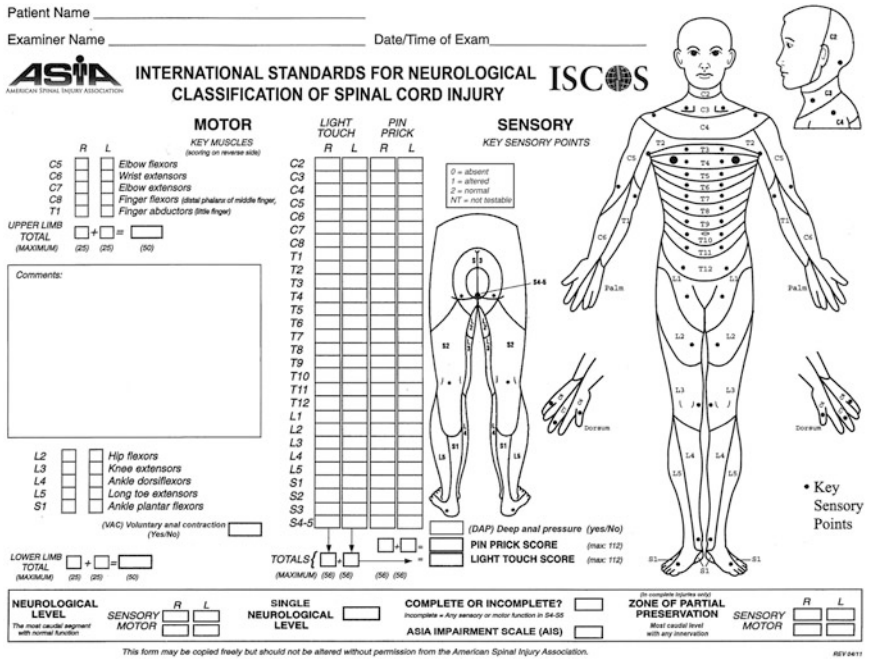

Fig. 35.2 American Spinal Injury Association. International Standards for Neurological Classification of Spinal Cord Injury

normal spinal cord function. The classification system requires 10 muscle groups and 28 key sensory points to be graded. This revised system allows the precise documentation of perioperative motor and sensory deficits, which is essential for accurate communication between clinicians.

35.3.1.5 Associated Conditions

Venous Thromboembolism

The incidence of deep vein thrombosis in SCI patients has been reported to be as high as 95 % and is clinically relevant in 25–35 % of patients. Acute pulmonary embolism is one of the leading causes of death in this group of patients. Venous thromboembolism (VTE) is predominantly due to the loss of vasomotor tone and prolonged immobility. For this reason, early administration of VTE prophylactics (within 72 h) is recommended. Vena cava filters are recommended for patients in whom anticoagulation therapies fail or who are not candidates for anticoagulation therapy, mechanical devices, or both [16].

Autonomic Hyperreflexia

Autonomic hyperreflexia should be expected in non-acute SCI patients with lesions above T7, and this can be treated by surgical manipulations. Cutaneous or visceral stimulation below the level of injury can induce intense autonomic reflexes. Sympathetic discharge produces hypertension and vasoconstriction below the transection and baroreceptor-mediated reflex bradycardia and vasodilation above the transection. Severe hypertension can cause pulmonary edema, myocardial ischemia, or cerebral hemorrhage and should be treated aggressively. Regional anesthesia and deep general anesthesia are effective in preventing hyperreflexia. Vasodilators and α-adrenergic blocking agents should also be used as appropriate.

35.3.1.6 Methylprednisolone

Methylprednisolone (MP) is the most widely used pharmacotherapeutic agent for the prevention or treatment of the secondary injury cascade in SCI. It exerts its protective effects by decreasing lipid oxidation, stabilizing the cell membranes, enhancing spinal cord blood flow, and decreasing vascular permeability and edema. To date, three large clinical trials termed the National Acute SCI Study (NASCIS) have been completed using MP and other agents to treat acute, non-penetrating SCI [17–20]. Based on the NASCIS series, the current recommendations are as follows: (a) the 24-h regimen (a bolus dose of 30 mg/kg over 1 h, followed by a continuous infusion of 5.4 mg/kg/h for 23 h) for cases in which treatment is initiated at less than 3 h from the time of injury, (b) the 48-h regimen (a bolus dose of 30 mg/kg over 1 h, followed by a continuous infusion of 5.4 mg/kg/h for 47 h) for cases in which treatment is initiated at 3–8 h after the time of injury, or (c) no MP treatment for cases in which more than 8 h have passed from the time of injury. Although the use of MP is often recommended, there remains notable controversy regarding the statistical significance of the therapeutic benefits of MP treatment, as well as various safety concerns. The American Association of Neurological Surgeons and the Congress of Neurological Surgeons (AANS/CNS) Joint Guidelines Committee concluded that there is no consistent or compelling medical evidence to justify the administration of MP for acute SCI. High-dose MP treatment is associated with harmful side effects including infection, respiratory compromise, gastrointestinal hemorrhage, and death. Therefore, MP should not be routinely used in the treatment of patients with acute SCI [21].

35.3.2 Intraoperative Management

35.3.2.1 Induction

Regional anesthesia is usually impractical and inappropriate for unstable patients with SCI. If time permits, hypovolemia should be at least partially corrected before the induction of general anesthesia. Fluid resuscitation and transfusion should continue throughout the induction and maintenance of anesthesia. Studies suggest that even after adequate fluid resuscitation, the induction dose requirements for propofol are greatly reduced in patients with major trauma. Even such drugs as ketamine and nitrous oxide, which normally indirectly stimulate cardiac function, can exhibit cardiodepressant properties in patients who are in shock and already have maximal sympathetic stimulation. If the patient is not intubated, the same principles of airway management described above should be followed in the operating room. It is important to discuss the severity of the surgical lesion and the planned method of intubation with the surgeon before proceeding. Regarding the tracheal tube, the use of a wire-reinforced tube should be considered as it allows for maximal bending of the tube during removal from the surgical field, and it will not be compressed by the retractor. A wire-reinforced tube is also desirable when the surgical procedure is to be performed in the prone position. Succinylcholine is reportedly safe to use during the first 48 h following SCI, but it should be avoided between 3 days and 9 months following SCI, because of the risk of hyperkalemia caused by the excessive release of potassium secondary to the increase in acetylcholine receptors outside the neuromuscular synaptic cleft [22]. Non-depolarizing neuromuscular blocking agents should be considered as an alternative.

35.3.2.2 Maintenance

Blood Pressure Management

The current standard of anesthetic management includes support of adequate arterial oxygenation and spinal cord perfusion pressure. Spinal cord perfusion pressure is the difference between mean arterial pressure (MAP) and cerebrospinal fluid pressure. The spinal cord is very vulnerable to ischemic injury because of its relatively high oxygen consumption and dependence on aerobic glucose metabolism. Interruption of spinal cord perfusion or metabolic substrate (glucose) availability or severe hypoxemia rapidly results in functional impairment. Similar to the brain, the spinal cord normally tolerates wide swings in blood pressure with little change in blood flow. Autoregulation of blood flow in the normal spinal cord occurs within the same MAP range as in the brain, namely, between approximately 50–150 mmHg [23–25]. Compounding the global systemic dysfunction is the loss of this protective regional autoregulation in neuronal tissues involved in acute SCI. Experimentally, it appears that autoregulation of blood flow is intact during the

initial 60–90 min after SCI, but is lost coincidently with the onset of ischemia [26]. However, there is little evidence regarding a target blood pressure and the duration of support required to improve outcomes in SCI. In the updated guidelines by the AANS/CNS Joint Guidelines Committee, the maintenance of MAP at 85–90 mmHg after acute SCI for 7 days is recommended [27].

Blood and Fluid Requirements

The ideal fluid management in SCI patients remains unknown. When patients are placed in the prone position, excessive fluid administration is associated with marked edema, cardiac failure, electrolyte abnormalities, coagulopathy, and prolonged duration of postoperative intensive care unit stay [28]. Hypotonic crystalloids may exacerbate cord swelling and should be avoided. Cardiac output monitoring devices might improve perioperative fluid administration and reduce the morbidity associated with excessive fluid administration. Blood transfusion is usually necessary when there has been extensive bony decompression and fusion, particularly in thoracolumbar spinal surgery. If large blood loss is anticipated, an intraoperative autologous blood recovery system should be considered to reduce the need for homologous blood transfusion. In the absence of severe cord compression, modest controlled hypotension might be helpful to decrease blood loss, although there is little evidence to support its practice [29].

Monitoring

In addition to standard monitors, invasive monitoring can be helpful in guiding fluid resuscitation. An arterial catheter is essential to monitor blood pressure and to measure arterial blood gas. A central venous pressure (CVP) catheter is recommended for the infusion of vasoactive drugs and for the monitoring of CVP. Body temperature should be monitored carefully, particularly in patients with chronic transections above T1, because chronic vasodilation and loss of normal reflex cutaneous vasoconstriction predispose patients to hypothermia.

Monitoring of Evoked Potentials

Indications for intraoperative monitoring of evoked potentials (EPs) include surgical procedures associated with possible neurological injury. Persistent absence of EPs is predictive of postoperative neurological deficit. However, EPs are also altered by many variables other than neurological damage. The effect of anesthetics on EPs is complex and cannot easily be summarized. In general, EPs are successively more affected by volatile inhalational agents, barbiturates, nitrous oxide, benzodiazepines, propofol, and opioids. Monitoring of motor-evoked potentials may require monitoring of the level of neuromuscular blocking. For this, the

usual method of anesthesia is total intravenous anesthesia, generally using continuous infusions of propofol and remifentanil, whereas volatile agents should be avoided or used at a constant low dose.

35.3.3 Postoperative Management

35.3.3.1 Complications

Airway Obstruction

When cervical fusion has been performed and the patient has been returned to a halo device or body jacket, it is desirable to leave the tracheal tube in place until the patient is fully awake, responding to commands, and able to manage his or her own airway. Airway obstruction usually occurs because of soft tissue edema or retraction injury to the recurrent laryngeal nerve. A useful method to test for airway patency is to deflate the cuff of the tracheal tube and determine whether the patient is able to breathe around the tube as well as through it. If there is any doubt about adequacy of the airway, it is prudent to consider inserting an airway exchange catheter (AEC) through the tracheal tube before its removal. AECs are well tolerated and can be left in place until one is confident that no further airway compromise will occur. This catheter will provide a conduit for immediate reinsertion of a tracheal tube if airway obstruction from early swelling, bleeding, or hematoma formation should occur. In an emergency, tracheostomy or cricothyrotomy can be lifesaving in patients with marked airway obstruction.

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Part IX
Anesthetic Management: Specific Situations in Neuroanesthesia

Chapter 36
Anesthesia for Spinal Surgery

Mishiya Matsumoto and Kazuyoshi Ishida

Abstract Most patients undergo spinal surgery for functional improvement and so find any ensuing deterioration in the quality of life unacceptable. Therefore, sufficient assessment and circumspect informed consent are necessary in performing such surgery in patients with complications likely to cause such problems. In anesthetic management, tracheal intubation strategies are important in patients with cervical spine lesions, and modification of the anesthetic protocol is necessary for electrophysiological monitoring of the spinal cord. Segment diagnosis based on accurate recordings of evoked potentials and neurologic and imaging findings enables more selective surgery. Moreover, the importance of intraoperative multimodal monitoring of spinal cord function increases when intraoperative damage to the spinal cord parenchyma is predicted. In addition, it is important to prepare for occasional massive bleeding. Among several measures tested to reduce bleeding, a large dose of tranexamic acid, an antifibrinolytic agent, has been found to be effective. Although postoperative visual loss occurs only very rarely, it is difficult to alleviate once developed. Furthermore, visual impairment seriously hinders rehabilitation, so elucidating the underlying mechanism of its onset is crucial. There is no doubt that close cooperation between surgeons and anesthetists is crucial.

Keywords Spine surgery • Wake-up test • Somatosensory evoked potential (SEP) • Motor evoked potential (MEP) • Visual impairment

36.1 Introduction

Most patients undergo spinal surgery for functional improvement and so find any ensuing deterioration in the quality of life unacceptable. Therefore, sufficient assessment and circumspect informed consent are necessary in performing such surgery in patients with complications likely to cause such problems. In anesthetic management, tracheal intubation strategies are important in patients with cervical

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spine lesions, and modification of the anesthetic protocol is necessary for electrophysiological monitoring of the spinal cord. In addition, it is important to prepare for occasional massive bleeding, as well as postoperative visual loss (POVL), even though the latter occurs only very rarely. There is no doubt that close cooperation between surgeons and anesthetists is crucial.

36.2 Cervical Spine Lesions and Tracheal Intubation

In the spine, the structure of the first cervical vertebra (atlas) and the second cervical vertebra (axis) is unique. For example, the anterior part of the odontoid process of the axis is supported by the bone (anterior arch of the atlas), while the posterior part is supported by only the ligament (transverse ligament of the atlas). Although this structure is suited to the rotary movement of the spine in the horizontal plane, it cannot support drastic movements in the sagittal plane, and laxity of the transverse ligament of the atlas can lead to atlantoaxial subluxation. It is well known that patients with rheumatoid arthritis are prone to have atlantoaxial subluxation when inflammation spreads to the transverse ligament of the atlas. In addition, people with Down syndrome are known to have laxity of the transverse ligament. This means that the possibility of an asymptomatic atlantoaxial subluxation cannot be ruled out in such individuals, and, thus, tracheal intubation should be performed with great care.

The physiological sagittal range of motion (ROM) is largest in the atlantooccipital joint. This is also large in the atlantoaxial joint, and the two joints together give an ROM of 45. Large movements in these two joints were also observed during tracheal intubation under direct vision [1]. This means that it is almost impossible to perform tracheal intubation under direct vision when the region from the occipital bone to the axis is fused (e.g., patients with rheumatoid arthritis). Conversely, one- or two-level fusion below axis will not affect tracheal intubation under direct vision, provided there are no other constraints.

Manual in-line stabilization and cervical traction using Gardner–Wells tongs were tested in fresh corpses to investigate whether they can prevent cervical movement during tracheal intubation in patients with cervical spine instability [2]. The study examined the body of both vertebrae before and after artificially damaging the posterior longitudinal ligament between the fourth and fifth cervical vertebrae and showed that manual in-line stabilization has almost no preventive effect on extension [2]. Thus, when treating patients with cervical spine instability, extreme care is needed during tracheal intubation under direct vision, even with manual in-line stabilization. On the other hand, cervical traction using Gardner–Wells tongs significantly inhibits extension of the atlantooccipital joint, but the risk of spinal injury due to cervical traction itself should be taken into account [2]. Whether the differences in the movements of the cervical vertebrae were attributed to the type of laryngoscope used (video or conventional laryngoscope)

was examined in several studies [3–5], but the findings were variable, probably because of differences in the devices.

Patients with severe cervical instability often wear a halo brace to immobilize the cervical spine. In such patients, performing tracheal intubation is impossible under direct vision and requires a bronchofiberscope. Sufficient time should be spent to explain the necessity and importance of using a bronchofiberscope for tracheal intubation before operation, and patients are likely to provide cooperation.

36.3 Spinal Function Monitoring

36.3.1 Wake-Up Test

The wake-up test is an intraoperative method for assessing whether patients can move their lower limbs and knee joints after awakening from shallow anesthesia. It may be the most definitive method for spinal function monitoring, but there are some disadvantages. Firstly, sufficient comprehension is necessary, and therefore it is difficult to perform in small children and in the elderly with cognitive dysfunction. Secondly, the test can be performed only when patients are awake. Once awake, blood pressure tends to be higher, and its decline upon the introduction of deep anesthesia may affect spinal cord function. Thirdly, it is possible that excessive movements themselves while awake can injure the spinal cord and that excessive forced breathing can cause air embolism.

The wake-up test can be performed only when definitive results are not obtained by intraoperative electrophysiological monitoring of the spinal cord.

36.3.2 Electrophysiological Monitoring of the Spinal Cord

In spinal surgery, electrophysiological monitoring is performed for segment diagnosis and spinal function monitoring. Identifying a culprit lesion has become relatively easy with advances in diagnostic imaging, but electrophysiological segment diagnosis, when the spine is exposed, enables more selective pressure relief. Furthermore, intraoperative spinal function monitoring indicates operative stress. There are three types of evoked potentials depending on the recording site: somatosensory evoked potentials (SEP) recorded on the scalp, spinal cord evoked potentials recorded at the site near to the spinal cord, and evoked electromyogram recorded in the skeletal muscle. Spinal cord evoked potentials are further divided into three types depending on the stimulation sites: transcranial, spinal cord, and peripheral nerve stimulation.

36.3.2.1 SEP

SEP records evoked potentials in response to peripheral nerve stimulation on the scalp. Depending on the latency, it is further classified into three types: short-latency SEP (SSEP) with latency of 50 ms, intermediate-latency SEP with latency of 50–100 ms, and long-latency SEP with latency $\geq$100 ms. SSEP is used for monitoring during spinal surgery and measures mainly the transmission of action potentials from the periphery to the somatosensory area through the conduction path of tactile and pressure sensations (Aβ peripheral nerve fibers). For example, upon stimulation of the left median nerve, positive waves P9, P11, and P13 are recorded at a peak latency of 9, 11, and 13 ms, respectively, and negative waves of N18 and N20 at a peak latency of 18 and 20 ms, respectively, by using an extracranial reference electrode and a recording electrode placed on the C3' (2 cm posterior to C3 in the international 10–20 system). It is considered that P13 represents the potentials occurring in the brainstem before the formation of synapses by ascending Aβ peripheral nerve fibers in the dorsal column. P13 is unaffected by anesthesia and thus serves as a good indicator of the monitoring of spinal cord function. P31 in response to stimulation of the posterior tibial nerve is comparable to P13 upon stimulation of the left median nerve. However, because of its small amplitude, antinoise measures are necessary, and the addition number of 200–350 (the minimum of 1 min of recording) is required.

36.3.2.2 Spinal Cord Evoked Potentials

Spinal Cord Evoked Potentials in Response to Transcranial Stimulation

For segment diagnosis, spinal cord evoked potentials upon stimulation of the area adjacent to the motor cortex (C3–C4) will be simultaneously measured using 6 electrodes, each of which are inserted into the yellow ligament between vertebra (from C2 to T1) in the operative area. Conditions of repetitive stimulation (20–100 times) are 150–300 V and around 5 Hz.

Figure 36.1 (upper left) shows typical waveforms. It is thought that direct stimulation of subcortical pyramidal tract neurons evokes direct (D) waves, while excitation of pyramidal tract neurons via intracortical synapses evokes indirect (I) waves. While I waves are affected by anesthetic agents and not recordable under general anesthesia, D waves are less affected, and recording them is relatively easy. Although the area adjacent to the motor cortex is electrically stimulated, transcranial stimulation does not necessarily stimulate the pyramidal tract selectively, and other conduction paths are likely to be involved.

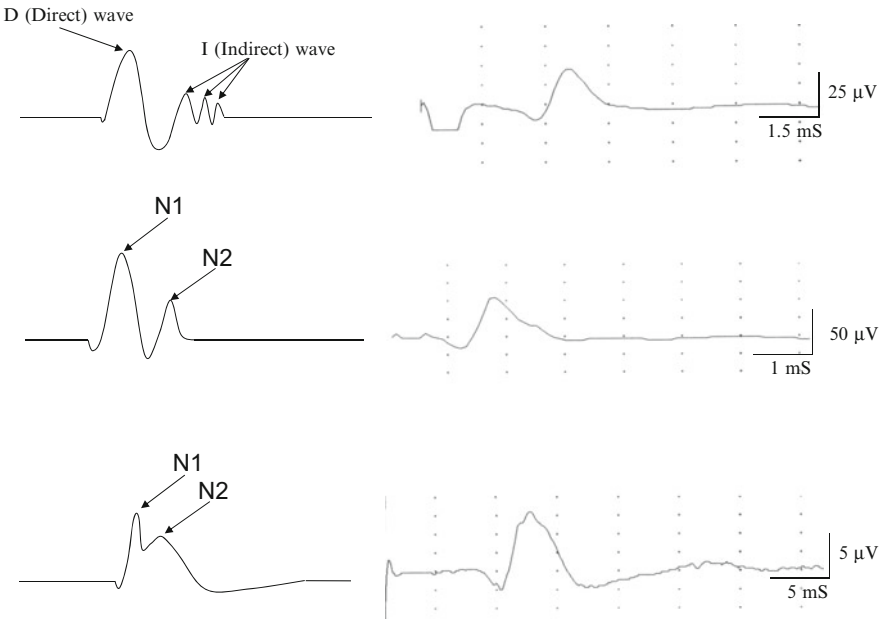

Fig. 36.1 Spinal cord evoked potentials
The *left* part shows the corresponding schema, while the *right* part shows the recorded waveforms. *Top*: transcranial stimulation. *Middle*: spinal cord stimulation. *Bottom*: peripheral nerve stimulation (Matsumoto [16])

Spinal Cord Evoked Potentials in Response to Spinal Stimulation

For segment diagnosis in the cervical spinal cord, a stimulation electrode catheter is inserted into the epidural space at the caudal part of the thoracic segment from the operative field, and spinal cord evoked potentials are simultaneously measured using 6 electrodes, each of which are inserted into the yellow ligament between vertebra (C2–T1) in the operative field. The area showing amplitude changes is considered a culprit lesion. On the other hand, for monitoring of spinal cord function, a stimulation electrode is inserted into the caudal part or cranial part of the operative field, while the corresponding recording electrode is inserted into the opposite part. Supramaximal stimulation (5 Hz) was repeated 20–100 times.

Typically, two negative waves are observed: N1 indicates a potential conducted through the tractus spinocerebellaris in the dorsolateral funiculus, while N2 indicates a potential, which represents deep sensation function and is conducted through the posterior funiculus (Fig. 36.1, middle, left panel). Sometimes, recorded waveforms do not show N2 waves. Of note, the fact that the direction from the stimulation site to the recording site is in the descending direction does not mean stimulation goes through the pyramidal tract. There are no synapses between the stimulation site and the recording site, and, thus, the effect of anesthetic agents is negligible.

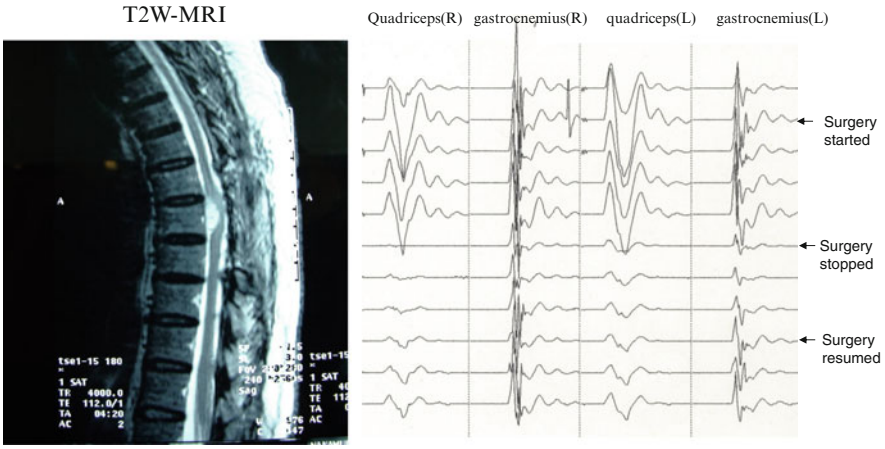

Fig. 36.2 MEP monitoring
Changes in MEP during surgical removal of meningioma (T7-9)
MEP amplitude decreased drastically on invasion of the spinal cord. Surgery was temporarily stopped, but resumed after the recovery of amplitude was confirmed. The amplitude at the end of surgery was less than half of that at the start of surgery, but postoperative motor function of the lower extremities was not lower than the preoperative level. Left: MRI T2-weighted contrast image (Matsumoto [16])

Spinal Cord Evoked Potentials in Response to Peripheral Nerve Stimulation

The median nerve or ulnar nerve is used for stimulation when the upper extremities are preferred, while the posterior tibial nerve is used when the lower extremities are preferred. Derivation at the intravertebral space where the peripheral nerves enter the spinal cord typically yields two negative waves (N1 and N2) (Fig. 36.1, bottom, left panel). N1 waves represent action potentials traveling through the conduction path via the dorsal cord and are called conductive potentials. On the other hand, N2 waves are thought to be the postsynaptic component in the conduction path in the posterior horn of the spinal cord and are called segmental potentials. The median nerve, ulnar nerve, and posterior tibial nerve enter the C6–T1, C8–T1, and L4–S2 myelomeres, respectively, and segmental and conductive potentials can be recorded at these sites. It is noteworthy that myelomeres and the intravertebral spaces do not match. A lack of N2 waves, which should be recorded at particular intravertebral spaces, suggests an injury to the posterior horn. N1 waves represent conductive potentials that do not involve synapses, and, thus, the effect of anesthetic agents is negligible.

36.3.2.3 Motor Evoked Potential (MEP)

MEP with transcranial stimulation (train of 3–5, 400–600 V, 500 Hz) is used for spinal function monitoring. The insertion position of a stimulating electrode is the

area adjacent to the motor cortex (C3–C4). MEP is easily affected by general anesthesia, and it was used to be difficult to perform under general anesthesia when single pulse stimulation was applied. The development of the train stimulation method enabled MEP recording under the influence of general anesthesia. Upon train stimulation with a 2-ms interval, which is shorter than the duration of excitatory postsynaptic potentials (7–10 ms), postsynaptic potentials which are easily suppressed by anesthetic agents accumulate to reach the threshold potential. Preferred derivation sites are the abductor digiti minimi muscle (C8), quadriceps muscle (L4), gastrocnemius muscle (S1), and flexor hallucis brevis muscle (S1), because they are convenient for recording both innervations and electromyograms.

MEP indicates the function of the pyramidal tract, which is linked directly to postoperative rehabilitation and is thus the most important aspect in spinal function monitoring. MEP recording does not require repetitive stimulation and consequently the minimum interruption of surgery. In spite of such advantages, it is easily affected by anesthetic agents and muscle relaxants, so anesthesia with propofol and narcotics with a minimal muscle relaxant effect are recommended. Surgery is usually interrupted when the amplitude of MEP is reduced by greater than 70 %. However, there is no consensus on the level of amplitude recovery allowing the restart of surgery, so the decisions are left to individuals depending on the circumstances. Recording of MEP in patients with considerable motor paralysis is difficult. In such patients, albeit not ideal, surgery may be performed only with the recording of spinal cord evoked potentials in response to spinal cord stimulation, but this previously resulted in worsening of motor impairment [6]. Kakimoto et al. [7] reported that amplitudes of MEP increased with tetanic stimulation of dominant nerves of recording muscles prior to the MEP recording: it is worth investigating the use of post-tetanic MEP when MEP recording is difficult due to motor impairment.

36.3.2.4 Effects of Anesthetic Agents on Evoked Potentials

In principle, anesthetic agents affect evoked potentials, albeit to different degrees, when synapses exist between the stimulation and recording sites. Among evoked potentials, MEP is most suppressed by anesthetic agents, but the levels of effects vary among agents: volatile anesthetics and barbiturates have a strong inhibitory effect; nitrous oxide, propofol, and benzodiazepine have intermediate effect; narcotics have weak effect; and ketamine have no effect [8] (Table 36.1). For example, when monitoring the spinal function under anesthesia with propofol and a narcotic, careful management, such as maintenance of the intracerebral propofol concentration at a constant level and operative stress management with a narcotic, is necessary.

Table 36.1 Effects of anesthetics on myogenic motor evoked potentials (MEPs)

Inhalational anesthetics	
Isoflurane	↓↓↓
Sevoflurane	↓↓↓
Nitrous oxide	↓↓
Intravenous anesthetics	
Barbiturate	↓↓↓
Benzodiazepine	↓↓
Propofol	↓↓
Ketamine	–
Fentanyl	– or ↓

Degree of suppression of MEPs:↓↓↓(severe); ↓↓(moderate); ↓(mild); –(no suppression)
(Kawaguchi [8])

36.3.2.5 Multimodality Monitoring

In segment diagnosis of lesions of the spinal cord and also in monitoring of spinal cord function, it is necessary to employ recordings of multiple types of evoked potentials. Recording of spinal cord evoked potentials appears to be useful for segment diagnosis of lesions. The use of stimulation in three ways, transcranial stimulation in the descending direction, spinal cord stimulation in the ascending direction, and peripheral nerve stimulation for recording of segmental potentials, will improve accuracy (Fig. 36.3) and also enable estimation of the range of injury on the cross section of the spinal cord (Fig. 36.4). For spinal cord function monitoring, recording of MEP closely associated with quality of life is most important. It is also important to monitor dorsal cord function associated with the position sense of all four extremities in addition to tactile and pressure sensations. Therefore, recording of spinal cord evoked potentials in response to spinal cord stimulation, as well as MEP, is desirable.

36.4 Measures Against Intraoperative Bleeding

Massive bleeding can occur during spinal surgery when the operative field is wide. In particular, epidural venous plexus hemorrhage is often difficult to stop because the bleeding site is near to the spinal cord parenchyma. Factors associated with the high possibility of blood transfusion are age $\geq$50 years; preoperative hemoglobin level $<$12 g/dL, fusion of more than two levels; and transpedicular osteotomy [9]. Interventions to reduce bleeding include: controlled hypotensive anesthesia, change of positions to release abdominal pressure, and administration of antifibrinolytic agents. On the other hand, interventions to reduce the volume of blood transfusion include preoperative autologous donation, intraoperative blood salvage, and intraoperative hemodilution [10].

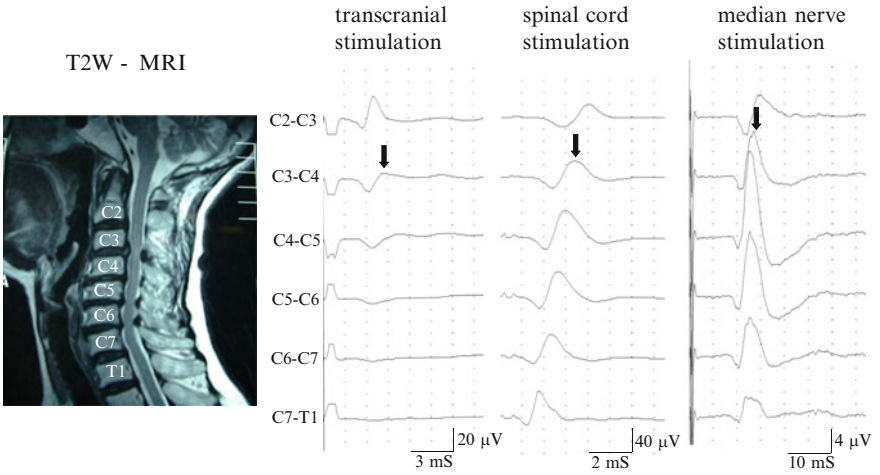

Fig. 36.3 Segment diagnosis based on spinal cord evoked potentials
A case of cervical spondylotic myelopathy. *Left*: MRI T2-weighted contrast image. Sudden decreases in amplitudes (*arrows*) were observed at C3–4, regardless of the site of stimulation (transcranial, thoracic segment of the spinal cord, and median nerve). These findings in combination with MRI findings indicate a culprit lesion in the C3–4 region (Matsumoto [16])

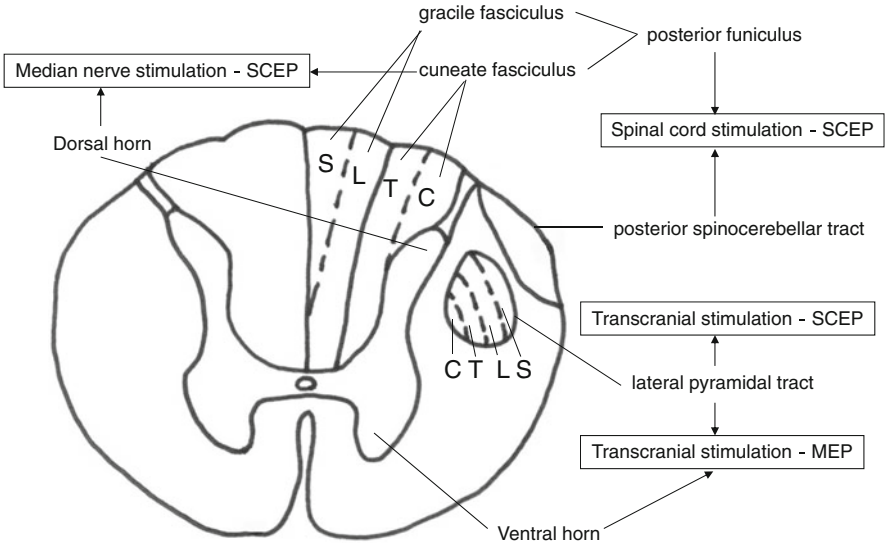

Fig. 36.4 Relationship between conduction paths of the cervical vertebrae (cross-sectional view) and evoked potentials
Types of evoked potentials and corresponding conduction paths are shown. The range of injury on the cross section of the spinal cord can be estimated on the basis of the waveforms of evoked potential recording (Matsumoto [16])

Controlled hypotensive anesthesia is safe to provide to young patients as long as mean arterial pressure is maintained in a range of 50–60 mmHg: it is also important to maintain a sufficient volume of circulatory blood. On the other hand, blood pressure should be maintained at satisfactory levels on the basis of the risk–benefit balance when giving controlled hypotensive anesthesia to elderly patients with cardiovascular complications. Unfortunately, whether controlled hypotensive anesthesia reduces the bleeding volume or not remains unclear [10]. Meanwhile, a large dose of tranexamic acid, an antifibrinolytic agent, reportedly reduces intraoperative bleeding without complications such as hypercoagulation [10, 11].

36.5 Visual Impairment After Spinal Surgery in the Prone Position

Visual impairment after spinal surgery in the prone position, which has an estimated incidence of about 0.03 % [12], is a considerable concern. Obstruction of the central retinal artery and ischemic optic neuropathy are the causes of visual impairment: according to the American Society of Anesthesiologists, 11 % (10 cases) and 89 % (83 cases) of cases were due to the former and latter cause, respectively [13]. The age at onset was 46 ± 13 years in patients with the former and 50 ± 14 years in patients with the latter: patients with ischemic optic neuropathy included a 10-year-old boy [13]. It is likely that increases in intraocular pressure by eyeball compression cause obstruction of the central retinal artery, and to date, only unilateral cases have been reported.

Ischemic optic neuropathy can be the anterior type or the posterior type, depending on whether the site of circulation impairment is the distal side or the proximal side of the lamina cribrosa sclerae, respectively. Ischemic optic neuropathy occurring after spinal surgery is the posterior type. Although the detailed mechanisms are unclear, impairment of the intraorbital optic nerve, which receives blood from the posterior ciliary arteries and the central artery of the retina branched off from the ophthalmic artery, is a likely cause of posterior ischemic optic neuropathy (Fig. 36.5) [14].

Characteristically, patients do not present abnormal findings of eyeground shortly after the onset of posterior ischemic optic neuropathy. All cases reported by the American Society of Anesthesiologists have been bilateral cases (male to female ratio: 7:3), and 68 % of them experienced total loss of sight at the time of onset and showed poor recovery. Factors associated with posterior ischemic optic neuropathy include male, obesity, use of a Wilson spinal frame, duration of anesthesia, volume of bleeding, and low usage rate of colloidal transfusion solutions [15]. Bleeding of 1,000 mL or more and anesthesia longer than 6 h are also associated with increased risk [13]. Special preventive measures do not exist, and, thus, provision of disease information may only heighten the sense of fear.

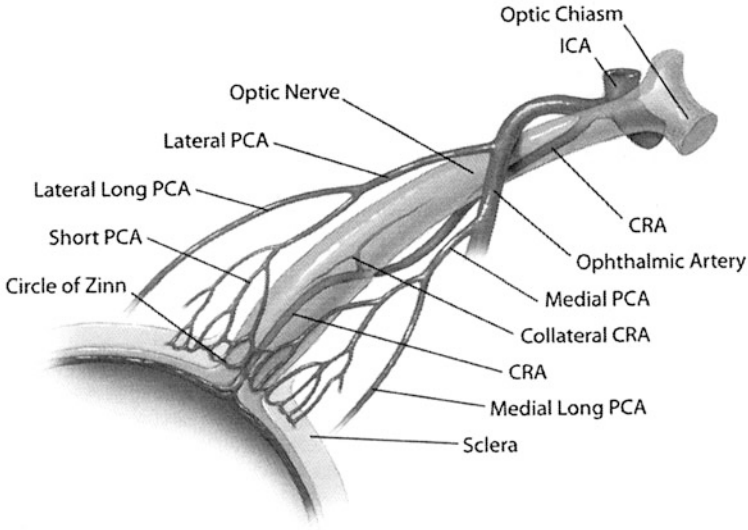

Fig. 36.5 Blood flow to the eye
The majority of the blood supply is provided by the ophthalmic artery, a branch of the internal carotid artery (ICA), posterior ciliary artery (PCA), and central retinal artery (CRA) (Kitaba et al. [14])

Nevertheless, it is necessary to inform patients of the risk of blindness when lengthy surgery and massive bleeding are expected.

36.6 Summary

Early rehabilitation after low invasive surgery is of particular interest in aging societies. In the field of spinal surgery, segment diagnosis based on accurate recordings of evoked potentials in combination with neurologic findings and image diagnosis enables more selective surgery. Moreover, the importance of intraoperative multimodality monitoring of spinal cord function will increase when damage to the spinal cord parenchyma is expected during surgery. Among several measures tested to reduce bleeding, a large dose of tranexamic acid, an antifibrinolytic agent, is considered effective. The incidence of visual impairment after spinal surgery in the prone position is low, but it is difficult to alleviate conditions once developed. Furthermore, visual impairment seriously hinders rehabilitation, so elucidating the mechanisms of onset is crucial.

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Chapter 37
Anesthesia for Epilepsy Surgery

Mitsuru Ida and Masahiko Kawaguchi

Abstract Surgical procedures for patients with intractable epilepsy include curative surgery and palliative surgery. It is important to identify the precise location of the seizure focus in resection surgery. Sevoflurane is suitable for producing an epileptic spike. However, when using motor evoked potential and somatosensory evoked potential, propofol is prefer to sevoflurane. Placement of vagal nerve stimulation has been conducted in intractable epilepsy. Cardiac complications such as bradycardia and asystole require attention.

Keywords Epilepsy • Interaction • Vagal nerve stimulation

37.1 Introduction

Epilepsy is a chronic noncommunicable disorder of the brain that affects people of all ages. About 50 million people worldwide have epilepsy [1]. Antiepileptic drugs have been improved, and approximately 70 % to 80 % patients have good control. However, approximately 20 % become drug resistant. In intractable epileptic cases, surgical procedures are considered. In this chapter, the author describes perioperative considerations in epileptic surgery.

37.2 General Preoperative Considerations

Anti-epileptics should be used until the day of surgery when non-epileptic surgery is scheduled to avoid perioperative seizure. However, patients do not have to take anti-epileptics when they are scheduled for epileptic surgery to detect the precise localization of the seizure focus. Each drug has side effects such as hepatic disorders, kidney disorder, and anemia (Table 37.1). Preoperative laboratory examinations should be done. Gingival overgrowth is a common adverse effect of

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Table 37.1 Antiepileptic drugs and side effects

Drug	Idiosyncratic reaction	Neurotoxic side effect	Long-term side effect
Carbamazepine	Eruption, liver disorder, pancytopenia, thrombocytopenia, SJS, TEN, DIHS	Diplopia, nystagmus, dizziness, ataxia, drowsiness, nausea, hyponatremia, cardiac conduction disturbance, heart failure, cognitive dysfunction	Osteoporosis
Clobazam	Rare	Drowsiness, ataxia, behavior disorder	
Clonazepam	Rare	Drowsiness, ataxia, behavior disorder	
Ethosuximide	Eruption, pancytopenia	Drowsiness, behavior disorder	
Gabapentine	Rare	Dizziness, ataxia, drowsiness, myoclonus	Weight gain
Lamotrigine	Eruption, liver disorder, pancytopenia, thrombocytopenia, SJS, TEN, DIHS	Dizziness, drowsiness, diplopia	
Levetiracetam	Rare	Drowsiness, behavior disorder	
Phenobarbital	Eruption, liver disorder, pancytopenia, thrombocytopenia, SJS, TEN, DIHS	Dizziness, ataxia, cognitive dysfunction, drowsiness	Osteoporosis
Phenytoin	Eruption, liver disorder, pancytopenia, thrombocytopenia, SJS, TEN, DIHS	Diplopia, nystagmus, dizziness, ataxia, drowsiness, cardiac conduction disturbance, peripheral neuropathy, heart failure, asterixis	Cerebellar atrophy, hypertrichosis, osteoporosis, gingival enlargement
Primidone	Eruption, liver disorder, pancytopenia, thrombocytopenia, SJS, TEN, DIHS	Dizziness, ataxia, drowsiness	Osteoporosis
Sodium valproate	Pancreatitis, liver disorder	Thrombocytopenia, tremor, hyponatremia, ammonemia, parkinson syndrome	Weight gain, alopecia, osteoporosis
Topiramate	Rare	Anorexia, drowsiness, speech impediment, acidosis, hypohidrosis	Weight loss, urinary calculus
Zonisamide	Rare	Anorexia, drowsiness, speech impediment, acidosis, hypohidrosis, cognitive dysfunction	Urinary calculus

SJS Stevens–Johnson syndrome, *TEN* toxic epidermal necrolysis, *DIHS* drug-induced hypersensitivity syndrome

therapy with phenytoin [2]. In such cases, difficult airway management may be needed [3].

In a child, premedication is usually administrated orally with midazolam or diazepam, which have interactions with anti-epileptics. If intraoperative electrocorticography (EEG) is scheduled, the dosage must be controlled [4]. There are also interactions between warfarin, amiodarone, β-blocker, and calcium channel antagonists and anti-epileptics such as carbamazepine, phenytoin, phenytoin, and primidone [5].

A ketogenic diet, including a high-fat and low-carbohydrate regimen, is an alternative treatment for intractable epilepsy. In patients with a ketogenic diet, plasma glucose levels, acid status, and serum bicarbonate levels should be monitored [4, 6].

37.3 Interaction Between Anti-epileptics and Anesthetic Drugs

Some anti-epileptic agents induce cytochrome P-450 enzymes. Long-term administration of anti-epileptics causes resistance to nondepolarizing neuromuscular blockers. For example, phenytoin [7], carbamazepine [8], and valproic acid [9] decrease the duration time of rocuronium. Because the dosage of neuromuscular blocker is different for each patient, we need to monitor the neuromuscular blocker intraoperatively. Long-term anti-epileptics also increase the dose of fentanyl [10].

37.4 Anesthetic Agents and Epilepsy [5, 11] (Table 37.2)

37.4.1 Sedatives

Benzodiazepines have anticonvulsant activity. They are widely used to treat seizures. Anti-epileptic drugs such as phenobarbital and carbamazepine have sedative effects and may increase the effects of benzodiazepines.

Thiopental and pentobarbital have significant anticonvulsant activity, and they can be used safely for the induction of anesthesia in patients with epilepsy.

Propofol has both pro-convulsant and anticonvulsant effects. Propofol can cause abnormal movements such as seizures, but these events do not seem to relate to epileptogenic activity. In the clinical situation, except for rare cases [14], there is evidence suggesting that propofol has an anticonvulsant effect, and it is considered a safe drug [15].

Table 37.2 Proconvulsant and anticonvulsant properties of anesthetic agents [12, 13]

Anesthetics	Proconvulsant	Anticonvulsant
Nitrous oxide	+	−
Halothane	++	++
Enflurane	+++	+
Isoflurane	++	+++
Sevoflurane	++	
Desflurane	−/++	−−
Thiopental	++	+++
Methohexital	+++	+++
Etomidate	+++	+++
Benzodiazepines	−−−	+++
Ketamine	++	+
Propofol	++	++
Opioids	+++	

Etomidate has a pro-convulsant effect at a clinical dose and ketamine has anticonvulsant effects at a clinical dose. Ketamine is particularly effective in status epilepticus refractory [16].

It is reported that dexmedetomidine can be used safely in the epileptic patient [11]. On the other hand, there is a report that dexmedetomidine induced epileptic seizures in a neonate [17].

37.4.2 Inhalation Anesthetics

Inhalation anesthetics have various reactions on EEG. Enflurane produces epileptiform activity not only in the epileptogenic area but also in normal areas. Isoflurane suppresses epileptiform activity in the epileptogenic area. Desflurane has anticonvulsant effects. Sevoflurane gives unique EEG changes. When the epileptogenic area was stimulated in keeping the end-tidal sevoflurane concentration at 2.5 %, epileptiform activity was caused in the epileptogenic area, although the normal area had no change [18]. Kurita et al. demonstrated that, although the number of patients was small, the areas of spikes under 0.85 % sevoflurane are similar to those at the seizure-originating zone in the awake state, whereas the areas of spikes under 2.5 % sevoflurane are similar to those during interictal periods in the awake state [19].

37.4.3 Opioids

Administration of fentanyl and remifentanil can cause lead pipe rigidity and myoclonus. However, EEG monitoring was not recorded, and it was difficult to

make the movements of a convulsive attack. Some reports showed that the administration of fentanyl and remifentanil elicited epileptogenic EEG activity [20, 21]; other reports showed no relationships between the use of fentanyl and remifentanil and epileptogenic EEG activity [22].

37.5 Surgical Procedures

Surgical procedures in epilepsy are mainly divided into curative surgery and palliative surgery. Curative surgery includes resection surgery and palliative surgery includes interrupt surgery and neuromodulation (Table 37.3).

It is important to identify the precise location of the seizure focus preoperatively [23]. To identify the seizure focus, magnetic resonance imaging, electroencephalogram, and other tests are conducted. General anesthesia is preferred because this procedure is a required craniotomy and may take a long time to complete. To prevent brain edema, hyperventilation, mannitol, and hypertonic saline may be required. After the operation, the anti-epileptic drug is usually stopped, and the rest is needed to detect seizure. Within about 1 or 2 weeks, the grid and strip electrodes are removed. The removal of grid and strip electrodes may be carried out simultaneously with resection surgery. If intracranial electrodes cannot be inserted, intraoperative monitoring is important.

37.5.1 Curative Surgery

The areas for removal are generally the seizure-originating zone. Anesthetic agents must be selected according to intraoperative monitoring methods (Table 37.4). Sevoflurane is suitable for producing epileptic spike (refer to 37.4.2) but it suppresses motor evoked potential (MEP) and somatosensory evoked potential (SEP) amplitudes. Desflurane also suppresses MEP/SEP amplitudes, but not to the extent that sevoflurane does [24]; therefore, propofol is suitable for monitoring MEP/SEP. There are advantages and disadvantages with each anesthetic drug, and it may be useful to combine inhalation agents and propofol [25]. Awake craniotomy is conducted to minimize postoperative neurological deficits. For details, refer to Anesthesia for Awake Craniotomy (Part VII.33).

37.5.2 Palliative Surgery

Interrupt surgeries represented by corpus callosotomy do not limit anesthetic techniques. However, there are risks of massive bleeding and venous air emboli.

Table 37.3 Surgical procedures

Curative surgery	Palliative surgery	
Resection surgery	Interrupt surgery	Neuromodulation
Lesionectomy	Multiple subpial transection	Vagus nerve stimulation
Corticectomy	Corpus callosotomy	Deep brain stimulation
Lobe resection	Emispherectomy	Responsive neurostimulation system

Table 37.4 Intraoperative monitoring

Intraoperative monitoring	Purpose	Anesthetic consideration
Electrocorticogram	Identify the seizure focus	Use of sevoflurane
Motor evoked potential	Prevent motor dysfunction	Use of propfol
		Avoid neuromuscular blocker
Somatosensory evoked potential	Identify central sulcus	Prefer propfol to inhalation anesthetics
Awake craniotomy	Keep functional area	Patient cooperation
		Maintain patient airway

The placement of vagal nerve stimulation (VNS) is an adjunctive therapy in intractable epilepsy. The exact mechanism by which VNS prevents the seizure attack is not completely understood. It is presumed that VNS results in the activation of central nerve systems through the activation of the limbic system, noradrenergic neurotransmitter systems, and generalized brainstem arousal systems [26]. The placement of VNS is performed under general anesthesia, and propofol is preferred to inhalation agents that produce an epileptic spike. The left vagal nerve is selected for the placement of VNS because there are a greater number of cardiac efferent fibers in the right vagal nerve, whose stimulation may cause cardiac complications [27]. It was reported that bradycardia and asystole occurred at 0.1 % during the intraoperative test of the VNS device [28]. Postoperative complications include facial muscle paralysis and vocal cord paralysis. Most of these complications are resolved spontaneously. Chronic vagal nerve stimulation may cause significant respiratory disorders, particularly in sleep [29].

Deep brain stimulation (DBS) has been conducted for treatment of involuntary movement disorder. It is shown that DBS also is useful for patients with intractable epilepsy [30]. Furthermore, the responsive neurostimulation system (RNS) has emerged recently as a new option for intractable epilepsy [31]. However, there are few reports about anesthetic considerations with DBS [32, 33] and SNS for patients with intractable epilepsy.

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Chapter 38
Anesthesia for Pituitary Surgery

Hiroki Iida

Abstract Patients with pituitary adenomas exhibit excessive anterior pituitary hormone release and/or local mass effects on adjacent structures due to expanding intrasellar mass. Anesthesiologists should pay special attention to patients with Cushing's disease or acromegaly. The symptoms induced by hormone excess and/or local mass effect should be assessed preoperatively.

Airway management is likely to be difficult in patients with acromegaly. Hypertensive responses are often encountered during pretreatment with local anesthetics and vasoconstrictor administration to mucosal surfaces when the transsphenoidal approach is taken. Steroid cover is essential in patients with panhypopituitarism or Cushing's disease. Postoperative care should focus particularly on neuroendocrine abnormalities (including diabetes insipidus), visual loss, cerebrospinal fluid leakage, and risk of meningitis.

Keywords Pituitary gland • Endocrine • Transsphenoidal • Craniotomy

38.1 Introduction

Patients with pituitary adenomas exhibit excessive anterior pituitary hormone release and/or local mass effects on adjacent structures due to expanding intrasellar mass. Anesthesiologists should pay special attention to patients with Cushing's disease or acromegaly. The symptoms induced by hormone excess and/or local mass effect should be assessed preoperatively.

Airway management is likely to be difficult in patients with acromegaly. Hypertensive responses are often encountered during pretreatment with local anesthetics and vasoconstrictor administration to mucosal surfaces when the transsphenoidal approach is taken. Steroid cover is essential in patients with panhypopituitarism or Cushing's disease. Postoperative care should focus particularly on neuroendocrine abnormalities (including diabetes insipidus), visual loss, cerebrospinal fluid leakage, and risk of meningitis.

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38.2 The Pituitary Gland

38.2.1 Anatomy and Physiology of the Pituitary Gland

38.2.1.1 Anatomy [1]

The pituitary gland consists of two parts: the anterior lobe (the adenohypophysis, making up two thirds of the volume of the gland) and the posterior lobe (the neurohypophysis, contributing the remaining one third of the total volume). It lies within the hypophyseal fossa, which is surrounded anteriorly, posteriorly, and inferiorly by a bone depression forming the sella turcica. The pituitary gland is enclosed within the dura mater and lies outside the blood–brain barrier. It forms a junction with the hypothalamus via the pituitary stalk, in front of which are the crossing fibers of the optic nerves (the optic chiasm). The pituitary gland is very close to some of the major cranial nerves, including the oculomotor (III), trochlear (IV), trigeminal [ophthalmic (V1) and maxillary (V2) divisions], and abducens (VI) nerves, as well as certain blood vessels such as the internal carotid artery and cavernous sinus. Because of the locality of these major structures, pathological changes to the pituitary gland can give rise to a wide spectrum of hormonal and neurological conditions.

38.2.1.2 Physiology [2, 3]

The Anterior and Posterior Pituitary Gland

The neurohypophysis (the posterior pituitary lobe), unlike the anterior pituitary lobe, is not a true gland. This is because hormones such as vasopressin and oxytocin, stored and released by the posterior pituitary lobe, are in fact produced by the neurons of the supraoptic and paraventricular nuclei of the hypothalamus. Listed in Table 38.1 are the individual hormones secreted by the anterior and posterior pituitary glands.

38.2.2 Pathology of Pituitary Tumors

Tumors of the pituitary gland account for approximately 6–10 % of diagnosed brain neoplasms. However, unselected postmortem studies indicate an incidence of 10–27 %, indicating that the majority of them are asymptomatic. The most commonly diagnosed pituitary adenomas are prolactinomas (20–30 %, Table 38.2), 20–25 % of which are nonfunctioning endocrine pituitary adenomas.

Table 38.1 The hormones of the anterior and posterior pituitary glands

Hormones	Stimulating factor	Effects
Anterior lobe		
Thyroid-stimulating hormone	Thyroid-releasing hormone	Synthesis and secretion of thyroid hormones ↑
(TSH)	(TRH)	Metabolic rate ↑
Growth hormone	Growth hormone-releasing hormone	Protein synthesis, lean body mass, hepatic glucose output ↑
(GH)	(GHRH)	Growth of long bones and chondrogenesis (in children)
Adrenocorticotropic hormone	Corticotropin-releasing hormone	Sustain the basal secretion of glucocorticoid and aldosterone
(ACTH)	(CRH)	Increase secretion of these hormones induced by various stresses
Luteinizing hormone (LH)	Gonadotropin-releasing hormone	Stimulate gonads of both sexes and produce germ cells
Follicle-stimulating hormone (FSH)	(GnRH)	Secretion of androgens and estrogens↑
Prolactin	Prolactin-releasing hormone	Cause milk secretion from female breast
(PRL)	(PRH)	Inhibit the action of gonadotropins on the ovary
Posterior lobe		
Vasopressin	Electrical activity at the axon endings	Urine volume ↓ and its concentration ↑
(ADH)		Constrict the vascular smooth muscle
Oxytocin	Electrical activity at the axon endings	Contract the myoepithelial cells in mammary tissue and the smooth muscle of the uterus

Table 38.2 Pathological classification of pituitary adenomas

Type of adenoma	Excess secretion	Frequency	Pathology for excess hormones
Somatotrophic	GH	5–10 %	Acromegaly in adults
			Gigantism in children
Corticotrophic	ACTH	10–15 %	Cushing's disease
Gonadotrophic	FSH, LH	5 %	Usually none
Lactophilic	Prolactin	20–30 %	Galactorrhea, hypogonadism, amenorrhea
			Infertility and impotence
Thyrotrophic	TSH	<3 %	Usually none
			(Occasionally hyperthyroidism)
Null cell	None	20–25 %	None
Others	None	20 %	None

Table 38.3 Neuroanatomical classification of pituitary adenomas

Grade	Size	Location	Changes in bone
I	<10 mm	Intrapituitary	None
II	>10 mm	Intrasellar or suprasellar expansion, no invasion	Sellar expansion
III	Any	Intrasellar or suprasellar expansion, local invasion	Sellar erosion
IV	>10 mm	Suprasellar expansion, invasion of extrasellar structures	Bone invasion

38.2.2.1 Classification of Pituitary Adenomas

Table 38.3 shows the anatomical and neuroradiological classifications of pituitary adenomas, determined on the basis of tumor size and the degree of local invasion at the time of discovery. This classification is based on that proposed by Hardy, which places pituitary adenomas into one of the four possible grades.

38.2.2.2 Clinical Symptoms of Pituitary Adenomas [2, 3]

Typically, patients with functioning adenomas present with symptoms of pituitary hormone excess. In addition, any type of pituitary tumor that extends beyond the normal boundaries of the sella turcica may cause a local mass effect on adjacent structures, leading to a somewhat different symptomology.

Mass Effects

Mass effects are typically more likely to occur with an expanding nonfunctioning macroadenoma (>1 cm diameter). Structures adjacent to the pituitary gland such as the cranial nerves and blood vessels are compressed, resulting in visual disturbance (typically, bitemporal hemianopia by compression of the chiasm) and cranial nerve palsy. Large tumors can also lead to hydrocephalus and raised intracranial pressure (Table 38.4).

Endocrine Hypersecretion

Hormonal hyperactivity may occur secondarily to hypersecretion in a functioning adenoma. Prolactinoma is most common. Cushing's disease, which is caused by ACTH hypersecretion, and acromegaly (gigantism), resulting from growth hormone hypersecretion, are rarer. However, anesthesiologists should pay special attention to Cushing's disease and acromegaly because of the characteristic symptoms of these conditions. Table 38.5 shows the representative clinical signs and symptoms of Cushing's disease and acromegaly.

Table 38.4 The mass effects of pituitary adenomas

Symptoms	Compression site
Visual field defects	Optic chiasm
Double vision	Cranial nerves III, IV, and VI
Facial numbness	Cranial nerve V (V1, V2)
Headache	Third ventricle
Panhypopituitarism	Pituitary gland or pathway between pituitary gland and hypothalamus
Diabetes insipidus	Hypothalamus
Pituitary apoplexy	Pituitary gland

Table 38.5 The systemic manifestations of Cushing's disease and acromegaly

Type of disease	Clinical signs and symptoms
Cushing's disease	Central obesity (moon face, airway obstruction)
	Hypertension (left ventricle hypertrophy)
	Diabetes mellitus
	Osteoporosis
	Muscle atrophy
	Electrolyte abnormality (hypokalemia, hypernatremia)
	Increased intravascular fluid volume
	Emotional disturbance
	Acne, hirsutism, abdominal striae, hyperpigmentation
Acromegaly	Facial changes (bony hypertrophy, macroglossia, large nose and lips)
	Obstructive sleep apnea (airway obstruction, laryngeal narrowing)
	Hypertension
	Cardiac disease (cardiomyopathy, coronary artery disease, etc.)
	Acral enlargement
	Glucose intolerance

Cushing's Disease [4]

Eighty percent of ACTH-secreting tumors occur in women, and the majority consist of microadenomas. The clinical condition which results from excess ACTH production from a pituitary adenoma is known as Cushing's disease, and it is characterized by a variety of symptoms (Table 38.5).

Acromegaly [5]

Growth hormone hypersecretion affects not only the extremities but also the systemic organ systems, including the cardiovascular and respiratory systems. It is well established that cardiac disease is a major cause of morbidity and mortality in acromegalic patients. Sleep apnea is a well-established complication seen in acromegaly. Respiratory airway obstruction is the major cause of sleep apnea, but central respiratory depression of unknown etiology may also occur. Other symptoms of note seen in acromegalic patients are given in Table 38.5.

Prolactinoma

More than half of all functioning pituitary tumors are prolactin-secreting tumors, typically microadenomas (<1 cm). Ninety percent of them occur in women. Female patients present with secondary amenorrhea and galactorrhea. Male patients also experience galactorrhea and present with impotence. Prolactin-producing macroadenomas (>1 cm) are more common in men and present with mass effects such as visual field defects.

38.3 Preoperative Evaluation

38.3.1 Cardiovascular Evaluation [6–8]

Cardiac conditions such as ischemic heart disease, cardiomyopathies, arrhythmia, and congestive heart failure are commonly associated with acromegaly and Cushing's disease. Systemic hypertension is commonly observed in 30–35 % of patients with acromegaly and in 80–85 % of patients with Cushing's disease. Obstructive sleep apnea (OSA) secondary to upper airway obstruction seems to be a related symptom in around 70 % of acromegalic patients and is also common among patients with Cushing's disease. Patients with chronic OSA can also develop right heart failure arising from pulmonary hypertension. Abnormalities in ECG findings are common in patients with acromegaly or Cushing's disease.

38.3.2 Neurological Evaluation [6–8]

Anesthesiologists should assess patients for raised intracranial pressure (ICP) and hydrocephalus. Visual field defects may also arise from the mass effects seen in patients with macroadenomas.

38.3.3 Preoperative Endocrine (Hormonal) Evaluation [6–8]

Endocrine abnormalities must be evaluated in the preoperative period; such abnormalities range from panhypopituitarism to hypersecretory conditions. In patients with panhypopituitarism, hormone replacement may be essential prior to surgery. Such patients are sensitive to anesthetic agents, and vasopressor drugs may also be needed to maintain blood pressure. Alternatively, there are medical therapies available that are aimed at alleviating some of the systemic effects of functional adenomas in elective surgery: for example, a somatostatin analog used in

acromegaly, ketoconazole for Cushing's disease, and dopamine agonists for prolactinoma. Anesthesiologists should pay special attention to patients with acromegaly or Cushing's disease due to their unique combinations of symptoms.

38.3.4 Airway Assessment [5, 9]

Acromegaly can contribute to problems with airway management by impairing mask fit and difficulty in tracheal intubation caused by macroglossia, hypertrophy of soft tissues of the oropharynx, and enlargement of the soft palate and epiglottis. In addition, recurrent laryngeal nerve palsy and enlargement of the thyroid observed in acromegalic patients contribute to the problems encountered in airway management. Preoperative airway assessment is likely to fail to predict problems arising during endotracheal intubation. In this situation, fiber-optic intubation performed while patients are conscious is likely to be the safest approach and, thus, should be the technique of choice. In view of this, all strategies used in problematic airway management should be made available to secure the airway in these types of patients. In contrast, there are no reports suggesting that particular problems are likely to arise in patients with Cushing's disease during endotracheal intubation. However, the airways in these patients should be managed with caution in view of the dangers associated with OSA and patient obesity.

38.3.5 Surgical Techniques [7, 10]

The two most commonly adopted approaches for the resection of pituitary adenomas are the transsphenoidal approach and craniotomy. The transsphenoidal method, employing an endoscopic or microsurgical approach, is used in over 95 % of pituitary adenoma cases. This technique is associated with lower morbidity in terms of visual disturbance and diabetes insipidus and lower mortality than is the case with open craniotomy.

38.4 Anesthetic Management

38.4.1 Anesthetic Techniques [6–8, 11]

As with other neurosurgical procedures, a neurological examination is performed soon after surgery. Therefore, to facilitate prompt emergence from anesthesia, rapidly metabolized agents such as propofol and remifentanil, or inhalation agents with low blood solubility such as desflurane or sevoflurane, should be used.

Mucosal surfaces are pretreated with combinations of local anesthetics and vasoconstrictors such as adrenaline. A hypertensive response frequently occurs as a result of this treatment. Short-acting drugs used to counter this deleterious response are available.

To ease visualization of a tumor and its surgical excision, mild permissive hypercapnia, or an occasional Valsalva maneuver, can be useful in displacing the suprasellar portion of the pituitary adenoma into the infrasellar space. In addition, the Valsalva maneuver may also be used to test for leakage of cerebrospinal fluid (CSF). The sella is then packed with autologous fat before being reconstructed.

Steroid cover is an essential therapeutic component in patients with panhypopituitarism or Cushing's disease, and antibiotic prophylaxis is warranted before incision.

Invasion of the cavernous sinus and carotid artery, both of which are laterally close to the area of surgery, increases the danger of significant bleeding. Adequate intravenous access, including central venous access, should be ensured.

38.4.2 Positioning [4, 8]

During transsphenoidal surgery, an upright head position can be employed not only to decrease venous engorgement but also minimize bleeding. However, an upright head position carries with it the danger of venous air embolism (VAE).

38.4.3 Monitoring [4, 8]

For patients with Cushing's disease or acromegaly who are considered to be at risk of hemodynamic instability during surgery, invasive arterial blood pressure monitoring is necessary. If a VAE is deemed likely to occur, precordial Doppler probe placement, central venous access, and end-tidal carbon dioxide monitoring are recommended.

38.5 Postoperative Care

38.5.1 Respiration [6–8]

All patients are at an increased risk of airway obstruction after the transsphenoidal approach in the event that blood and mucosal secretions enter the pharynx and nasal packs. Acromegalic patients with OSA have an especially high risk of developing respiratory obstruction and hypoventilation and should be closely monitored during the postoperative period.

38.5.2 Nausea and Vomiting [4, 12]

Nausea and vomiting are very common postoperative complications in patients who have undergone this procedure. Pharmacologic prophylaxis seems reasonable given the harmful effect of vomiting on ICP.

38.5.3 Pain [4, 12]

The most common patient complaint after transsphenoidal surgery is headache. Craniotomy is associated with greater levels of pain and stronger analgesia may be required. Postoperative analgesia is an important issue, because pain, like vomiting, is likely to increase arterial blood pressure and ICP. Opioids are very effective agents in pain relief, but the danger of overdose must not be overlooked.

38.5.4 Hormonal Replacement [13]

Generally, almost all patients who receive hormone replacement also require postoperative cortisol replacement, which must be administered carefully if successful management is to be achieved. Although the ideal approach is to measure cortisol levels in order to ascertain the ideal dosage, a standard regimen, such as 100 mg hydrocortisone/day on the first postoperative day, 50 mg/day on the second, reduced to 30 mg/day by the third day, could alternatively be employed. In patients with Cushing's disease, normal corticotrophin levels are chronically suppressed, requiring replacement to be maintained over long periods of time.

38.5.5 Diabetes Insipidus [4, 12]

There is the possibility that diabetes insipidus (DI) might develop postoperatively, usually occurring in the first 24 h after surgery. However, DI may, very rarely, arise intraoperatively. Fluid intake, urine output, urine specific gravity, and serum electrolytes should all be closely monitored. Hypoosmolar urine associated with increased serum osmolality strongly indicates the presence of DI. A diagnosis of DI is established as shown in Table 38.6.

Table 38.6 Diagnosis of diabetes insipidus

Urine	Output	3 mL/kg/h or 200 mL/h
	Specific gravity	<1.005
	Sodium	<15 mEq/L
	Osmolality	<200 mOsmol/L
	Osmolality (vs. serum)	Lower
Serum	Sodium	>150 mEq/L (hypernatremia)
	Osmolality	>320 mOsmol/L (hyperosmolality)

Table 38.7 Complications of hypophysectomy

Type of surgery	Complications
Transsphenoidal	Panhypopituitarism
	CSF leakage
	Diabetes insipidus
	Visual loss
	Meningitis
	Sinus disease
	Vascular injury
	Hydrocephalus
Craniotomy	Cranial nerve neuropathy
	Visual loss
	Anosmia
	Diabetes insipidus
	Vascular injury
	Cerebral edema

38.5.6 Cerebrospinal Fluid Leakage [4, 12]

Leakage of CSF associated with rhinorrhea is a potential complication in this type of surgery. Autologous fat packing or placement of a lumbar subarachnoid drain to reduce the pressure on the surgical tear can be used to treat postoperative leakage.

38.6 Complications [6–8]

Commonly occurring complications resulting from transsphenoidal and craniotomy procedures are listed in Table 38.7. Endocrine disorders commonly encountered are hypopituitarism, DI, and syndrome of inappropriate antidiuretic hormone secretion, the last usually becoming apparent one week after transsphenoidal surgery and being managed by fluid intake restriction (500–1,000 mL/day).

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Chapter 39
Anesthesia for Interventional Radiology

Mitsuru Ida and Masahiko Kawaguchi

Abstract The role of interventional neuroradiology (INR) has expanded over the last decade. Carotid artery stenting (CAS) for carotid artery stenosis and coiling for cerebral aneurysm are representative INR procedures, and both can be performed under local anesthesia. Some neuroradiologists, however, prefer hemodynamics to be stabilized and the patient immobilized under general anesthesia for such interventions. Diverse systematic complications often occur in patients undergoing CAS or coiling, so it is crucial that these complications, and particularly cardiopulmonary conditions, be evaluated preoperatively. Moreover, attention must be paid to cerebral hyperperfusion syndrome in CAS or rebleeding and cerebral vasospasm in coiling.

Keywords Carotid artery stenting • Cerebral aneurysm coiling • Endovascular treatment

39.1 Introduction

Interventional neuroradiology (INR) is a rapidly expanding specialty, and the anesthesiologist plays an important role in endovascular neuroradiological procedures, often being requested to stabilize hemodynamics and respiratory status, immobilize the patient, and so on. In this chapter, the author gives his opinions on treatment options in carotid artery stenting and intracranial aneurysm clipping.

39.1.1 Carotid Artery Stenosis [1]

Carotid artery stenosis is a common reason for ischemic stroke and is responsible for 15–20 % of ischemic stroke. Carotid endarterectomy (CEA) and carotid artery stenting (CAS) are popular surgical treatments. In the stenting versus

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endarterectomy treatment of carotid artery stenosis (CREST), patients with asymptomatic carotid stenosis were allocated to CAS or CEA. There were no significant differences in occurrences of stroke and death between CAS and CEA after 1 year of treatment [2]. However, one recent meta-analysis report indicated that the incidence of stroke or death was significantly higher in CAS patients than in CEA patients in symptomatic carotid artery stenosis after 1 year of treatment [3]. Therefore, we cannot conclude which procedures are to be recommended for patients with carotid artery stenosis. This section gives opinions about anesthetic managements of CAS.

39.1.1.1 Preoperative Management

Atherosclerosis frequently occurs at carotid bifurcation and the proximal internal carotid artery. It is important to evaluate patient's cardiac status, particularly coronary artery disease (CAD), because atherosclerosis is considered to be a generalized disease. It is reported that the prevalence rates of echographic carotid artery stenosis are 7.0 %, 14.5 %, 21.4 %, and 36.0 % in patients with 0-, 1-, 2-, and 3-vessel CAD, respectively [4]. Single-photon emission computed tomography (SPECT) with acetazolamide is useful to predict postoperative cerebral hyperperfusion syndrome (CHS).

39.1.1.2 Intraoperative Management

Anesthetic Management

Some physicians prefer local anesthesia (LA) to evaluate intraoperative neurological symptoms, while others prefer general anesthesia (GA) to stabilize hemodynamic changes and immobilize patients. There is no evidence to show advantages of a specific anesthetic technique for patients undergoing CAS. Considering hemodynamic stability, immobility, and anxiety, GA is recommended for all patients except for the shortest procedures in the most cooperative patients.

Monitoring [5, 6]

There is no evidence about neuromonitoring during CAS. It is not possible to speak under GA, although it can be useful to speak under LA. Referring to neuromonitoring during CEA, the following monitoring tools are used: electroencephalogram, near-infrared spectroscopy, transcranial Doppler ultrasonography (TCD), and somatosensory evoked potentials. These tools each have strengths and weaknesses (Table 39.1).

Table 39.1 Neuromonitoring techniques during carotid artery surgery [1]

Monitoring modality	Measured changes (clinical relevance)	Advantages	Disadvantages
Neurologic status	Mentation (decreased CBF/cerebral ischemia)	Gold standard	Not assessable in sedated or anesthetized patients
EEG	Changes from baseline/asymmetry (decreased CBF/cerebral ischemia)	Continuous	Requires skilled interpretation
		Sensitive/good evidence base	Affected by anesthetic agents
SSEP	Decreased amplitude/increased latency (decreased CBF/cerebral ischemia)	Sensitive	Affected by anesthetic agents
		Blood pressure dependent/ noncontinuous	
TCD	Reduction/increase in VMCA (decreased CBF/CHS)	Noninvasive	Not a measure of absolute CBF
	Signal change (microemboli)	Continuous	Absent acoustic window in some patients
NIRS	Reduction in rSO2 from baseline (cerebral ischemia)	Simple to apply	Ischemic thresholds not established
	Increase in rSO2 from baseline (CHS)	Noninvasive/ regional	Absolute values of uncertain relevance

CBF cerebral blood flow, *CHS* cerebral hyperperfusion syndrome, *EEG* electroencephalogram, *NIRS* near-infrared spectroscopy, *rSO2* regional cerebral oxygen saturation, *TCD* transcranial Doppler ultrasonography, *SSEP* somatosensory evoked potentials

Hemodynamic Instability (HI) [7]

Hemodynamic instability, bradycardia, and/or hypotension are well-known complications during CAS, and the frequency has been reported from 7.2 to 80 %. HI should be prevented and treated because systolic blood pressure decreasing more than 50 mmHg is related to postoperative stroke or transient ischemic attack [8], while persistent hypotension is associated with postoperative adverse events [9]. There are many risk factors for HI (Table 39.2). Atropine or glycopyrrolate is often administered to prevent and treat HI. However, the optimal dose and timing remain to be confirmed. Temporary pacing is another preventive measure.

39.1.1.3 Postoperative Management

Cerebral Hyperperfusion Syndrome (CHS)

CHS occurs in 6–11 % of patients and is characterized by an acute rise in cerebral blood flow of more than 200 % with headache, hypertension, and seizures. In terms of timing, it is earlier after CAS than after CEA, and it usually occurs within a few days. The main treatment is strict blood pressure management, maintaining a level

Table 39.2 Predictors of hemodynamic instability

Variables	Hypotension [10] Odds ratio (95 % confidence interval)
Male	2.5 (1.3–24.9)
Carotid bulb lesion	1.6 (1.1–25.9)
Internal carotid artery lesion	2.0 (1.4–17.2)
Variables	Bradycardia [10] Odds ratio (95 % confidence interval)
Minor stroke	1.7 (1.4–17.9)
Preoperative transient ischemic attack	1.5 (1.0–10.9)
Carotid bulb lesion	1.4 (1.0–16.3)
Variables	Hypotension and/or bradycardia [11] Odds ratio (95 % confidence interval)
Stenosis of more than 70 %	2.2 (1.0–5.1)
Severe calcification	3.0 (1.1–7.6)
Bilateral stenting	4.5 (1.3–15.8)
Pressure of balloon dilation of >8 atm	2.9 (1.6–5.3)

between 90 and 140 mmHg. Risk factors for CHS are old age, severe contralateral disease, poor collateral flow, and hypertension [12, 13]. Preoperative SPECT and TCD are useful to predict CHS.

Contrast-Induced Nephropathy (CIN) [14]

Contrast nephropathy is defined as a rise in the serum creatinine level of at least 0.5 mg/dl within 48 h of contrast medium administration. Risk factors are creatinine more than 1.3 mg/dl, dehydration, diabetes mellitus, and the concomitant use of nephrotoxic medications. It is important to be well hydrated. Isotonic hydration is superior to half-normal saline.

39.1.2 Aneurysmal Subarachnoid Hemorrhage [15]

The incidence of subarachnoid hemorrhage (SAH) is different in each country. For example, the incidence of SAH is 8 cases per 100,000 persons per year in Germany [16] and 10 cases per 100,000 persons per year in the United States [17]. Most cases occur more in people over 40 years old. Approximately 80 % of nontraumatic SAH are caused by a ruptured cerebrovascular aneurysm. In the International Subarachnoid Aneurysm Trial (ISAT), patients with a ruptured intracranial aneurysm were allocated to endovascular coiling or neurosurgical clipping. Endovascular coiling, in terms of survival-free disability at 1 year, was significantly superior to clipping

Table 39.3 Complications of aneurysmal subarachnoid hemorrhage [19]

Rebleeding (without aneurysm occlusion 27)
On day 1: 15 %
By 1 month: 40 %
After 6 months: 3 % per year
Immediate cerebral ischemia
Due to raised intracranial pressure and hence reduced cerebral perfusion pressure
Delayed cerebral ischemia
Peaks between days 4 and 14 after subarachnoid hemorrhage
Hydrocephalus
Seizures
Cardiopulmonary dysfunction—predicted by elevated cardiac troponin Iw7
Hyponatremia or hypomagnesemia—caused by salt wasting

[18]. This section gives opinions about anesthetic management of cerebral aneurysm coiling.

39.1.2.1 Preoperative Management

SAH may cause various complications that include rebleeding, cerebral ischemia due to cerebral vasospasm, cardiopulmonary dysfunction, electrolyte disturbances, and so on (Table 39.3).

Blood Pressure [20]

Strict blood pressure management is required to maintain cerebral blood flow and prevent rebleeding. The predictors of rebleeding include Hunt-Hess grade on admission (odds ratio (OR), 1.92; 95 % confidence interval (CI), 1.33–2.75) and maximal aneurysm diameter (OR, 1.07; 95 % CI, 1.01–1.13).

Cardiopulmonary Function

It is important to evaluate cardiopulmonary function because severe SAH is frequently accompanied by Takotsubo cardiomyopathy and neurogenic pulmonary edema. These abnormalities are probably the result of excessive catecholamine release due to an injured hypothalamus.

Electrolyte Disturbance [21]

Because electrolyte disturbance can adversely affect outcome, the serum levels of electrolytes should be closely monitored and treated appropriately. Hyponatremia, which does not worsen the outcome, occurs in approximately 30 % of cases as a result of either cerebral salt-wasting syndrome or a syndrome involving inappropriate secretion of antidiuretic hormones. On the other hand, hypernatremia, although less common, is significantly associated with poor outcome. Both hypokalemia and hypomagnesemia are also related to poor outcomes.

39.1.2.2 Intraoperative Management

Anesthetic Management

In an unruptured aneurysm, LA can be administered if patients can cooperate. In a ruptured aneurysm, GA is recommended to stabilize hemodynamic and respiratory status and to immobilize patients. In addition to routine monitoring, a 5-lead electrocardiogram is used if cardiomyopathy is suspected. Anesthetic drugs can affect cerebral blood flow and intracranial pressure. Considering these effects, intravenous anesthesia may be preferable to volatile anesthesia. Mannitol and furosemide are sometimes administered to relax the brain. Administering these drugs may cause electrolyte disturbance, and it is reported that mannitol causes hypokalemia and hyperkalemia. Hyperthermia tends to induce infarction in the ischemic brain [22], and an intraoperative hypothermia for aneurysm surgery trial (IHAST) showed that mild hypothermia was not helpful to protect the ischemic brain [23]. Therefore, body temperature should be maintained at a normal level.

Intraoperative Aneurysm Rupture

The incidence of intraoperative aneurysm rupture with a ruptured aneurysm is estimated at about 4–11 %, and intraoperative rupture of an aneurysm results in high morbidity and mortality. Once an aneurysm ruptures, reversal heparin with protamine and blood pressure management may be required. Temporary vessel occlusion is also effective.

39.1.2.3 Postoperative Management

Cerebral vasospasm occurs at 3–5 days after SAH and affects 30–70 % of patients with SAH. Cerebral vasospasm results in cerebral infarction known as delayed cerebral ischemia (DCI) and increases morbidity and mortality after SAH. The mechanism of DCI is not clear and several complex factors seem to be interrelated. There is strong evidence for a higher risk of DCI in smokers (pooled OR, 1.2; 95 %

CI, 1.1–1.4) and moderate evidence for an increased risk in patients with hyperglycemia (OR, 3.2; 1.8–5.8 and hazard ratios, 1.7; 1.1–2.5), hydrocephalus (OR, 1.3; 1.1–1.5 and hazard ratios, 2.6; 1.2–5.5), history of diabetes mellitus (pooled OR, 6.7; 1.7–26), and early systemic inflammatory response syndrome (pooled OR, 2.1; 1.4–3.3) [24]. Nimodipine, 60 mg orally or by nasogastric tube at 4 h intervals every day for 3 weeks, is the only treatment with evidence to prevent cerebral vasospasm after SAH (relative risk, 0.67; 95 % CI, 0.55–0.81) [25].

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Chapter 40
Neuromodulation: Deep Brain Stimulation

Hideki Oshima, Toshiki Obuchi, and Yoichi Katayama

Abstract Deep brain stimulation (DBS) is a surgical procedure used to treat various neurological disorders such as intractable pain, Parkinson's disease, essential tremor, dystonia, and other movement disorders. It involves implanting electrodes in the brain, which send electrical impulses to modulate brain activity. This procedure is not considered radical and can significantly improve disabling neurological symptoms. Such symptoms used to commonly require invasive surgeries such as thalamotomy and pallidotomy, which destroy those parts of the brain where abnormal activity has occurred. In recent years, such surgeries have been performed less frequently because of the risk of severe complications and the availability of DBS, which is safer and has fewer complications. Deep brain stimulation allows abnormal brain activity to be regulated without destruction of brain tissue. This means that DBS offers numerous advantages over conventional surgeries as it is reversible and enables the surgeon to modulate and improve specific functions or symptoms. Despite DBS having become widely accepted as an effective therapy for various neurological disorders, its fundamental principles and mechanisms are still not precisely defined.

Keywords Deep brain stimulation • Stereotactic surgery • Movement disorder

40.1 Introduction

Deep brain stimulation (DBS) is a surgical procedure used to treat various neurological disorders such as intractable pain, Parkinson's disease, and other movement disorders. It involves implanting electrodes in the brain, which send electrical impulses to modulate brain activity. Such symptoms used to commonly require invasive surgeries such as thalamotomy and pallidotomy. In recent years, however, such surgeries have been performed less frequently because of the risk of severe complications and the availability of DBS, which has fewer complications. Moreover, being less destructive than these conventional procedures, DBS offers

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numerous advantages over conventional surgeries as it is reversible and enables the surgeon to modulate and improve specific functions or symptoms.

40.2 DBS System

The DBS system consists of three components: a DBS electrode (lead), an implantable pulse generator (IPG), and an extension cable (Fig. 40.1). The lead is placed in a specific part of the brain by stereotactic surgery. The IPG is a device similar to a heart pacemaker and is implanted subcutaneously in the chest or abdomen. The lead is connected to the IPG subcutaneously by means of the extension cable. The DBS generates electrical impulses, which directly modulate brain function. The physician can use a programming device to adjust electrical stimulation to target a specific symptom or function without eliciting adverse effects. Radio waves allow communication between the programming device and the IPG through clothing or skin.

40.3 Applications and Targets

Deep brain stimulation is used to treat a wide variety of neurological disorders, so the location of the electrodes will depend on the problem targeted. We would recommend DBS in cases where medication has proved inadequate or the side effects too severe to allow continuation of treatment.

40.3.1 Parkinson's Disease

Deep brain stimulation provides a useful means of controlling various symptoms such as tremor, rigidity, bradykinesia, and postural instability. The stimulation sites include the thalamic nucleus ventralis intermedius (Vim), globus pallidus internus (GPi), and subthalamic nucleus (STN). When tremor is the symptom to be treated, Vim should be selected, while either GPi or STN is appropriate for controlling the various motor symptoms that accompany Parkinson's disease [1, 2]. Stimulation at GPi inhibits dopa-induced dyskinesia [3], while that at STN can reduce the need for medication, which helps prevent the adverse effects that can arise from such treatment [4, 5]. Usually, patients with Parkinsonism other than Parkinson's disease are not candidates for this procedure, however.

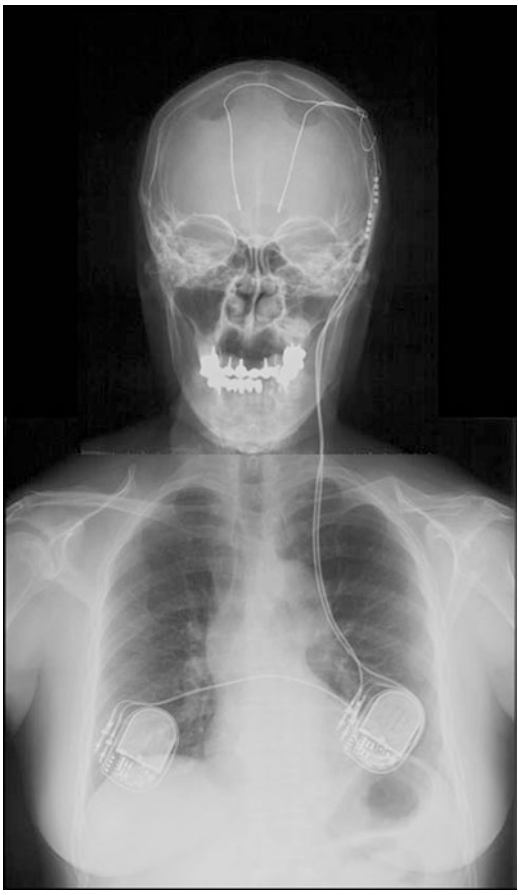

Fig. 40.1 DBS system: X-ray image after DBS surgery

40.3.2 Essential Tremor

Essential tremor (ET) is a movement disorder characterized by tremor of the upper limbs. A number of medications are available for ET, including beta-adrenergic blockers and anticonvulsants. The symptoms, however, are often progressive. It is thought that ET is caused by electrical dysfunction within the brain, although its precise etiology remains uncertain. If the effects of medication are unsatisfactory, DBS should be considered. Commonly, Vim is selected as the stimulation site for ET and has been confirmed to be effective in the treatment of ET [5, 6].

40.3.3 Dystonia

Dystonia is a movement disorder in which involuntary muscle contractions cause repetitive movements or abnormal postures. Medication has little effect on this condition, and it eventually tends to impair the patient's quality of life. Deep brain stimulation cannot cure dystonia, but it can alleviate the muscle contractions. The GPi is the commonly accepted stimulation site. The effects of DBS often appear gradually over months to years following surgery, and while it is particularly effective in the treatment of primary and generalized dystonia [7, 8], its effect is only limited or mild in the case of secondary dystonia [9, 10].

40.3.4 Intractable Pain Syndrome

Deep brain stimulation has been used to treat various types of intractable pain syndrome such as peripheral neuropathic, phantom limb, and post-stroke central neuropathic pain. Here, the stimulation sites include the thalamic ventral postero-lateral/posteromedial nucleus, the internal capsule, and the periventricular gray. The reported effects vary widely, and candidates should therefore be selected with care [11, 12].

40.3.5 Other Clinical Applications

In addition to its application as an effective therapy for movement disorders and intractable pain syndrome, DBS is also under clinical study as a treatment for psychiatric diseases such as Tourette's syndrome, obsessive-compulsive disorder, major depression, and Alzheimer's disease.

40.4 Stereotactic Surgery

The DBS electrode is placed in the brain by means of stereotactic surgery (Fig. 40.2), the essential concept of which is to allow manipulation within a three-dimensional space. Stereotactic surgery thus enables an action to be performed on a small target located deep in the brain with minimal risk of surgical complications. The first use of stereotactic surgery for humans was reported by Spiegel and Wycis in 1947. Various stereotactic instruments have been developed in the last half a century, but most of the popular stereotactic systems are arc centered; that is, the three coordinates indicate the center of a semicircular arc. The apparatus consists essentially of a semicircular arc with a probe holder (electrode

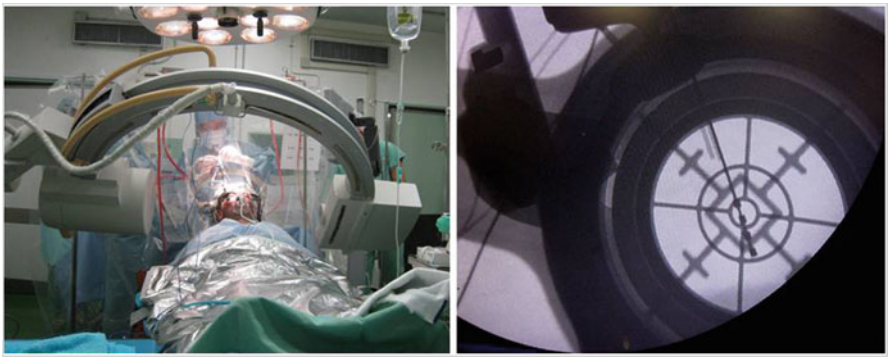

Fig. 40.2 Operative settings and insertion of DBS electrode during stereotactic surgery. Patient is placed in supine position and cranial X-ray fluoroscopy performed bilaterally (*left*). Lateral X-rays are obtained to verify route of DBS leads to planned target (*right*)

carrier) and head frame. The head frame is attached to the skull with pins. The patient is scanned by X-ray, computed tomography, or magnetic resonance imaging (MRI) to calculate the three Cartesian coordinates (X, Y, and Z) of the target in relation to the head frame (Fig. 40.3). Since the target is always located in the center of the arc, it is possible to approach it from various angles. Recently, stereotactic planning has become computer based, and the target and trajectory can be accurately planned using a neuro-navigation system. The stereotactic device attached to the head frame is adjusted to the coordinates of the target, and the probe can reach any specific part of the brain from almost any burr hole. Although general brain surgery often requires a large incision and craniotomy, stereotactic surgery requires only a burr hole in the skull. Stereotactic surgery is a minimally invasive and safe operation. Currently, the stereotactic technique is employed for various brain surgeries, including ablation, needle biopsy, radiosurgery, implantation, and insertion of DBS electrodes.

40.5 Surgical Procedure

Deep brain stimulation usually requires two separate procedures. The first operation comprises insertion of the DBS electrode into the brain, while the second consists of subcutaneous implantation of the IPG in the chest or abdomen. These two operations can be performed on the same or on separate days.

40.5.1 First Operation

The DBS electrode is placed deep in the brain using stereotactic surgical technique. This operation is usually performed under local anesthesia, as it is important to

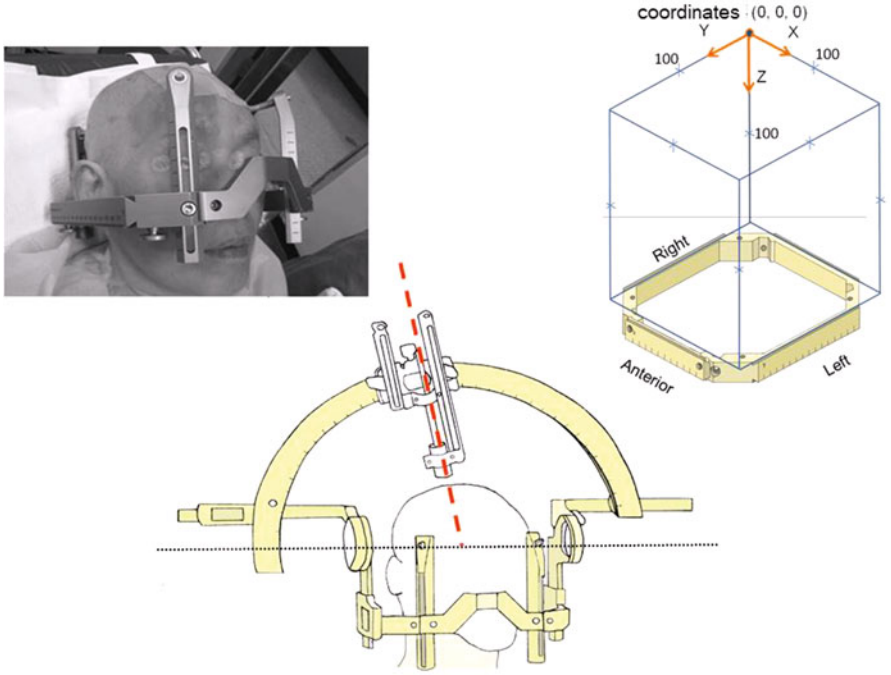

Fig. 40.3 Coordinate system of stereotactic apparatus (Leksell). Application of base ring with Leksell model G stereotactic instrument attached to skull (*left upper*). Coordinate system of Leksell model G stereotactic base ring. Coordinate 0 of frame is located on upper posterior right side (*right upper*). Leksell stereotactic arc is attached to base ring (*lower*). Probes are always directed toward the center of the arc

monitor all ongoing clinical and adverse effects that may accompany the procedure. The stereotactic head frame is fixed to the skull using pins. Gadolinium-enhanced MRI is carried out with the MRI indicator attached to the stereotactic frame. The MRI data sets obtained are then transferred to a neuro-navigation system and the target area and trajectories identified with stereotactic planning software. Under local anesthesia, a burr hole approximately 15 mm in diameter is made in the forehead. The dura mater is opened and the arachnoid membrane and cortical surface are coagulated at the point of electrode insertion via the burr hole.

Neural activity is recorded in order to confirm the position of the electrode. Observing these patterns of neural activity can help ensure that the electrode is optimally placed. Test stimulation is performed during the procedure to evaluate any improvement in symptoms or side effects that might occur. Thus, intraoperative testing is used to determine the final location at which the electrode is to be placed. A permanent DBS electrode is then implanted and fixed to the skull.

40.5.2 Second Operation

After the electrode has been implanted, the first operation is completed. The second operation involves implantation of the IPG. This is usually carried out under general anesthesia. The IPG is implanted under the skin or fascia in the anterior chest or abdomen. The extension cable, which is passed through the subcutaneous portion of the head, neck, and chest, connects the DBS electrode in the brain to the IPG in the chest (or abdomen). The incisions are closed, and all devices are placed under the skin. The IPG is turned on within a few days after completion of the second operation.

40.6 Complications and Adverse Effects

While DBS is considered to be a safe and effective treatment, there are potential complications and adverse effects. Intracranial hemorrhage, possibly due to tissue damage during electrode insertion, is the most serious complication of DBS surgery and can even lead to serious neurological disability in some cases. Symptomatic intracranial hemorrhage occurs in less than 2 % of patients who have undergone stereotactic surgery. Older age and a history of hypertension increase the risk of intracranial hemorrhage [13, 14]. Hardware-related complications also represent a crucial problem and include infection, erosion, allergic reaction, and breakage of devices. The complication rate is between 4.0 and 9.7 % and will often necessitate surgical removal or replacement of the device [15, 16]. Rare complications include seizure, confusion, and venous air embolism. When applied to the basal ganglia, DBS carries the potential risk of adverse psychiatric effects, which may include mood disorders, cognitive dysfunction, and executive dysfunction in patients with Parkinson's disease who have undergone STN-DBS, in particular [17].

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Chapter 41
Anesthesia for Stereotaxic Neurosurgery and Deep Brain Stimulation

Takeshi Maeda, Yuko Kondo, and Takahiro Suzuki

Abstract Deep brain stimulation (DBS) is an effective treatment in patients with neurogenic disorders who have alterations of function such as Parkinson's disease and movement disorders. The insertion of a DBS device is a minimally invasive procedure that includes the placement of electrodes into deep brain structures to obtain microelectrode recordings, macrostimulation for clinical testing of the patient, and connection of the DBS device to an implanted pacemaker. The anesthesiologist plays a key role in the management of patients undergoing this procedure. This chapter reviews current knowledge regarding anesthetic techniques for DBS device insertion and neurostimulator implantation. Various anesthetic issues and possible perioperative complications will be examined. Finally, anesthesia in patients with a neurostimulator implant will be discussed.

Keywords Deep brain stimulation (DBS) • Parkinson's disease • Movement disorders • Microelectrode recordings • Implantable pulse generator (IPG)

41.1 Introduction

Deep brain stimulation (DBS) is an effective treatment in patients with neurogenic disorders who have alterations of function such as Parkinson's disease, essential tremor, dystonia, and chronic pain [3, 12]. A multicenter randomized trial has demonstrated that DBS can add value to the best medical treatment [6], and the National Institute for Clinical Excellence has confirmed it to be a cost-effective intervention [11].

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The main points of DBS are as follows: (1) The procedure comprises the insertion and placement of the electrode leads of a deep brain stimulator and the implantation of an implantable pulse generator (IPG). The insertion and placement of the electrode leads are often performed under local anesthesia, while IPG implantation is performed under general anesthesia; (2) the insertion of the DBS device is a minimally invasive procedure that includes the placement of electrodes into deep brain structures to obtain microelectrode recordings, macrostimulation for clinical testing of the patient, and connection of the DBS device to an implanted pacemaker; (3) insertion and placement of the electrode leads under general anesthesia is selected in patients with severe involuntary movements or in cases in which awake surgery is expected to be difficult; (4) while the complications of DBS include intracranial hemorrhage and seizures, careful attention needs also to be paid to air embolism and airway obstruction. For the details of the surgical procedures and mechanisms involved in DBS, please refer to Machado et al. [8].

The anesthesiologist plays a key role in the management of patients undergoing the insertion of a DBS device. The anesthetic technique varies depending on the requirements of the institution at which it is performed and includes monitored care under local anesthesia, conscious sedation, and general anesthesia. The purpose of this chapter is to describe anesthetic management of patients undergoing DBS insertion.

41.2 Preoperative Evaluation and Assessment for DBS Electrode Insertion

Successful DBS depends on proper patient selection. The selection of an ideal candidate includes an overall assessment of the patient with respect to diagnosis, cognitive and psychiatric status, access to care, and expectations by the patient, as well as the patient's response to medical treatment. There are specific challenges and considerations to be faced in the anesthetic management of patients undergoing insertion of a DBS device (Table 41.1) [16]. Such patients require additional consideration because they may present with many comorbidities related to the disease processes for which DBS is indicated (Table 41.2) [16]. In addition to the routine preoperative assessment and preparation required for the administration of anesthesia, it is necessary to assess blood coagulability and confirm that no antiplatelet drug has been administered because DBS electrodes are inserted toward the deep brain. Furthermore, it is also necessary to confirm whether the patient can maintain the same posture for a long period of time with a stereotactic frame placed on the head.

Table 41.1 Anesthetic considerations [16]

1. Patient-related considerations
(a) Primary disease (Parkinson's disease, dystonia, essential tremor, chronic pain, epilepsy)
(b) Comorbid medical conditions of patient and disease
(c) Age (child or elderly)
(d) Appropriate patient selection and preparation
(e) Polypharmacy and altered pharmacokinetics and dynamics
(f) Potential drug interactions
(g) Medication "off state"—worsening of symptoms
2. Procedure-related considerations
(a) Different sites for patient care (magnetic resonance imaging and operating room)
(b) Use of stereotactic frame—potential for airway difficulties
(c) Positioning of patient on operating room table—difficulties with movement disorders
(d) Semi-sitting position—risk of venous air embolism and hypovolemia
(e) Blood pressure control—prevention of hemorrhage from hypertension during electrode insertion
(f) Microelectrode recordings—possible impairment through anesthetic effects
(g) Macro stimulation testing—need for awake and cooperative patient
(h) Long duration of procedure—patient fatigue
(i) Complications—airway obstruction, seizures, neurologic deterioration, and hypertension

Table 41.2 Disease-specific considerations [16]

1. Parkinson's disease
Hemodynamic instability—hypovolemia, orthostatic hypotension, autonomic dysfunction
Respiratory/restrictive lung disease—poor cough
Dysphagia, poor nutrition—anemia, low albumin
Depression, dementia—cooperation during surgery, possible worsening after surgery
Potential drug interactions and adverse effects between anti-Parkinson's medications and anesthesia drugs
Worsening of symptoms in "off-drug" state, intra- and postoperatively
2. Dystonia
Hemodynamic instability—hypovolemia
Laryngeal dystonia—laryngospasm
Spasmodic dysphonia—communication
Poor nutrition
3. Essential tremor
Bradycardia and cardiac arrhythmias due to treatment with beta blockers
4. Epilepsy
Developmental delay
Seizures
Medications—altered pharmacokinetics and dynamics, drug interactions

41.3 Anesthesia for DBS Electrode Insertion

In most cases, DBS electrode insertion is performed under local anesthesia while the patient is sedated with propofol into a semiconscious state. Electrode insertion comprises a surgical procedure in which depth electrodes are guided to target areas with an accuracy of millimeters, using the techniques for stereotactic brain surgery. After adequate local anesthesia with 0.3 % ropivacaine has been achieved, a frame indicating references to the coordinates of the target areas is placed on the head to perform magnetic resonance imaging (MRI). Based on information concerning the three-dimensional positional relations obtained by MRI, depth electrodes are inserted from burr holes toward the coordinates of the target areas while the action potentials of brain neurons are monitored. The duration of surgery is usually approximately 6–8 h when depth electrodes are inserted into both the right and left hemispheres. The depth electrodes are inserted while the absence of adverse reactions such as motor stimulation, visual stimulation, dysarthria, abnormal postural reflexes, dyskinesia, and induced involuntary movements is confirmed by applying stimuli from the electrodes. Since such adverse reactions are strongly affected by excessive sedation and anesthesia, serious adverse reactions may be masked under general anesthesia. Therefore, the procedure is carried out while the patient is in a conscious state under local rather than general anesthesia. Moreover, it is not easy to perform MRI under general anesthesia outside of the operating room. In addition to problems associated with the transfer of the patient between the operation room and the MRI room, no syringe pump necessary for continuous infusion of general anesthetics can be placed in the MRI room. Moreover, an MRI compatible ventilator and vital-signs monitor need to be prepared.

At some institutions and/or in some patients, conscious sedation is employed for DBS device insertion, especially during the opening and closure stages of the procedure. Frequently used drugs include midazolam, propofol, opioids such as fentanyl or remifentanil, and dexmedetomidine. However, there are concerns with all of these drugs [2, 9, 14, 17]. The advantages and disadvantages of the various drugs employed for conscious sedation are summarized in Table 41.3 [16]. Propofol has been widely used, most frequently as a continuous infusion, alone or combined with remifentanil. The mean infusion rate for propofol is approximately 50 μg/kg/min [1, 5, 7].

However, DBS electrode insertion under general anesthesia has occasionally been reported in recent years [4, 15]. This procedure may be effective in patients with severe involuntary movements for whom surgery performed in a conscious state is expected to be difficult. The reported modalities of general anesthesia are mainly total intravenous anesthesia with propofol and remifentanil administration under endotracheal intubation. The blood concentration of propofol is maintained at 2.0–3.0 μg/mL using a target-controlled infusion device, and remifentanil is administered at a dose of 0.1–0.3 μg/kg/min. As MRI is performed, a conventional tracheal tube is employed instead of a spiral tube. Since the electrodes are inserted for various neural monitoring procedures and measurement of brain cell potentials,

Table 41.3 Advantages and disadvantages of drugs used for conscious sedation [16]

Agents	Advantages	Disadvantages
GABA receptor agonists		
Benzodiazepines	Anxiolysis	Abolishes MER
		Alters threshold for stimulation
		Induces dyskinesia
Propofol	Widely used	Abolishes tremors
	Short acting	Attenuation of MER
	Predictable emergence profile	Pharmacokinetic model different in patients with Parkinson's disease
		Induces dyskinesia
		Tendency to cause sneezing
Opioids		
Fentanyl	Minimal effect on MER	Rigidity
Remifentanil	Short acting	Suppression of tremors
Alpha-2 agonist		
Dexmedetomidine	Non-GABA-mediated action	High doses can abolish MER
	Less effect on MER	Hypotension, bradycardia
	Anxiolysis and analgesic effects	
	Sedation—easily arousable	
	Does not ameliorate clinical signs of Parkinsonism	
	Maintains hemodynamic stability	
	Preserves respiration	

MER microelectrode recording, *GABA* γ-aminobutyric acid

it is important to maintain the level of anesthesia as constant as possible. In view of the fact that motor reaction is monitored, muscle relaxants are used only at induction of general anesthesia, and no additional dose should be given. A detailed comparison between insertion placement of the DBS electrode leads under local anesthesia and general anesthesia has not yet been undertaken to elucidate the relative effects of the anesthetics [10].

41.4 Anesthesia for Implantable Pulse Generator Implantation

An IPG is sometimes permanently implanted after DBS electrode insertion. In general, although stimulation testing to assess therapeutic effect is often carried out within 1–2 weeks after electrode insertion, an increasing number of institutions perform IPG implantation following DBS electrode insertion in a single phase. The electrode leads protruding from the inside of the head to the scalp are passed

through one side of the neck with extension leads and the IPG subcutaneously implanted under the right or left clavicle. The estimated duration of surgery is approximately 1 h. The surgical field extends from the head to the neck and the chest. Since the head and neck areas are covered with a drape during surgery, access to a tracheal tube is often difficult. Moreover, because the head is greatly rotated and extended, the use of supraglottic airway devices such as a laryngeal mask airway (LMA) is not recommended. In principle, endotracheal intubation is performed for respiratory management. There is no particular limitation on the anesthetics to be employed. Either inhalation anesthesia with sevoflurane or desflurane or intravenous anesthesia with propofol can be used.

Deep brain stimulation is often employed in the treatment of involuntary movements such as tremor. However, caution is required in patients with underlying diseases causing autonomic nervous system ataxia such as Parkinson's disease, because blood pressure may be markedly reduced at the induction of general anesthesia. Elevation of the lower limbs is undertaken as a precautionary measure, and vasopressors are administered if needed.

41.5 Intraoperative Complications of DBS Electrode Insertion

Intraoperative complications have been reported to occur in 12–16 % of patients, and respiratory complications are of great concern, occurring in 1.6–2.2 % of patients [5, 16]. The reported intraoperative complications include intracranial hemorrhage, seizures, hypertension, air embolism, and airway obstruction due to secretion [1, 13]. Since DBS electrode insertion is performed with the upper body elevated by approximately 30°, air embolism is liable to form at the burr-hole sites. It is necessary to monitor the expiratory carbon dioxide concentration, as well as oxygen saturation. Moreover, oversedation during surgery can increase the possibility of respiratory depression and airway obstruction due to secretion. In the case of airway obstruction, mask ventilation and endotracheal intubation are difficult to perform because a stereotactic frame is placed on the head. The insertion of supraglottic airway equipment such as an LMA or removal of the stereotactic frame should be considered.

41.6 Anesthesia in Patients with an Implanted DBS Device

Patients with an implanted DBS device may undergo surgery for other diseases. The points to consider in the perioperative management of patients with an implanted IPG are basically the same as those for patients with an implanted cardiac pacemaker. In principle, MRI is contraindicated. In the proximity of the device,

monopolar electrocautery should not be employed, but bipolar electrocautery should be used. Puncture of the internal jugular vein ipsilateral to the IPG should be avoided because there is a risk of infection spreading from the central venous catheter to the extension leads. When cardioversion or electrical defibrillation is performed, no pad should be placed directly above the IPG.

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Chapter 42
Anesthetic Management of Pregnant Women with Stroke

Kenji Yoshitani and Yoshihiko Onishi

Abstract Stroke during pregnancy is rare, but when it occurs, most patients have serious neurological sequelae. Hemorrhagic stroke during pregnancy often requires emergency surgery. The potential for fetal harm, as well as significant maternal physiological changes, should be considered during anesthetic management of such patients. Whether Cesarean section or neurosurgical intervention should be prioritized or performed simultaneously is an important issue in pregnant women with stroke. Another clinically significant issue is whether general or spinal and epidural anesthesia should be used. Here, we review the anesthetic management of pregnant women with stroke.

Keywords Pregnant women • Cerebral stroke • Anesthesia

42.1 Introduction

Stroke during pregnancy has been reported to be rare, but once it happened, most patients plunge into serious neurologic conditions. Hemorrhagic stroke often requires emergency surgical intervention. In addition to significant maternal physiological changes, the potential for fetal harm should be considered during anesthetic management of these patients. In pregnant women with stroke, whether Cesarean section or neurosurgical intervention should be prioritized or performed simultaneously is an important issue. Whether the patients receive general or spinal and epidural anesthesia is another clinically significant issue. Here, we review anesthetic management of pregnant women with stroke.

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42.2 Maternal Physiological Changes During Pregnancy

There are important maternal physiological changes that could affect anesthetic management and are mainly the result of hormonal and anatomical changes.

42.2.1 Hormonal Changes

Various hormonal alterations occur to sustain the pregnancy. Human chorionic gonadotropin allows the corpus luteum, which produces progesterone and estrogen, to be maintained. Endorphins and aldosterone are also secreted as shown in Fig. 42.1.

42.2.1.1 Estrogen and Progesterone

Both estrogen and progesterone are important pregnancy-sustaining hormones that lead to endometrial hyperplasia. These hormones also lead to dilatation of blood vessels, which may cause cerebral aneurysms to increase in size [1]. In addition, meningiomas and other neoplasms expressing estrogen and progesterone receptors exhibit faster growth during pregnancy [2]. Increased levels of progesterone, along with an increased rate of carbon dioxide production during pregnancy, are responsible for increases in ventilation. Oxygen consumption also increases by as much as 60 % during pregnancy [3]. As a result, functional residual capacity decreases by as much as 20 % by the end of the third trimester [4]. Progesterone sensitizes the

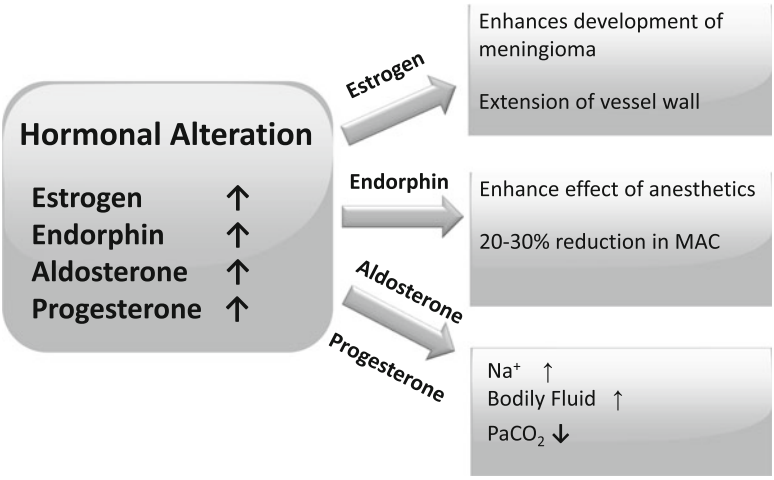

Fig. 42.1 Hormonal changes during pregnancy

respiratory center to carbon dioxide, and $PaCO_2$ falls to approximately 30 mmHg by the 12th week of gestation.

42.2.1.2 Endorphins

In the central nervous system, increased concentrations of endorphins have been found during pregnancy in animal models [5]. Beta-endorphin was identified as an endogenous agonist for the μ-opioid receptor, resulting in reduced requirements for anesthesia.

42.2.1.3 Aldosterone

Higher levels of aldosterone are also observed during pregnancy, with concomitant increases in total body sodium and water [6]. These hormonal changes induce significant physiological changes that affect anesthetic management.

42.2.2 Anatomical Changes

Uterine growth leads to alterations in the respiratory and circulatory systems. A gravid uterus compresses the inferior vena cava, which decreases cardiac output unless the woman is in the left lateral position. An enlarged uterus also compresses the kidneys and may change renal function, decreasing urinary output, for example. In addition, the gravid uterus elevates the diaphragm, shifting the bifurcation of the trachea to a higher position; this may lead to one-lung ventilation if intubation is too deep. However, total circulatory blood volume increases due to water retention induced by aldosterone, leading to anemia and mucosal edema. We need to take both phenomena into account (Fig. 42.2).

42.3 Neurosurgery and Pregnancy

The 28th week of gestation is a turning point for surgical intervention. After the 28th week of gestation, the survival rate of neonates whose birth weight is more than 1250 g reaches 90 % [7]. Therefore, neurosurgical intervention should be performed while continuing the pregnancy before 28 weeks of gestation. On the other hand, neurosurgical intervention should be done after Cesarean section after the 28th week of gestation. Generally, decisions on fetal management can be based on the obstetric condition. In either case, the third trimester is an important determinant of when neurosurgical intervention should be performed.

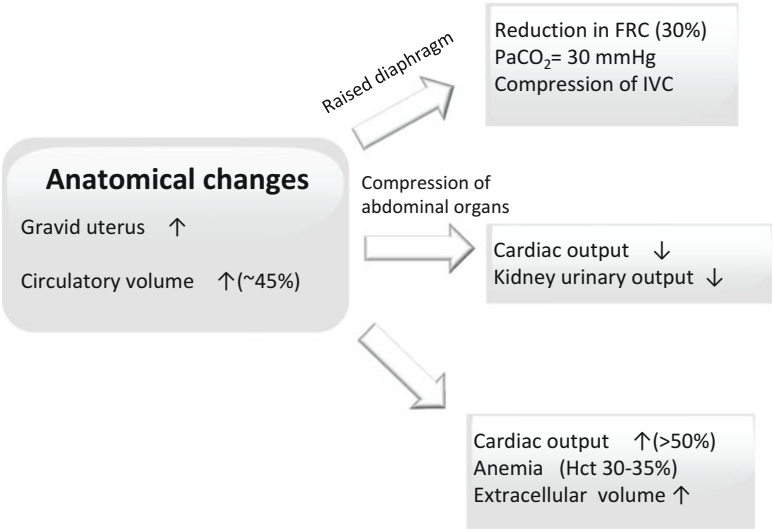

Fig. 42.2 Anatomical changes during pregnancy

42.3.1 Before the 28th Week of Gestation

Before the third trimester, neurosurgery would be performed with a view to maintaining the fetus in utero. Interventional neuroradiology such as coiling of aneurysms, for example, provides an alternative to surgical clipping. Several case reports have demonstrated successful use of endovascular techniques during pregnancy [8, 9].

42.3.2 After the 28th Week of Gestation

Cesarean delivery could be considered before neurosurgical intervention because most fetuses can survive without any complications. Whether cerebral aneurysms have an increased risk of rupture with the progression of pregnancy remains controversial [10]. However, increased progesterone and cardiac output due to hormonal and hemodynamic changes may enlarge cerebral aneurysms [8]. In regard to bleeding from arteriovenous malformations, pregnancy does not confer an increased risk of hemorrhage, but the risk of rebleeding is 25 % during the same pregnancy [11].

After 28–32 weeks of gestation, Cesarean delivery is followed by immediate craniotomy. Interventions during neurosurgery, such as the management of hypotension, use of osmotic diuretics, and mechanical hyperventilation, are risks for the fetus. Therefore, Cesarean delivery is performed before craniotomy.

42.4 Anesthetic Management for Cesarean Delivery and Craniotomy

42.4.1 Premedication

Sedative agents may be appropriate for patients with extreme anxiety. However, the risk of hypoventilation, hypercarbia, and subsequent high intracranial pressure (ICP) should be taken into account. Further, pregnant patients are at an increased risk of vomiting and aspiration of gastric contents. To minimize this risk, non-particulate antacids and H_2 blockers should be administered.

42.4.2 Anesthesia Induction

To prevent regurgitation and aspiration of gastric contents, rapid sequence induction is recommended. Cricoid pressure should be maintained until tracheal intubation is confirmed by capnography. However, hemodynamic responses to intubation can be dangerous for patients with increased ICP. Opioids such as fentanyl should be administered to prevent maternal and fetal hemodynamic deterioration.

42.4.2.1 Tracheal Intubation

Increased aldosterone levels during pregnancy, with increases in total body water and the accumulation of extracellular fluid, produce soft tissue edema, especially in the upper airway. Smaller tracheal intubation tubes (6.0 mm) are useful. Additional equipment for managing a difficult airway, such as the Pentax Airway Scope™, Airtraq™, or bronchial fiberscope, should be readily available for any potential difficulties. In addition, decreases in functional residual capacity can lead to rapid maternal desaturation. At least 2 min of preoxygenation and denitrogenation with 100 % oxygen administered through a tightly fitting face mask is strongly recommended before tracheal intubation of pregnant patients [12]. The gravid uterus raises the diaphragm, facilitating one-lung intubation due to a raised carina tracheae. We need to take this into consideration.

42.4.3 Anesthetic Management

42.4.3.1 Hemodynamic Considerations

To preserve cerebral and uteroplacental perfusion, every effort should be made to maintain hemodynamic stability during neurosurgical intervention. Appropriate

fluid administration, prevention of aortocaval compression, and the prophylactic use of vasopressors should be considered. The alpha-adrenergic receptor agonist, phenylephrine, has been recommended as a vasopressor based on an animal study demonstrating better maternal cardiovascular stability and improved neonatal acid–base status [13]. Generally, blood pressure should be maintained within a narrow range, from 140/90 to 160/110 [14].

42.4.3.2 Ventilation Management

Due to increased ventilation and the effects of progesterone, the normal range of $PaCO_2$ during pregnancy decreases to 30–32 mmHg. While it is controversial whether this clinically affects placental blood flow, severe hyperventilation below 25 mmHg of $PaCO_2$ may cause uterine artery vasoconstriction [15]. Therefore, hyperventilation to reduce ICP should be kept in the range of 25–30 mmHg.

42.4.3.3 Anesthetic Depth Monitoring

Excessively deep anesthesia should be avoided to prevent hemodynamic instability. Endorphins may enhance the effects of anesthetic agents, which may lead to deep anesthesia. Therefore, measuring anesthetic depth is an important part of anesthetic management during pregnancy. Bispectral index monitoring or an alternative method of monitoring consciousness would be useful.

42.4.3.4 Fluid Management

Management of ICP, which reduces brain bulk and preserves blood flow to penumbral areas, is a crucial element in the treatment for stroke. Mannitol has been used to control ICP in patients with stroke. Earlier reports have demonstrated that mannitol is associated with a risk of fetal dehydration [16]. However, more recent individual case reports have shown that 0.25–0.5 mg/kg of mannitol has no significant adverse effect on fetal fluid balance [17, 18]. Clinically, mannitol should be safe for neonates.

42.5 Anesthetic Considerations Concerning Interventional Neuroradiology During Pregnancy

Endovascular coiling of cerebral aneurysms during pregnancy may be better than surgical clipping in regard to hemodynamic stability during the intervention because the skin incision is limited to the femoral region. However, radiation exposure during the intervention may compromise the mother and the fetus.

42.5.1 Radiation Exposure

The suggested maximum acceptable radiation exposure is 10 mSv for pregnant women and 5 mSv for fetuses [19]. When radiation exposure exceeds 120 mSv, risk to the fetus is significantly increased. Yet at doses of less than 40 mSv, the risk for radiation-induced abnormalities is considered negligible [20].

The actual radiation dose used during coiling of cerebral aneurysms is 3 mSv. Cerebral angiography delivers a dose of 1 mSv to the fetus if the abdomen of the pregnant woman is shielded with a lead apron in the front and back [8]. Although the dose is usually less than what is considered hazardous, radiation doses should be minimalized.

42.5.2 Emergency Cesarean Delivery During Interventional Neuroradiology Procedures

Fetal deterioration during interventional neuroradiology procedures raises the possibility that emergency Cesarean delivery needs to be performed in the radiology suite. The neuroradiology suite is separated from the operating room. However, there is one report of delivery in the radiology suite [21]. Recently, hybrid operating rooms capable of supporting both open surgery and endovascular procedures have been introduced. This type of room requires easy-to-use, high-quality imaging equipment, radiation burden-minimizing capabilities, specially trained personnel, and ergonomic features to support both open and percutaneous procedures in a sterile environment [22]. In a hybrid operating room, Cesarean section during interventional radiology procedures may be performed safely.

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Chapter 43
Anesthesia for Patients with Neuromuscular Disease

Yuki Gotanda and Kazuo Ushijima

Abstract Patients with neuromuscular disease can suffer from various perioperative problems such as respiratory failure, cardiac failure, malignant hyperthermia-like syndrome, and an abnormal sensitivity to anesthetics, including neuromuscular blocking agents (NMBA). Anesthesiologists should attempt to preoperatively predict potential complications, make precise perioperative management plans, and provide patients and their families with sufficient information about the risks of anesthesia. The sensitivity of patients with neuromuscular disease to NMBA varies depending on their condition. The recent development of sugammadex, a novel agent that reverses the neuromuscular block induced by steroidal NMBA, might result in changes in the use of NMBA in patients with neuromuscular disease.

Keywords Neuromuscular diseases • Neuromuscular blocking agents • Anesthetics • Malignant hyperthermia

43.1 Introduction

Patients with neuromuscular disease can suffer from various perioperative problems such as respiratory failure, cardiac failure, malignant hyperthermia-like syndrome, and an abnormal sensitivity to anesthetics, including neuromuscular blocking agents (NMBA). These patients require preoperative prediction of potential complications, appropriate choice of anesthetic agents, and close perioperative monitoring. Anesthesiologist should provide patients and their families with sufficient information about the risks of anesthesia. Here we describe the outlines of each disease and anesthetic considerations of patients with neuromuscular disease.

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43.2 Motor Neuron Disorders

43.2.1 Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). The symptoms of MS vary as it induces multifocal regions of inflammation and demyelination in the CNS. The most common symptoms include paralysis, sensory disturbances, a lack of coordination, and visual impairment [1]. Typically, MS patients initially exhibit a relapsing-remitting course, but most patients eventually develop secondary progressive MS [2].

Although the exact disease mechanism remains unclear, it is assumed that it is caused by environmental factors and a genetic predisposition to the activation of a T-cell-based autoimmune response against the CNS [3]. Multiple sclerosis is primarily diagnosed on the basis of the patient's medical history and the results of neurological examinations and magnetic resonance imaging, that is, whether there is evidence of temporally and spatially separate CNS plaques [4]. The incidence of MS (per 100,000) in Japan, the northern regions of the United States, and northern Europe is 2–4, 6–14, and 30–80, respectively [5].

43.2.1.1 Anesthetic Considerations

Stressful conditions such as surgery, infection, hyperpyrexia, and fatigue can exacerbate symptoms in MS patients or cause a relapse [6]. Patients with MS sometimes have problems with ventilating functions due to damage to the inspiratory centers in the medulla oblongata or cervical or thoracic spinal cord. As pulmonary function tests produce normal or slightly abnormal results in patients with mild MS, they do not necessarily reflect the degree of respiratory muscle weakness. Therefore, clinical symptoms might be more useful in assessing respiratory muscle function [7].

With regard to general anesthesia, inhaled anesthetics have been used safely in MS patients. Suxamethonium should not be used because it causes hyperkalemia. Patients with MS can exhibit resistance to non-depolarizing NMBA due to denervation and upregulated acetylcholine receptor expression. On the other hand, muscle weakness and loss of muscle mass can increase MS patients' sensitivity to NMBA [8]. Peripheral nerve stimulation is considered to be unreliable in patients with upper motor neuron lesions [9]. Sugammadex might be useful, although there are no reports about its use in MS patients.

Although spinal and epidural anesthesia has been reported to worsen neurological status, a recent retrospective study found no evidence of relapse after neuraxial anesthesia [10]. Since the safety of spinal and epidural anesthesia for MS patients

has not been established, anesthesiologists should consider the risks and benefits on a case-by-case basis. Peripheral nerve block is not contraindicated for MS patients [11].

Body temperature should be carefully controlled during surgery because hyperthermia has been implicated in worsening MS [12]. It is important to postoperatively manage pain and body temperature in order to avoid symptom exacerbation.

43.2.2 Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that is typically characterized by adult-onset degeneration of the upper and lower motor neurons [13]. It results in progressive paralysis and is usually fatal within a few years of onset [14]. It displays an incidence of about 2 per 100,000. The etiology of ALS has not been elucidated, although various causative factors have been suggested [14]. Only riluzole, an anti-excitotoxicity drug, has been shown to slow the progression of the disease [15].

43.2.2.1 Anesthetic Considerations

Pulmonary function tests must be performed since ALS involves atrophication and weakness of the respiratory muscles, resulting in respiratory failure. Furthermore, chest radiography should be performed to detect aspiration pneumonitis due to bulbar paralysis. Gas exchange is usually well maintained until the loss of lung volume becomes severe.

In ALS patients, the main areas of concern regarding NMBA are suxamethonium-induced hyperkalemia and increased sensitivity to non-depolarizing NMBA. However, the use of peripheral nerve stimulators to monitor the effects of NMBA is considered to be unreliable for dosage guidance in patients with upper motor neuron lesions [9]. Therefore, either NMBA should be avoided or their dosages should be minimized. However, sugammadex has been successfully used in a previous case [16].

Neuraxial anesthesia and peripheral nerve blocks have been reported to be safer modalities than general anesthesia with regard to the risk of respiratory failure. However, administering a local anesthetic close to the nerve could worsen preexisting neurological damage. Anesthesiologists should consider the risks and advantages of regional anesthesia, although it is not contraindicated for ALS patients.

43.3 Neuromuscular Junction Disorders

43.3.1 Lambert-Eaton Syndrome

Lambert-Eaton myasthenic syndrome (LEMS) is a rare disease characterized by proximal limb muscle weakness. It is associated with the production of antibodies directed against the voltage-gated calcium channels (VGCC) in presynaptic motor nerve terminals, which leads to a reduction in the release of acetylcholine. Approximately 50 % of LEMS cases are caused by small-cell lung cancer. The typical symptoms are muscle weakness and autonomic dysfunction. In LEMS, the muscle weakness nearly always starts in the proximal muscle groups. A diagnosis of LEMS can be suspected from the presence of its typical clinical symptoms such as proximal muscle fatigability in the lower limbs, and the diagnosis can be confirmed by electromyography and the detection of serum VGCC antibodies [17]. The standard treatment for LEMS is 3,4-diaminopyridine (3,4-DAP), an agent that increases presynaptic acetylcholine release, in combination with immunosuppressants such as prednisolone and azathioprine [17].

43.3.1.1 Anesthetic Considerations

It might be better to continue administering 3,4-DAP perioperatively. Patients with LEMS show extreme sensitivity to both depolarizing and non-depolarizing NMBA. Therefore, NMBA should be avoided or their doses should be minimized. If NMBA are used, it is necessary to monitor the patient's train-of-four (TOF) ratio during surgery, although it might only have limited value because LEMS patients sometimes show insufficient responses to nerve stimulation [18].

As both 3,4-DAP and pyridostigmine are used to treat LEMS patients, antagonism of the residual neuromuscular block with an anticholinesterase might prove ineffective. Sugammadex might be a new option for reversing neuromuscular block, although there are no reports of its use in LEMS patients.

Patients with LEMS are at risk of postoperative respiratory failure. The postoperative respiratory management strategy for LEMS patients is similar to that for patients with myasthenia gravis.

43.3.2 Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction which decreases the capacity of the neuromuscular end plate to transmit nerve signals, resulting in muscle weakness and fatigue [19]. Its incidence has been reported to vary from 1.7 to 10.4 per million depending on the study location. It is characterized by autoantibody attacks, which mainly target the skeletal muscle

acetylcholine receptor (AChR) but sometimes target the muscle-specific receptor tyrosine kinase or low-density lipoprotein receptor-related protein 4 [20, 21]. The treatments for MG include cholinesterase inhibitors, plasma exchange, intravenous immunoglobulins, immunosuppressive agents, and thymectomy.

43.3.2.1 Anesthetic Considerations

Elective surgery should be performed during a stable phase. In cases requiring emergency surgery, plasma exchange should be considered if the patient suffers a myasthenic crisis.

Routine premedication with sedatives or opioids should not be used to avoid respiratory depression. It is disputed whether cholinesterase inhibitors should be continued until the time of the operation [22]. A previous study suggested that preoperative bulbar symptoms, a preoperative serum level of anti-AChR antibody of >100 nmol/L, and intraoperative blood loss of >1,000 mL are prognostic factors for postoperative myasthenic crisis [23].

Concerning general anesthesia, the most important consideration is the use of NMBA and their reversal. Myasthenia gravis patients demonstrate increased sensitivity to non-depolarizing NMBA, as they possess fewer AChR in their synaptic clefts. It is necessary to evaluate the patient's TOF ratio during surgery to obtain a certain degree of neuromuscular block. However, the anesthesiologist must take into account that the response of the adductor pollicis is not necessarily a good indicator of the response of the respiratory muscles to NMBA [24]. Anticholinesterases such as pyridostigmine, neostigmine, and edrophonium can be used safely. However, it is better to wait for the patient to spontaneously recover from non-depolarizing neuromuscular block because MG patients can develop prolonged depolarizing blocks following the administration of neostigmine. The decrease in the number of functional end-plate receptors in MG patients can result in a decreased response to depolarizing NMBA. Thus, high doses of suxamethonium might be required for rapid sequence tracheal intubation in MG patients. On the other hand, the response to suxamethonium is increased in patients who receive preoperative pyridostigmine because their plasma cholinesterase activity is decreased.

In a previous case, the use of sugammadex made it possible to safely achieve general anesthesia with NMBA without prolonged mechanical ventilation [25].

Spinal anesthesia produces excellent block while maintaining protective airway reflexes. However, a high level of spinal anesthesia might impair respiratory function. In addition, the use of intrathecal opioids can cause respiratory muscle weakness and central respiratory depression. Epidural block is an effective means of achieving postoperative analgesia and minimizes the need for NMBA during surgery. However, ester-type local anesthetics comprising metabolized cholinesterase might cause problems, particularly in patients taking anticholinesterases [26].

Myasthenic crises caused by stressors such as pain are the most common postoperative issue. Local anesthesia, peripheral nerve block, and epidural analgesia are useful for avoiding the side effects of opioids such as respiratory depression. Noninvasive ventilation, that is, the use of continuous positive airway pressure or biphasic positive airway pressure, might obviate the need for tracheal intubation in patients exhibiting postoperative respiratory failure [27].

43.4 Muscle Disorders

43.4.1 Duchenne Muscular Dystrophy and Becker's Muscular Dystrophy

Muscular dystrophies are a heterogeneous group of progressive neuromuscular disorders that are classified into several types based on various factors such as their clinical presentation, family history, and molecular characterization [28, 29].

Duchenne muscular dystrophy (DMD) and Becker's muscular dystrophy (BMD), which exhibit X-linked recessive patterns, are caused by mutations in the dystrophin gene [30]. The prevalence of DMD is 1 per 3,500 and that of BMD is 1 per 30,000 [31]. The characteristic symptom of DMD is progressive symmetric muscular weakness, and its onset usually occurs at around 3–5 years of age [32]. Most DMD patients lose the ability to walk by the age of 12 and usually die by the end of adolescence [33]. Respiratory impairment occurs due to respiratory muscle or diaphragm weakness. Dilated cardiomyopathy is present in almost all patients by 18 years of age [34]. The symptoms of BMD occur later than those of DMD and progress at a slower rate [31].

There are no cures for these diseases, although glucocorticoids slow the decline in muscle strength and delay the onset and progression of respiratory dysfunction [35].

43.4.1.1 Anesthetic Considerations

Patients with muscle dystrophy frequently exhibit respiratory impairment. Therefore, pulmonary function tests should be performed and preoperative training in both noninvasive positive pressure ventilation and manual and mechanically assisted (e.g., with a bronchial secretion clearance device) coughing be considered [36]. Detailed cardiac inspections are also required in order to evaluate cardiac abnormalities such as dilated cardiomyopathy and arrhythmia.

Muscle dystrophy is associated with anesthesia-related risks such as potentially fatal reactions to certain anesthetics, upper airway obstruction, hypoventilation, atelectasis, congestive heart failure, cardiac dysrhythmia, and respiratory failure [31].

Suxamethonium should not be used due to the risks of hyperkalemia and rhabdomyolysis. Although the risk of malignant hyperthermia was not found to be increased in muscle dystrophy patients, they can develop a malignant hyperthermia-like syndrome characterized by rhabdomyolysis during anesthesia induced by inhaled anesthetics [31, 37]. In addition, rhabdomyolysis sometimes occurs in the recovery room after surgery [38]. While volatile anesthetics are not completely contraindicated, it seems to be better to avoid using them. Propofol can be used instead of volatile anesthetics, although its long-term infusion can cause rhabdomyolysis.

In patients with DMD, the induction of anesthesia with non-depolarizing NMBA takes longer and it also takes longer for the patients to recover from the anesthesia [39]. Sugammadex might be useful because DMD patients exhibit unpredictable reactions to anticholinesterases. There are some reports of the safe use of sugammadex in muscular dystrophy patients [40].

Although regional anesthesia can be used instead of general anesthesia to avoid triggering rhabdomyolysis, high spinal anesthesia can occur if the patient has a spinal deformity.

Close monitoring of the patient's electrocardiogram, body temperature, serum potassium and creatine kinase levels, and blood gases is indispensable. Moreover, attentive observation to respiration is necessary due to the risk of postoperative respiratory impairment.

43.4.2 Myotonic Dystrophy

Myotonic dystrophy (DM) is the most common type of muscular dystrophy in adults and exhibits an autosomal dominant inheritance pattern. The prevalence of DM is 1 per 8,000 [41]. Its clinical characteristics include myotonia and progressive muscle degeneration [42]. Two types of DM exist, type 1 (DM1) and type 2 (DM2), which result from the expansion of CTG and CCTG DNA repeat sequences, respectively [41]. The symptoms of DM1 are facial weakness, ptosis, distal limb weakness, frontal pattern baldness, and selective atrophy of the sternocleidomastoids. Cardiac conduction defects and tachyarrhythmia are common in DM1 patients, but cardiomyopathies are not. Patients with DM2 exhibit a variable clinical phenotype [41]. Respiratory complications can occur due to many factors such as weakness of the pharyngoesophageal and respiratory muscles or central mechanisms [43].

43.4.2.1 Anesthetic Considerations

Upper abdominal surgery and severe muscular disability, as assessed by the presence of proximal limb weakness, are considered to increase the risk of perioperative pulmonary complications [42, 44]. A cardiac inspection should be performed to

evaluate cardiac conduction defects and myocardial function. It is important to confirm which drugs the patient is taking—whether they are taking phenytoin, quinine, or procainamide, for example—as these drugs interact with some anesthetics.

Maintaining a normal intraoperative body temperature is necessary as shivering can cause myotonia.

Suxamethonium is contraindicated for DM patients because it causes prolonged muscular contractions. Non-depolarizing NMBA produce a variable response. It is necessary to use neuromuscular monitoring—by assessing the patient's TOF ratio, for example—during surgery to obtain an adequate degree of neuromuscular block. Anticholinesterases should be avoided because they can precipitate myotonia. Sugammadex has been reported to help DM patients recover from neuromuscular blocking with rocuronium [44].

The use of volatile anesthetics is controversial due to the potential risk of malignant hyperthermia, although some reports have described their successful use in maintaining anesthesia.

Opioids have been reported to increase the risk of prolonged respiratory depression after surgery and to cause muscle rigidity and vocal cord closure. However, short-acting opioids such as remifentanil have been safely used in DM patients [45, 46].

Neuraxial anesthesia has been reported to be useful in DM patients, while high spinal anesthesia can cause respiratory impairment [47].

Particular attention should be paid to the risk of aspiration when patients drink or eat.

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Chapter 44
Management for Massive Hemorrhage During Surgery

Eiichi Inada

Abstract Although the incidence of massive hemorrhage during surgery is low, the prognosis of massive hemorrhage is poor. When we encounter massive hemorrhage, systematic approach is mandatory. Physicians, nurses, and technicians at the scene, staff in the transfusion department, and the staff in the blood center work as a team. Achieving hemostasis by surgical maneuvers and restoration of blood volume to maintain organ perfusion and oxygenation is essential. If the patient requires vasopressors and lack of crossmatched red cell concentrate (RCC), type-specific RCC should be used. When the situation is life-threatening, un-crossmatched type-compatible RCC should be used. To correct coagulopathy, judicious use of blood components such as fresh frozen plasma and platelet concentrates is mandatory. It may require cryoprecipitate, a fibrinogen product, when fibrinogen level is very low. To improve patient's outcome, understanding of current blood transfusion guidelines and institutional simulation is important.

Keywords Platelet concentrate • Fresh frozen plasma • Cryoprecipitate • Fibrinogen • Crossmatch • Massive transfusion protocol

44.1 Introduction

Blood loss due to bleeding is a reversible process as long as the amount of blood loss is compensated by physiological mechanisms, fluid resuscitation, and blood transfusion. However, the amount and rate of bleeding far greater than compensatory mechanisms lead to a vicious cycle which worsens bleeding tendency and impairs major organ dysfunctions (Fig. 44.1) [1]. It may result in permanent neurological damage and death.

Annual survey of the critical incidents related to anesthesia by the Japanese Society of Anesthesiologists (JSA) repeatedly demonstrated that critical bleeding is one of the major causes of intraoperative cardiac arrest [2, 3]. The JSA studies

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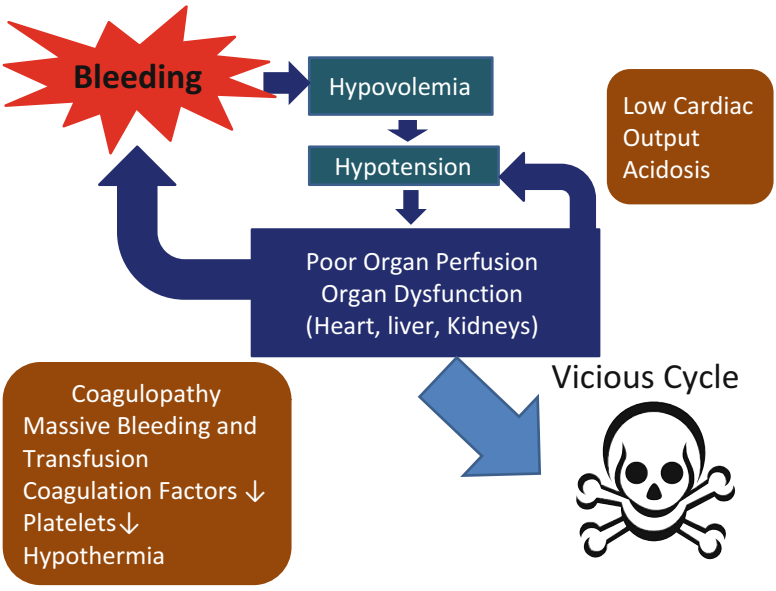

Fig. 44.1 Vicious cycle due to critical bleeding. A simple problem may go into a complex, catastrophic problem

demonstrated that critical bleeding in the perioperative period was the leading cause of the perioperative death in the first week postoperatively [4, 5]. About a half of perioperative critical bleeding was related to preoperative hemorrhagic shock by multiple traumas, rupture of the large blood vessels, and so on. The rest were related to intraoperative bleeding associated with surgical manipulation. Although the possibility of massive and rapid bleeding was usually anticipated and some preventive and treatment measures were taken to deal with critical bleeding, prognosis was still grave.

The Subcommittee on Surveillance of Anesthesia-Related Critical Incidents of the JSA analyzed the data. Contributing factors included far greater rate and amount of bleeding than anticipated, delay in decision to start blood transfusion and to order additional blood products, hesitation to use ABO-compatible red cell concentrates (RCC) including group O blood without crossmatching, delayed transportation of the blood products from the Red Cross blood centers, and inadequate manpower. In patients with critical bleeding, blood loss was greater than 12 L/60 kg (body weight) in 35.2 % of the patients, and the maximal estimated bleeding rate was greater than 240 ml/60 kg (body weight)/min in 44.9 % of the patients (Fig. 44.2). Despite shortage of blood products in the hospital, crossmatching test was waived in 13.4 % of the patients, and ABO-compatible blood products including type O blood were used only in 1.3 % of the patients. It suggests that risks of using un-crossmatched blood might be a major concern in the physicians in Japan even in the life-threatening situation.

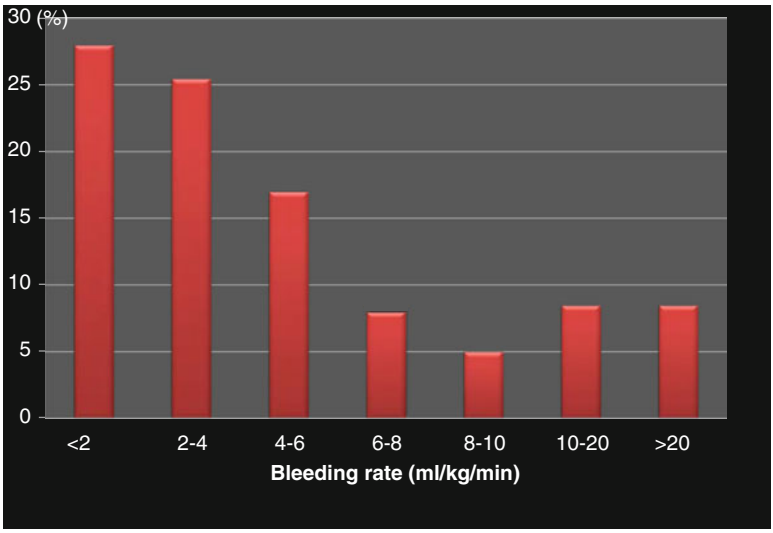

Fig. 44.2 Estimated rate of bleeding in patients with critical bleeding

Although the national guidelines for blood transfusion made by the Japanese Ministry of Health, Labour and Welfare exist, the issues on critical bleeding were not fully discussed, and clear guidelines were not described. Massive bleeding is commonly defined as the loss of one blood volume within a 24 h period. A variety of definition of critical bleeding has been used such as a rate of blood loss of 150 ml/min or more than 50 % loss of circulating blood volume within 3 h. The JSA has arbitrarily defined the critical bleeding as acute bleeding which is very likely to result in life-threatening situation in a short period of time, i.e., within a few minutes to a few hours. Immediate and appropriate therapy to stabilize the patient and to avoid secondary damages is required. The JSA and the Japan Society of Transfusion Medicine and Cell Therapy made the guidelines for treatment of critical bleeding to improve patient outcome in 2007.

44.2 "Guidelines for Actions Against Intraoperative Critical Hemorrhage"

44.2.1 Outlines of the "Guidelines for Actions Against Intraoperative Critical Hemorrhage"

The JSA established "Guidelines for Actions Against Intraoperative Critical Hemorrhage" (Guidelines) in collaboration with the Japanese Society of Blood Transfusion and Cell Therapy in 2007. Fundamental concept is that lifesaving measure is

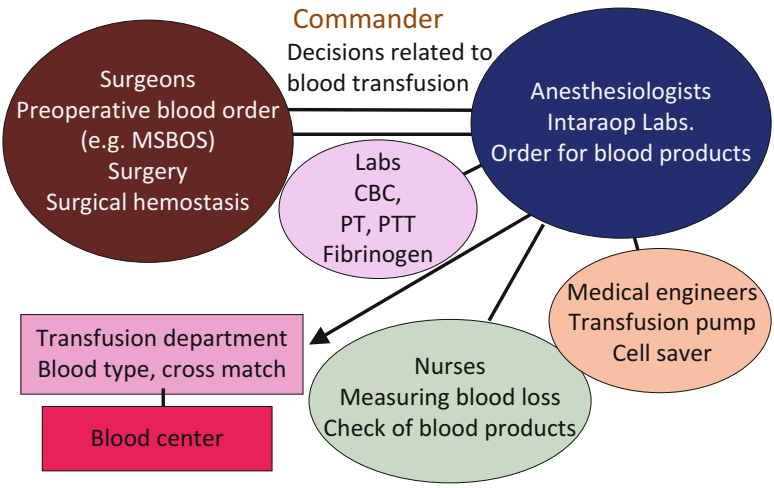

Fig. 44.3 Work as a team when critical bleeding occurs

much more important than theoretical complications in the setting of life-threatening critical bleeding.

There are a few basic strategies as follows:

1. Physicians and nurses, medical engineers in the operating room and emergency room, staff in the blood transfusion department, and staff in the blood center work as a team (Fig. 44.3). Intense communication between them is mandatory.
2. The nominated commander is in charge of the important decisions related to blood transfusion strategies and patient management (Table 44.1).
3. Surgeons concentrate on hemostasis rather than on proceeding the planned procedure. Damage control surgery should be considered.
4. Anesthesiologists insert a few large-bore intravenous lines; draw serial blood samples for blood cell counts, electrolytes, and coagulation studies; and request blood products according to the amount and rate of hemorrhage, vital signs, laboratory data, the prospect of hemostasis, and the patient's preoperative general status.
5. The commander determines the urgency of blood transfusion in accordance with the situation and notifies the transfusion department using the code (Fig. 44.4). Un-crossmatched ABO-compatible blood products should be used without hesitation if necessary.
6. Euvolemic status should be maintained to keep adequate perfusion pressures of major organs and to maintain their functions.
7. Hypothermia should be best avoided because hypothermia worsens bleeding tendency and increases the risk of disseminated intravascular coagulation. Devices such as warming blankets and efficient blood warmer should be used.
8. Electrolyte imbalance such as hyperkalemia and hypocalcemia should be aggressively treated.

Table 44.1 Roles of the commander

Declarations of critical bleeding
Call for help
Notify the transfusion department
Know the amount of blood products in storage
Declaration: critical bleeding, resolution
In the OR
Communicate with the surgeons
Decide to proceed or to change the procedure to damage control surgery
Assess bleeding/hemostasis
Take blood samples for CBC, electrolytes, and coagulation studies and fibrinogen levels
Get ready to use equipments including cell saver and blood transfusion pumps

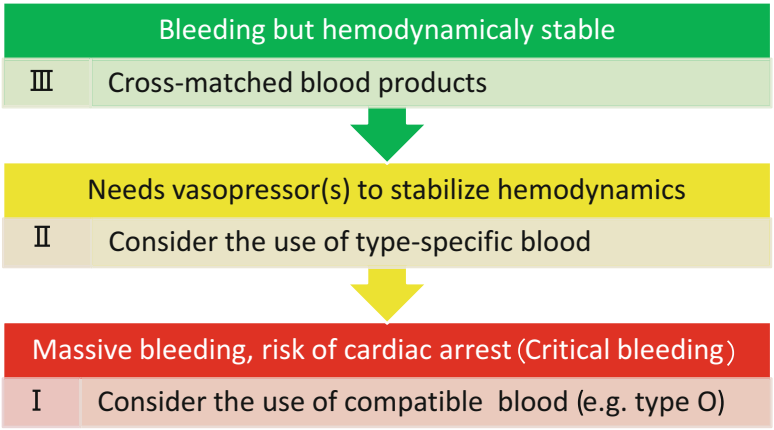

Fig. 44.4 Emergency blood transfusion codes

9. The institutional structure of the blood transfusion system and transport time from the blood center should be understood by the staff concerning blood transfusion.
10. The institutional guidelines for critical and massive bleeding should be established according to the Guideline.
11. Simulation training involving all departments related to blood transfusion should be performed.

44.2.2 Commander and the Team

When critical bleeding occurs, one single physician should become the commander who will direct and organize the overall therapy including blood transfusion. The commander declares a state of emergency. Most often, the anesthesiologist will

become the commander in the operating room (OR) because the anesthesiologist knows the general condition of the patient and is aware of the situation around the OR including diagnostic laboratory data, storage of blood products in the institution, and transport of blood products from the Red Cross blood center. After the life-threatening condition was evaded, the commander declares the end of emergency.

The personnel in the OR, the emergency room (ER), diagnostic laboratories, the department of blood transfusion, and the Red Cross blood center work together as a team in the setting of critical bleeding (Fig. 44.3). Close communication among all departments is essential. Anesthesiologists would start new large-bore intravenous lines (16 or 14 gauge catheters) for fluid resuscitation and blood transfusion, take blood samples for blood gases, and complete blood cell count, electrolytes, coagulation studies, and crossmatching. Arterial and central venous lines may be inserted if the situation permits. The commander requests blood products according to the general condition of the patients, laboratory data, and availability of blood products. Surgeons concentrate on hemostasis rather than on completing the planned procedure. Damage control surgery should be considered. Medical engineers prepare for intraoperative autologous blood transfusion devices and rapid infusion pumps. Nurses measure the amount of blood loss and keep contact with the blood bank and check blood product bags.

Postoperative management in the intensive care unit is probably required. Postoperative mechanical ventilation may be required.

44.2.3 Fluid Resuscitation Using Crystalloids and Colloids

It is important to maintain tissue perfusion by appropriate volume status and vasopressors if necessary. Restoration of circulating volume is initially achieved by rapid infusion of crystalloids such as lactated, acetated, or bicarbonate Ringer's solution and normal saline. Artificial colloids such as hydroxyethyl starch (HES) are usually indicated when blood loss is greater than 20 % of one blood volume. HES is indicated in critically bleeding patients. The amount of HES is commonly limited to 1,000 ml or 20 ml/kg of body weight because HES potentially induces platelet inhibition and renal dysfunction. HES is known to interfere with coagulation according to molecular weight. Because the currently available HES in Japan contains relatively low and medium molecular weight, interference with coagulation may not be significant. Duration of plasma volume expansion may be short-lived. The upper limit of HES is not described in the Guideline.

The use of albumin solution has been controversial [6, 7]. Currently 5 %, 20 %, and 25 % albumin solutions are available in Japan. Plasma protein fraction is also available. The Guideline did not prohibit the use of albumin solutions in the setting of critical bleeding. It should be kept in mind that the use of albumin may worsen the prognosis of patients with head injury [8].

44.2.4 Blood Transfusion

44.2.4.1 Red Blood Cell Transfusion

Fully crossmatched RCC is used in the routine cases. However, in the critical bleeding, there would not be enough time to prepare crossmatched RCC. Lifesaving is far important than to avoid remote risk of delayed hemolysis and other minor blood transfusion reactions. It is important to consider the risks and benefits of specific blood products in terms of availability and timing.

If blood typing and screening is performed preoperatively, RCC would be available within 10–15 min after blood typing or computer crossmatching (Table 44.2). The ABO group type-specific RCC can be used. If the ABO group type-specific RCC is not available in a short period of time, ABO-compatible RCC including group A or type B, then type O RCC should be used. If the patient's blood type is AB, either type A or type B, RCC should be used if available.

Distribution of ABO and Rh types varies from country to country. In Japan, the distribution of blood types is different from European countries. The blood types of Japanese roughly consist of type A 40 %, type O 30 %, type B 20 %, and type AB 10 %. The ratio of Rh-D(+) is over 99 % in Japan. The population of people with type AB, Rh-D(−) is less than 1/2,000 population.

Even the existence of alloantibody to red blood cells is known, the risk of hemolysis needs to be assessed against the risk of withholding blood transfusion until compatible RCC can be provided. The Guidelines recommend that un-crossmatched blood should be used when time does not allow for waiting the crossmatched RCC even in patients with red cell antibody. Rh-D(+) blood is most safely used even in the patient with Rh-D(+). Use of anti-Rh-D immunoglobulin in patients with Rh-D(−) should be considered postoperatively.

There is a risk of delayed hemolysis when un-crossmatched type-specific RCC is used. Overall risk of delayed hemolysis due to alloantibody and Rh incompatibility is up to 1 %. The patient with alloantibody to red cell who received un-crossmatched blood products should be observed closely for a few weeks to

Table 44.2 Approximate time for expedited release of red cell concentrate

ABO group	Crossmatch	Approximate preparation time in blood bank (min)	Risk of incompatibility
O	None	5	RBC alloantibody
ABO specific	None	10–15	RBC alloantibody
ABO specific	Abbreviated	30	Screen negative = none
			Screen positive = RBC alloantibody
ABO specific	Full	45–60	None

find signs of hemolysis promptly. Delayed hemolysis occurring after a few days to a few weeks can be managed without difficulty.

Irradiation is indicated to the RCC and platelets to prevent transfusion-related graft-versus-host disease (GVHD). Even in the setting of critical bleeding, irradiated blood products should be used.

44.2.4.2 Autologous Blood Transfusion: Intraoperative Blood Salvage

Use of preoperative autologous blood donation is limited. Effectiveness of preoperative autologous blood donation has been controversial. Preoperative autologous blood donation is encouraged in patients with rare blood type undergoing major surgery with the possibility of large blood loss. Our studies suggested that in obstetric patients with placenta previa and other factors, leading large blood loss may be benefited from the preoperative autologous blood donation. The median amount of preoperative autologous blood donation was 800 ml.

Use of intraoperative autologous blood salvage is encouraged when the contraindications for this method do not exist. Contraindications include contamination of malignant tumor cells and infectious organism. The help of medical engineers may be required. This technique may be quite useful in patients with ruptured major blood vessels.

44.2.4.3 Fresh Frozen Plasma

The major recommended indication of fresh frozen plasma (FFP) is to supplement multiple coagulation factors for bleeding tendency due to deficiencies in coagulation factors. Trigger levels are prothrombin time (PT) activity equal to or less than 30 % or prothrombin time-international normalized ratio (PT-INR) equal to or greater than 2.0, activated partial prothrombin time (aPTT) greater than two times the upper limit of the institutional standard level or activity equal to or less than 25 %, or fibrinogen level less than 100 mg/dl in Japan.

The indications for FFP are similar in other countries. The practice guidelines for perioperative blood transfusion by the American Society of Anesthesiologists state that FFP transfusion is indicated for (1) correction of excessive microvascular bleeding (coagulopathy) in the presence of PT greater than 1.5 times normal or INR greater than 2.0 or an aPTT greater than two times normal and (2) correction of excessive microvascular bleeding secondary to coagulation factor deficiency in patients transfused with more than one blood volume and when PT and aPTT cannot be obtained in a timely fashion [9].

In bleeding patients, these criteria may be fulfilled when the blood loss is greater than one blood volume. Fibrinogen concentration may become less than 100 mg/dl before other coagulation factors fall below the minimum hemostatic levels by bleeding [10, 11]. PT may not reflect decreased level of fibrinogen.

The fibrinogen concentration which causes microvascular bleeding is considered 50–80 mg/dl. It should be avoided to let fibrinogen concentration fall below this level in actively bleeding patients.

However, performing these coagulation studies may not be practical in actively bleeding patients with unstable hemodynamics. It also delays administration of FFP because of preparation time. Therefore, it is recommended to draw blood samples for later coagulation studies and to give FFP without waiting the final results.

Cryoprecipitates are useful to increase fibrinogen level efficiently with small amount of volume. Each unit of cryoprecipitate contains 150 mg of fibrinogen in about 15 ml of plasma. Unfortunately, cryoprecipitates are not commercially available in Japan. The only current indication for fibrinogen concentrates is congenital fibrinogen deficiencies with bleeding tendency. Fibrinogen products were approved for treatment of acquired low fibrinogenemia in the past. An estimated 10,000 cases of hepatitis C infection have been attributable to the use of inappropriately heated fibrinogen in Japan. It became a social issue, and citizens may hesitate to receive fibrinogen products even though the currently available products are properly produced and safe.

Recombinant activated factor VII concentrates are indicated with the specific factor deficiency with antibodies and are very expensive. Some anecdotal cases indicated the usefulness of factor VII products in patients with massive bleeding. Although some people recommend to use recombinant activated factor VII when other ordinary hemostatic measures have failed, one retrospective study suggested last-ditch recombinant activated factor VII therapy was ineffective to rescue the patients who were resistant to conventional treatment [12]. Recent review by Johannsson did not support the routine use of recombinant activated factor VII concentrates for patients with massive bleeding [13]. It may increase risk of thromboembolic events. Therefore, the use of recombinant activated factor VII was not mentioned in the Guideline.

ABO-compatible FFP can be used when type-specific FFP is not available.

44.2.4.4 Platelet Concentrates

Platelet concentrates are indicated when platelet count is less than 50,000 associated with bleeding tendency in usual surgical patients. The minimum level of 100,000/mm^3 is recommended for ophthalmologic and intracranial surgery. In the critical bleeding, platelet concentrates should be administered to maintain platelet count greater than 50,000/mm^3. The trigger of platelet transfusion may be higher than usual (e.g., 75,000/mm^3) in patients with critical bleeding. ABO-compatible platelet concentrates can be used when type-specific platelet concentrates are not available.

Serial and frequent measurements of blood cell count are necessary because platelet count changes rapidly in the setting of critical bleeding.

44.2.4.5 Avoidance of Adverse Effects and Complications of Rapid Blood Transfusion

Although blood transfusion may save lives in patients with critical bleeding, it presents risks to the patients. The potential risks include accidental transfusion of the incompatible unit of blood; transmission of viral, bacterial, and other microbial infections; graft-versus-host disease (GVHD); transfusion-related acute lung injury (TRALI); transfusion-associated circulatory overload (TACO); and so on. These complications can be fatal either in a short term or in a long term. Correct identification of the recipient blood group and use of compatible blood products are of paramount importance. It is strongly recommended to check the recipient blood group twice before blood transfusion. In an emergency situation, some physicians often check blood type only once. To avoid blood transfusion-related GVHD, irradiation to the blood products is highly recommended. Some institutions receive only irradiated blood products, and some receive nonirradiated blood products and irradiate blood products immediately before blood transfusion to avoid the risk of hyperkalemia [14]. Sometimes, there is no time to irradiate blood products in life-threatening situation. It is helpful to store irradiated blood products and to order irradiated blood products from the blood center for emergency.

Acute complications related to rapid blood transfusion including hypothermia, acid-base abnormalities, and electrolyte imbalance should be considered and appropriately treated.

It is important to avoid hypothermia. Hypothermia reduced platelet aggregation and vascular reactivity, leading to increased blood loss [15]. Efficient blood warmer should be used. Warm forced-air system and other devices should be used to keep normothermia.

Hyperkalemia due to the old RCC and irradiated blood can be fatal in massive blood transfusion [16]. Although it is rare to see life-threatening hyperkalemia due to blood transfusion, it may occur in the presence of impaired renal function and severe acidosis. It may also occur in infants and small children. Serial measurements of blood samples are necessary. Electrocardiogram changes including tall T wave may not be sensitive and often overlooked. Hyperkalemia should be treated by alkalization of the blood by hyperventilation and administration of sodium bicarbonate, furosemide, and calcium chloride (or calcium gluconate). After massive blood transfusion, hypokalemia may occur.

Hypocalcemia may occur with rapid transfusion of the RCC and FFP which include citrate. In the usual setting, hypocalcemia can resolve spontaneously in 10 min. However, in massive and rapid blood transfusion, severe hypocalcemia resulting in cardiac depression and circulatory collapse is a real possibility. Hypocalcemia should be treated by calcium products such as calcium chloride.

Use of rapid transfusion device is optional. Although these devices are capable of transfusing blood rapidly in the critically bleeding patients, these are not designed for this purpose. Some fatal accidents have occurred because of lack of

experience and neglect of the proper use. These rapid transfusion devices should be used by the experienced medical engineers or physicians.

44.2.4.6 Importance of Institutional Guidelines and Simulation

The guidelines set by the JSA and the Japan Society of Transfusion Medicine and Cell Therapy can be modified according to the situation of each institution. Our studies demonstrated that more than 80 % of the major institutions had their own blood transfusion guidelines. However, only one-third of the institutions performed simulations. Although these guidelines are well known and understood by the staff in the blood bank, these are not well understood by surgeons and obstetricians particularly working for the small institutions.

It is not clear how much blood products should be stored in each institution. The more the storage, the higher the amount of the wasted blood products. It is also important to know the transfer time from the Red Cross blood center. It takes more than 60 min to receive the blood products from the Red Cross blood center in the emergent situation in some institutions. It is also important to know how long it takes to determine blood types and to crossmatch. These factors should be taken into consideration when to order blood products.

44.3 Current Status

We have been following the situation of critical bleeding and blood transfusion in different departments including anesthesia, pediatric anesthesia, emergency medicine, obstetrics, and blood transfusion in Japan [17]. The study was supported by the Grant of the Ministry of Health, Labour and Welfare (H.19-MP-General-031) since 2007.

We performed a questionnaire survey regarding the present status of critical bleeding (≧5,000 ml) occurring in major hospitals in Japan in 2006 [18]. A total of 692,241 cases managed by anesthesiologists in 247 institutions were registered. There were 2,657 cases of massive hemorrhage over the circulating blood volume in the operating room, and 404 of them were considered critical. Thus, the number of patients with massive bleeding was 6.6 times that of patients with critical bleeding. In 1,257 patients with massive blood loss (≧5,000 ml), 196 patients (15.6 %) died within 30 postoperative days, and 160 patients (12.7 %) had major sequelae including permanent brain damage. While the amount of transfused RCC was 25.2 ± 24.2 units (one unit means RCC from 200 m of donated blood), the amount of RCC storage for emergency in the hospital was 12.7 ± 10.1 units for type A, 9.7 ± 7.3 units for type B, 11.9 ± 9.6 units for type AB, and 11.3 ± 11.0 units for type O. The un-crossmatched, type-specific blood transfusion and compatible, different blood type transfusion were performed in 8.2 % and 4.3 %, respectively. The lowest hemoglobin concentration was below 5 g/dl in 16.7 % of

the patients, but un-crossmatched, type-specific blood transfusion was performed only in 19.0 % and compatible, different blood type RCC transfusion in 5.2 %. Intraoperative blood salvage was performed in 5.7 % in patients undergoing noncardiac surgery.

The JSA performed the survey of massive blood loss defined as blood loss greater than 5,000 ml in the OR in 2011 [19]. One thousand and nine hundred cases were registered from 170 JSA-certified hospitals. A total of 643,999 cases managed by anesthesiologists in 186 institutions were registered. The number of the critical cases with blood loss greater than 5,000 ml was 1,900. The incidence of critical bleeding was 25.9 per 10,000 anesthetic cases. One-week mortality was 10.9 %. ABO type-compatible blood was used in 10.9 % of the cases. It seems that ABO type-specific blood was used more frequently in patients with massive bleeding. The 30-day mortality seems to be improved.

These surveys suggest recognition of the guidelines by the JSA was improved and timely judgment of blood transfusion was facilitated.

44.4 Massive Transfusion Protocol (MTP)

Recently, massive transfusion protocol (MTP) has been advocated in patients with massive bleeding and anticipated massive bleeding [20–22]. It is suggested that MTP improved the mortality of trauma patients during war. MTP includes not only blood transfusion but also general supportive measures.

General supportive measures should be taken to maintain oxygenation, cardiac output, tissue perfusion, and metabolic homeostasis. Hypothermia should be avoided, and body temperature should be kept over 35 °C. Significant metabolic acidosis should be aggressively treated to keep pH greater than 7.2, base deficit less than −6, and lactate levels below 4 mmol/L. Hypocalcemia should be corrected to keep calcium level greater than 1.1 mmol/L.

Permissive hypotension and minimal volume resuscitation are generally preferable, while active hemorrhage is being controlled. However, permissive hypotension is contraindicated in patients with traumatic brain injury, because hypotension decreases cerebral perfusion pressure (i.e., mean arterial pressure minus intracranial pressure) to the dangerous level. The safe low threshold for blood pressure is not clearly demonstrated.

Various MTPs have been used in different institutions. The effects of dilutional coagulopathy and hypovolemia may be minimized by using MTP. The optimal ratio of RCC to other blood components such as FFP and PC has not been determined yet. MTP often includes 1:1:1 ratio of RCC, FFP, and PC.

If the commander at the scene determines that the patient meets criteria for MTP activation, the commander notifies the blood bank and laboratories to activate MTP.

Once a patient is in the protocol, the blood bank is able to insure rapid and timely availability of blood components to facilitate resuscitation. A pack of RCC, FFP, and PC will be delivered to the OR or ER immediately. The pack of blood products

will be delivered to the OR or ER until bleeding is under control. If fibrinogen level is very low, cryoprecipitate will be delivered. Once definitive control of bleeding has been achieved, a restrictive approach to blood product transfusion is preferred because of the well-known risks and negative outcomes of transfusion.

There is no definitive data showing that MTP is useful in patients with intraoperative surgical bleeding.

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Part X
Anesthetic Management: Neuroanesthesia for Pediatric Surgery

Chapter 45
Anesthesia for Pediatric Tumor Surgery

Hiroshi Otake

Keywords Pediatric anesthesia • Oncology • Malignancy

45.1 Introduction

Children are not simply "small adults," so it is important for the anesthesiologist to understand "how children are different from adults." The management of children with malignancies presents tremendous challenges for the medical practitioner, who has to deal with a wide variety of pathologies, preserve physical and mental development, and provide various types of support for the patient's family, including financial and psychological. The survival rate in such patients, however, has improved dramatically over the last few decades due to the development of new strategies. The combination of surgery, chemotherapy, and radiotherapy is commonly used, and new diagnostic and therapeutic devices are being introduced. Progress in cancer treatment has brought not only benefits for children and families but also challenges for anesthesiologists. Children with cancer are required to undergo brief but noxious diagnostic and therapeutic procedures, which can result in great fear and anxiety. Therefore, it is necessary for the anesthesiologist to provide sedation, general anesthesia, and pain management. The anesthesiologist, therefore, forms a key part of the multidisciplinary team, along with pediatric oncologists, surgeons, co-medicals, and family, which cares for such patients.

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45.2 Epidemiology

Cancer is the most common cause of death from disease in children aged 1–14 years [1]. In children, tumors of the brain and CNS are the second most commonly diagnosed cancer next to leukemia. The incidence of pediatric brain and CNS tumors in the United States is approximately 5.3 cases per 100,000 population per year [2], which is significantly less than that in adults (about 27.4 cases per 100,000 population) (Table 45.1). Brain and CNS cancers account for 25 % of pediatric cancers, but only 3 % of adult cancers [3, 4]. The 5-year survival rate in pediatric brain tumor patients is about 65 %, which is much higher than the adult survival rate at 23 % [5].

The distribution of location and histology of brain and CNS cancers differs between pediatric and adult patients (Table 45.2 and 45.3) [6]. According to a survey conducted in the United States, nearly 30 % of pediatric brain tumors are located in the posterior fossa, which often involves the brain stem and cerebellum, as opposed to only 7 % of primary brain tumors in adults. This locational issue makes anesthetic management in pediatric neurosurgery more difficult. On the other hand, as shown in Table 45.2, 65 % of brain tumors are located in the cerebrum in adults, as opposed to only 24 % in children. A midline location, such as with pineal and pituitary tumors or ventricular system involvement, is another feature of pediatric tumors. As shown in Table 45.3, there are several brain tumor types specific to pediatric oncology: pilocytic astrocytoma, medulloblastoma, and germ cell tumors. Among these, one interesting report on medulloblastomas indicated an increased risk in babies born during the fall [7]. Although no clear

Table 45.1 Average annual age-adjusted incidence rates of brain and CNS tumors (per 100,000 population)

	Children (0–19 years old)	Adults (20+ years old)
Malignancy	3.3	8.9
Benign	1.9	18.5
Total	5.3	27.4

Table 45.2 Distribution of primary brain and CNS tumors by location (%)

	Pediatric patients (0–19 years old)	Adult patients (20+ years old)
Cerebrum	24	65
Cerebellum	16	3
Brain stem	12	4.3
Pituitary	8	7
Spinal cord	5.6	4.2
Ventricles	5.6	1.8
Cranial nerves	4.6	1
Pineal	3	0

Table 45.3 Distribution of primary brain and CNS tumors by histology according to age (%)

	0–14 years old	15–19 years old		20+ years old
Pilocytic astrocytoma	20.9	14	Meningioma	30.1
Embryonal (including medulloblastoma)	16.8	6.7	Glioblastoma	20.3
Other astrocytomas	10.5	10.4	Astrocytoma (grades II–III)	9.8
Ependymoma	7	4.6	Nerve sheath	8
Germ cell tumors	3.9	6.8	Pituitary	6.3
Craniopharyngioma	3.1	2.7	Oligodendroglioma	3.7
Glioblastoma	2.8	3.2	Lymphoma	3.1
Pituitary	0.8	10.1	Ependymoma	2.3
Other	32	36	Other	15

pathophysiological mechanism has been proved, this seasonal variation suggests community infection or chemical exposure during pregnancy or early childhood.

45.3 Preoperative Considerations

The preoperative evaluation of pediatric oncology patients differs from that of adult patients or even non-oncologic pediatric patients [8, 9]. Many of these children will be required to undergo multiple operations and procedures, so it is important to establish a good relationship with the child and their family. A thorough history and examination, including congenital or familial problems, are quite important in such children. There is insufficient evidence about recommended preoperative laboratory tests. Anemia and coagulation abnormality are often seen due to the cancer itself, as well as the adverse effects of chemotherapy. Nausea and vomiting are common symptoms, which one third of patients with pediatric brain tumors experience. It is important, therefore, to evaluate hydration, electrolyte balance, and nutritional status.

In addition to general condition, the cancer type, location, and process have strong implications for the preoperative evaluation and anesthesia plan. Patients with elevated intracranial pressure frequently show focal neurological signs, epilepsy, cognitive and behavioral disturbances, and endocrine and growth disturbances. Neurologic deterioration is not uncommon due to increased intracranial pressure. Some patients presenting with acute deterioration, including obtundation or visual disturbance, may be urgent candidates for surgical intervention.

It is helpful to involve a pediatric neurologist, if the patient presents a complex clinical picture. Epilepsy or seizure should be fully investigated with electroencephalograms and/or magnetic resonance imaging. The epilepsy should be controlled. Prophylactic anticonvulsants are often given, especially in patients with supratentorial lesions, although the evidence is controversial [10]. Endocrinopathy is common among children with craniopharyngioma or optic/hypothalamic glioma

[11]. Endocrinological screening such as weight, height, pubertal status, and nutritional and fluid balance should be assessed not only preoperatively but also postoperatively.

Therapy-related symptoms should be identified, especially in patients undergoing chemotherapy. Neurotoxicity and myelosuppression are common adverse effects. Anthracyclines such as doxorubicin and daunorubicin are associated with myocardial depression and bleomycin with pulmonary fibrosis. To conduct safe anesthesia, it is important for the anesthesiologist to know what kind of drugs are being used and the potential adverse effects associated with chemotherapy.

45.4 Treatment Options and Anesthetic Considerations

The treatment of pediatric malignancies has several goals: first, to cure or control the disease and then increase long-term survival; second, to prevent long-term complications from the various diagnostic and therapeutic modalities used; and third, to minimize the psychosocial impact of the diagnosis and treatment on the child and family [6]. Currently, the combination of surgery with chemotherapy and/or radiotherapy is the mainstream in treating pediatric patients with brain tumors. Anesthesiologists are involved in not only surgical but also diagnostic and therapeutic procedures.

45.4.1 Anesthetic Considerations for Surgery

The goals of surgery are to accurately define the extent of the tumor, resect as much of the tumor as possible without causing neurological sequelae, correct secondary hydrocephalus, and reconstruct CSF pathways. The anesthesiologist should share the clinical strategies and goals with the surgeon.

Neurologic deterioration during surgery is not uncommon in advanced-stage patients, and the anesthesiologist must be prepared to control intracranial pressure, risk of aspiration, seizures, and other considerable symptoms.

Preoperatively, it is quite important to obtain adequate venous access such as with a central venous line, inserting an arterial line, placing a urinary catheter, and attaching monitors before taking position, as these are all difficult intraoperatively. A central venous line will already have been obtained in some patients undergoing preoperative chemotherapy.

Kinking or displacement of the endotracheal tube can occur easily, especially when the patient is in the prone or sitting position, so careful fixation of the endotracheal tube is necessary. It is also important to monitor end-tidal carbon dioxide waveform to make sure that the airway is intact.

Attention should also be paid to maintaining body temperature, particularly in small children, by using warm air, warming light, or a blanket. Children are at

greater risk for hypothermia than adults for the following reasons: smaller children have a smaller ratio of body mass to surface area, which leads to increased heat loss; younger children have limited glycogen stores to support increased heat production in response to cold; and infants do not have the ability to increase heat production through shivering.

Adequate positioning is key in surgery for pediatric neuro-oncology patients. The prone position is commonly used for posterior fossa tumors, which occupy nearly 30 % of brain tumors, and occipital supratentorial lesions. Excessive neck flexion should be avoided, and the chin should not touch the chest. Careful eye protection with pads and tapes is required to prevent postoperative visual disturbance. A horseshoe ring, rather than three-point head fixation, is recommended for pediatric patients, especially those of younger age, as CSF leaks and depressed skull fractures occur easily. Gupta [12] reported a combined horseshoe and pin system for children from 6 months to 14 years of age. Adequate protection with pads or sponges should be used for pressure points such as on the chest and pelvis. In the sitting position, which is sometimes used for high vermis, brain stem, or pineal lesions, there will be cardiovascular instability with postural hypotension and the risk of venous air embolism and paradoxical air embolism. The risk of air embolism in the sitting position is 30–45 %, and children are more vulnerable than adults [13].

45.4.1.1 Neurologic Monitoring and Anesthetic Considerations

Several tools have been developed to minimize neurological defects, such as intraoperative navigation systems, real-time imaging, and real-time functional monitoring. Electrophysiological monitoring is very useful in identifying the potential damage of the procedure, allowing the surgeon to determine how much of a lesion may be safely removed. Motor evoked potentials (MEP) and somatosensory evoked potentials (SSEP) allow continuous monitoring, which is useful in patients whose surgery is adjacent to the pyramidal and sensory tracts. For brain stem procedures such as posterior fossa surgery, brain stem auditory evoked responses are also useful in tailoring the surgical resection of tumors to minimize neurological injury. Most volatile anesthetics cause a dose-dependent depression in amplitude and a dose-dependent increase in latency. These changes start at 0.2 % minimum alveolar concentration (MAC) for MEP and at 0.5 % MAC for SSEP. Most intravenous anesthetics cause similar effects to volatiles, but opioids have a milder effect on MEP and SSEP. Propofol exerts a dose-dependent effect, but recovery is relatively quick. Barbiturates and benzodiazepines induce prolonged and marked depression of MEP, but the effects on SSEP disappear quickly. Ketamine is preferred in terms of neurologic electrophysiological monitoring as it enhances the amplitude of SSEP and MEP while increasing intracranial pressure. Therefore, the patient should be chosen very carefully in the event of resort to this drug. Dexmedetomidine exerts a minimal effect on MEP and SSEP and is therefore appropriate for intra- or postoperative sedation if continuous monitoring of MEP or SSEP is required. While muscle relaxants do not affect SSEP, they do exert a

profound effect on MEP. If MEP monitoring is required, injection of muscle relaxants should only be done after intubation.

45.4.2 Radiology

In many pediatric brain tumors, surgery and chemotherapy cannot eliminate all the cancer cells, so radiation therapy is often applied. Radiation can sometimes bring about long-term complications in the immature brain, particularly the white matter [14, 15]. Stereotactic radiosurgery is commonly used for lesions smaller than 2.5–3 cm in diameter, in which a high single dose of radiation is applied to a defined intracranial volume. There are three techniques available here: Gamma Knife radiosurgery, linear accelerator, and proton beam radiosurgery. Anesthetic assistance is needed with these therapies, especially in younger children, as immobilization is indispensable. The patient is secured in a fixation frame or mask, which is usually made the first day of treatment, which allows the patient to assume the same position throughout the course of therapy. The anesthesiologist will often stay outside of the radiation suite and observe the patient from the next room, so it is important to monitor the patient properly. The procedure itself is not painful, so most such patients require only sedation. Propofol infusion with or without titrated bolus provides adequate sedation and early emergence. A laryngeal mask is a very strong tool as it does not interfere with radiation.

45.4.3 Procedures

In addition to being used to decrease intracranial pressure or cure hydrocephalus, lumbar puncture is also conducted for diagnostics. Lumbar CSF has a much better predictive value and higher positive rate than ventricular CSF. Cerebral spinal fluid is collected for cytology and tumor marker analysis [16]. The procedure is uncomfortable for the patient, so analgesia is an important component of management. Ketamine was the preferred choice until the 1990s, and it is still used as a supplement to propofol [17]. Short-acting opioids may be also used with propofol, but are associated with nausea and prolonged sedation [8].

45.5 Postoperative Care

Potential endocrine deficiency or hypothalamic thirst center dysregulation requires close postoperative monitoring and management of endocrine function. Postoperative epilepsy may require consultation with a neurologist. Postoperative neurologic deficits such as cerebellar symptoms and mutism after posterior fossa

surgeries and cranial neuropathy after brain stem surgeries can cause discomfort and stress in the patient and their family. It is important to establish a rapport between the patient and the medical team, including pediatric psychologists. It is the duty of the anesthesiologist to help reduce the emotional stress of multiple painful procedures and surgeries by providing a calm, nonthreatening environment and by managing complications effectively, especially pain, nausea, and vomiting. Patient-controlled analgesia is widely and successfully used by children older than 6 years of age.

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Chapter 46
Anesthesia During Surgery for Pediatric Traumatic Brain Injury

Yuichiro Toda

Abstract Survival and neurological outcomes in children with traumatic brain injury (TBI) remain poor, despite the great effort toward improving outcomes in such patients. No single anesthetic protocol is suitable for all children with TBI undergoing surgical procedures. Although propofol offers advantages in terms of cerebral blood volume, a larger dose is required in children, increasing the risk of propofol infusion syndrome. Intracranial pressure monitoring should be considered when managing children with TBI. Hyperventilation (PCO_2 of <25 mmHg) may cause cerebral ischemia. Temperature management is also very important, and hypothermia (32–33 °C) followed by rapid rewarming (0.5 °C every 2 h) is not recommended. Notably, hyperthermia in the early phase of TBI may cause poor neurological outcomes. Hemodynamic parameters are also critical, and the cerebral perfusion pressure should be >40 mmHg. Hypertonic saline may be used to avoid hyponatremia, which may cause brain edema and intracranial hypertension. Adequate postoperative sedation is required in the intensive care unit. Several pharmacological therapies have been developed to improve outcomes in children with TBI. Corticosteroid administration, however, is not recommended. Phenytoin may be used to prevent posttraumatic seizures. Barbiturates can be used to reduce intracranial pressure. Cerebrospinal fluid drainage may also effectively reduce intracranial pressure.

Keywords Anesthesia • Children • Traumatic brain injury • Pediatric

46.1 Introduction

Approximately 500,000 children aged 0–14 years visit emergency departments annually in the United States for the treatment of traumatic brain injury (TBI) [1]. Among these patients, 35,000 require treatment in an intensive care unit (ICU), 2,000 of whom will die of this life-threatening condition. In Japan, the total number

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of deaths in 2012 among children and adolescents (0–14 years of age) was 4,200 according to the annual report issued by the Ministry of Health, Labour and Welfare. In that report, accidents including TBI were listed as the second highest cause of death (9.9 %) in this age group [2].

Surgical treatment includes epidural hematoma evacuation, subdural hematoma evacuation, insertion of intracranial pressure (ICP) monitoring catheters, parenchymal mass lesion evacuation, decompressive craniectomy, and repair of depressed cranial fractures [3]. These procedures are performed to both save the lives of children with TBI and minimize possible neurological sequelae. Patients who urgently require these procedures show altered consciousness, unstable hemodynamics, and respiratory problems. This chapter reviews several concerns regarding anesthesia in children with TBI.

46.2 Preoperative Evaluation

46.2.1 Cause of Injury

The leading cause of TBI in children 0–14 years of age is falls, which account for about half of all cases of TBI in children in the United States. The second leading cause of TBI in children is being struck by or colliding against a moving or unmoving object; such events account for approximately 25 % of all cases of TBI. Motor vehicle accidents are the largest cause of TBI-related death [1].

46.2.2 Diagnostic Exclusion of Injury Other than TBI

Urgent surgery is usually required in children and adolescents with TBI. However, patients with TBI caused by falls or motor vehicle accidents often sustain multisite injuries. Chest and abdominal trauma are often life-threatening and require urgent circulatory and/or respiratory support. The decision regarding which surgical operation is most urgent should be made before TBI treatment procedures are carried out. TBI secondary to being struck by or colliding against an object may be an isolated injury.

46.2.3 Preoperative Examination

Preoperative examination is mandatory in patients with TBI. Plain chest and abdominal radiography should be performed as soon as possible. Computed tomography may be required to rule out injuries other than TBI. Measurement of the

Table 46.1 Pediatric Glasgow Coma Scale

Section	Response	Points
Eye opening (E)	Spontaneous	4
	To speech	3
	To pain	2
	None	1
Best verbal response (V)	Coos, babbles	5
	Irritable, cries	4
	Cries to pain	3
	Moans to pain	2
	None	1
Best motor response (M)	Normal spontaneous movement	6
	Withdraws to touch	5
	Withdraws to pain	4
	Abnormal flexion	3
	Abnormal extension	2
	None	1

The sum of the points in each section (E, V, and M) represents the Pediatric Glasgow Coma Scale score. The lowest possible score is 3 points, and the highest is 15 points

hematocrit and platelet count and performance of coagulation tests are also necessary. Patients with TBI often undergo preoperative mechanical ventilation mainly because of their altered consciousness and poor hemodynamics. If patients have not yet been intubated, the anesthesiologist must obtain information regarding the time at which they last ate. Such patients are at high risk of aspiration, and traumatic events cause stress that may intensify sympathetic stimulation on a full stomach. This is especially true when a traumatic event occurs immediately following a meal. The Pediatric Glasgow Coma Scale (GCS) [4] should be used to diagnose the severity of impaired consciousness [5] (Table 46.1). Availability of various blood products is also important, especially for patients with multisite trauma.

46.2.4 Indication for Surgery

In adults, an epidural hematoma with a volume of >30 cm^3 or a hematoma that causes a midline shift of >5 mm may require surgical evacuation regardless of the GCS score. In a pediatric study, the average midline shift was 4.0 mm in patients who underwent operative management and only 0.5 mm in patients who underwent nonoperative management. The hematoma volume was also greater in the operative group than in the nonoperative group (41 vs. 8 cm^3, respectively). However, patients with a comatose status associated with anisocoria and a GCS score of <9 should undergo urgent evacuation.

46.2.4.1 Indication for Insertion of ICP Monitoring Devices

Secondary injury to the brain after TBI is likely to be a more important factor than the direct brain injury itself in the determination of survival and/or neurological outcomes. This secondary injury includes global or focal ischemic injury and cerebral herniation caused by intracranial hypertension or other mechanisms. An earlier study demonstrated a high incidence of intracranial hypertension in children with TBI; the ICP in 86 % of the study population was >20 mmHg [6]. Although no randomized trials have investigated whether ICP monitoring improves outcomes in children, two fair-quality small observational studies showed a relationship between intracranial hypertension and high mortality or poor neurological outcomes [7, 8]. In another study, children treated with ICP-guided therapy had better outcomes than did children who did not undergo ICP monitoring [9]. In contrast, one investigation showed no association between intracranial hypertension and poor outcomes [10]. Thus, the decision regarding whether to perform ICP monitoring in pediatric patients with TBI should be left to each individual institution. However, children with a GCS score of >9 are less likely to require ICP monitoring [11].

46.2.4.2 Indication for Decompressive Craniectomy

Decompressive craniectomy involves removal of a skull bone with or without duraplasty to reduce the ICP in patients with TBI or a large cerebral infarction that is likely to cause brain swelling. The procedure varies among studies; the craniectomy is unilateral or bilateral; subtemporal, hemispheric, circumferential, or bifrontal; and relatively small or extensive. Thus, confounding factors may hinder the understanding of study results, although many studies are nonrandomized cohort analyses [12, 13]. Decompressive craniectomy can not only reduce the ICP [14] but also stabilize it or make it controllable under medical treatment [15]. Whether craniectomy improves the clinical outcome is unknown. In a small case series, patients in the craniectomy group exhibited better neurological recovery at a mean of 3 years after injury than did those in the medical treatment group [16]. In a randomized trial involving 150 adults, the ICP in the craniectomy group was significantly lower than that in the control group; however, the clinical outcomes as estimated by the extended Glasgow Outcome Scale were worse in the craniectomy group than in the control group [14]. Only one previous study evaluated pediatric patients with TBI [17]. Although the authors concluded that early craniectomy may be beneficial, the study results should be interpreted with caution because of the study's inclusion of children with a GCS score of >9. Likewise, as described in the previous section, patients with a GCS score of >9 are less likely to require decompressive craniectomy. The ICP trigger for craniectomy was 20 mmHg in one randomized controlled trial involving adults [14]. The ICP threshold for craniectomy is 25 mmHg in a currently ongoing randomized trial

involving 400 participants, including pediatric patients (>10 years of age) [18]; thus, patients with an ICP of <20 mmHg should not undergo decompressive craniectomy.

46.3 Anesthetic Management

46.3.1 Induction Agents

Any induction agent may cause hypotension regardless of the amount given. This is especially true when a child sustains multisite trauma. Physicians should be aware of the risk of unstable hemodynamics in these patients because they may be hypovolemic. As previously mentioned, these patients may have injuries other than TBI, especially when they have been involved in a motor vehicle accident. When anesthesiologists induce general anesthesia, they should be aware of possible cervical spine and airway injuries. Airway injuries are often particularly critical in young children; thus, the airway must be carefully evaluated before induction. Other considerations when dealing with pediatric patients include uncooperative behavior, confusion, and increased ICP. Rapid-sequence induction is preferred because these patients may have a full stomach; securing intravenous access before induction is mandatory and will be useful for fluid administration and/or blood transfusion. Any intravenous anesthetics can be used for induction of anesthesia in children with TBI. However, physicians should be aware of hemodynamic effects of these agents, especially if relatively large dose of induction agents is administered.

46.3.1.1 Midazolam

The cerebral blood flow (CBF) decreases with the administration of 0.15 mg/kg of midazolam in adults [19]. This agent may be preferable for patients with intracranial hypertension. The dose for anesthetic induction varies among studies from 0.1 to 0.5 mg/kg [20, 21]. Although hypotension should be noted at induction in these patients, their hemodynamic profiles may be more stable than with propofol induction [20]. However, because midazolam usually requires a longer induction time than other agents [21], it may not be suitable for rapid-sequence induction in children with a full stomach.

46.3.1.2 Thiopental

Thiopental at 5 mg/kg can usually be used as an anesthetic induction agent in children [22, 23]. However, hypotension is a potential side effect, especially when

patients are hypovolemic, because of this agent's negative inotropic and vasodilatory effects [24]. Under halothane and fentanyl anesthesia, additional thiopental loading further reduces both cerebral metabolism and blood flow by approximately 15 % [25]. This was supported in a previous animal study in which thiopental infusion caused a dose-dependent reduction in the CBF and cerebral metabolic rate [26]. In children with TBI, a 5-mg/kg dose of thiopental reduces the ICP by 48 % and reduces the middle cerebral artery flow velocity by approximately 15–21 %; however, the cerebral perfusion pressure (CPP) remains unchanged [27].

46.3.1.3 Propofol

Propofol reduces both the CBF and cerebral metabolic rate in humans after bolus administration. In one study, propofol reduced the CBF in healthy volunteers by approximately 65 % [28]. Propofol also reduced the cerebral metabolic rate to about 60 % of baseline, like sevoflurane. Furthermore, although sevoflurane may not reduce the cerebral blood volume (CBV), propofol reduces the CBV to 80 % of baseline in both the cortex and cerebellum [29]. Thus, induction of general anesthesia by propofol in children with suspected or diagnosed intracranial hypertension is preferred. The usual induction dose of propofol in children aged 6–12 years is 2.2 mg/kg, while that in infants is 2.9 mg/kg [30] and that in adults is 1.00–1.75 mg/kg [31]. However, the negative inotropic and vasodilatory effects of this medication should be noted in patients with multiple trauma who may be hypovolemic.

46.3.1.4 Ketamine

Ketamine should be cautiously used in children with TBI because it may increase both the CBF and cerebral metabolic rate of oxygen ($CMRO_2$) [32]. However, in a recent study of a pediatric population, 1.5 mg/kg of intravenous ketamine prevented further increases in the ICP and treated refractory intracranial hypertension [33]. Furthermore, ketamine causes sympathetic stimuli that lead to increases in the heart rate and blood pressure. Thus, some anesthetists prefer this medication as an induction agent for patients with trauma.

46.3.2 Opioids

Bolus administration of narcotics usually decreases both the CBF and $CMRO_2$ [34]. Thus, narcotics can also reduce the ICP. These data were mostly derived from studies of noninjured patients and animal studies. Although adults with TBI have been investigated in some studies, investigation of the effects of opioids on the cerebral physiology of pediatric patients with TBI is very limited.

46.3.2.1 Fentanyl

In noninjured adults, the CBF and $CMRO_2$ decreased by 21 % and 26 %, respectively, with an average fentanyl dose of 17 μg/kg [34]. Because fentanyl is usually given together with other hypnotic agents at the time of anesthetic induction, hypotension may occur. When the CBF is effectively autoregulated, reductions in the CPP induce cerebral vasodilation to maintain an adequate CBF. This situation increases both the CBV and ICP [35]. However, in one study, the ICP remained unchanged when approximately 3 μg/kg of fentanyl was followed by continuous infusion in patients with TBI while maintaining a normal mean arterial blood pressure [36]. The optimal dose of fentanyl in the pediatric population varies widely from 2 to 100 μg/kg according to the clinical situation or surgical procedure [30]. Fentanyl should not be administered to hypotensive patients to avoid affecting the cerebral physiology. Bolus administration of 2–10 μg/kg of phenylephrine may be acceptable to maintain the blood pressure in pediatric patients [37].

46.3.2.2 Remifentanil

Remifentanil is a new short-acting opioid that is now widely used. A recent study found that a low dose of remifentanil can increase the CBF. Moreover, this relative increase in the CBF is greater with higher doses [38, 39]. Studies on remifentanil administration in patients with TBI are very limited; to the best of our knowledge, no such studies have been performed in pediatric patients. In a mixed population of patients with TBI and after neurosurgery, the length of time until effective assessment of the patients' neurological status could be performed was shorter in the remifentanil group than in the fentanyl or morphine group [40]. However, various doses of remifentanil were not effective in preventing suction-induced cough or increased ICP when endotracheal suction was performed in patients with TBI in the ICU. Additionally, higher doses of remifentanil were associated with more frequent hypotension [41]. Remifentanil is a very useful medication in pediatric patients. One multicenter study showed no difference in the blood pressure, heart rate, extubation time, or adverse events between remifentanil and halothane anesthesia in infants undergoing surgery [42]. However, rapid neurological assessment in older children is very helpful because children with a relatively better GCS score awaken sooner after surgical procedures [30]. The required doses of remifentanil in children are approximately twice those of adults under both sevoflurane and propofol anesthesia because children may be less tolerant of these agents with respect to hemodynamics [43, 44]. The dose of remifentanil is usually decreased when administered to neonates and infants because of their immature liver and kidney function. However, according to a pharmacokinetic study of children, even neonates may be able to eliminate remifentanil as quickly as older children and adults because of the larger volume of distribution and higher clearance in younger children. Nevertheless, there are no age-related differences in the half-life of

remifentanil [45]. An initial bolus dose of 0.10–0.25 μg/kg and an infusion rate of 0.25 μg/kg/min may be used. However, bolus doses should be determined with caution because a bolus dose of 5 μg/kg may cause hypotension, even in general pediatric patients [45]. Postoperative pain management is mandatory because remifentanil is quickly metabolized. Additionally, physicians should be aware of acute opioid tolerance in young children at higher doses of 0.6–0.9 μg/kg/min [46].

46.3.2.3 Morphine

Morphine is one of the oldest but most commonly used opioids. Its effects are usually long-lasting in both adults and children. Both the CBF and $CMRO_2$ decrease with large doses of morphine, although this effect is very small. A dose of 0.1–0.2 mg/kg is usually chosen. The dose may be reduced in neonates and young infants because the elimination of morphine in these age populations requires a long period of time [47]. Continuous infusion may be performed at a dose of 10–30 μg/kg/h in neonates and 20–80 μg/kg/h in older children when postoperative sedation or analgesia is indicated [37].

46.3.3 Neuromuscular Blockade

The ideal neuromuscular blocking agents for patients undergoing surgical procedures have a rapid onset, induce quick recovery, and have a low incidence of side effects such as histamine release and autonomic reactions. Succinylcholine is now rarely used in such patients because of the risk of increases in ICP and possible malignant hyperthermia. Pancuronium is another choice, but anesthetists generally prefer not to use this medication because of its long duration of action and sympathetic effects. In Japan, vecuronium has played a major role in neuromuscular blockade. However, rocuronium is now replacing vecuronium because it is metabolized into 3OH-vecuronium, which possesses approximately 70 % of the neuromuscular blocking effects of vecuronium. Moreover, sugammadex, which is perfectly antagonistic to rocuronium but not completely to vecuronium, is now available.

46.3.3.1 Rocuronium

Traditionally, it is thought that neuromuscular blocking agents decrease oxygen consumption and ICP [48]. Potential reasons for these effects include reduced airway and intrathoracic pressure, increased venous return, and immobilization. Administration of rocuronium during surgical procedures is generally accepted as a routine practice [49]. In one study, however, no changes occurred in the mean arterial pressure, heart rate, ICP, or even CPP after bolus administration of

rocuronium [49]. Although early initiation of neuromuscular blocking agents improved survival, no studies have evaluated the effects of intraoperatively administered neuromuscular blocking agents on survival or neurological outcomes [50]. Additionally, age-related differences are present among various doses of rocuronium. Rocuronium doses should be reduced in neonates and small infants, but children aged 2–8 years require higher doses than do adults [51]. This is supported by pharmacokinetic analysis results. In one study, a 0.6-mg/kg bolus of rocuronium facilitated tracheal intubation in as little as 30–60 s in children <1 year of age [52]. A longer duration of time is required to facilitate intubation with a 0.6-mg/kg bolus in children aged 1–5 years; thus, larger doses of rocuronium may be recommended in rapid-sequence induction [53]. A 0.9-mg/kg bolus of rocuronium enables intubation in children as rapidly as does succinylcholine [54, 55]. Neuromuscular recovery may occur more rapidly in children aged 1–5 years. Thus, frequent additional doses are required in these age populations to maintain neuromuscular blockade during anesthesia. Continuous infusion of rocuronium at 5–15 μg/kg/min may be used for anesthetic maintenance and paralyzation in the ICU.

46.3.4 Inhalational Agents

46.3.4.1 Sevoflurane

No studies have compared sevoflurane with other inhalational agents or intravenous agents in terms of outcomes in pediatric patients with TBI. Because sevoflurane may be the most popular anesthetic agent for pediatric patients worldwide, anesthesiologists should be aware of the characteristics of this medication in pediatric patients. The minimum alveolar concentration (MAC) of sevoflurane is highest in neonates, potentially reaching 3.3 %. The MAC is higher in all pediatric age groups than that in adults: 3.2 % in infants 1–6 months old and 2.5 % in children >6 months old [56, 57]. Because all volatile anesthetics possess vasodilatory effects as their concentration increases, potential increases in the CBF and thus the ICP must be considered. However, together with its effects of decreasing the $CMRO_2$ and mean arterial pressure, sevoflurane at 1.0 MAC produces a net decrease in both the CBF and CBV, which may in turn reduce the ICP [28]. However, whether the cerebral physiology in an uninjured brain is the same as that in an injured brain remains unclear. An increased ICP was not improved by hyperventilation in an experimental setting [58]. However, it is currently known that healthy people anesthetized with sevoflurane have a significantly lower CBF than do awake people. In one study, 1.0 MAC of sevoflurane decreased the CBF by 38 % and the $CMRO_2$ by 39 % compared with awake controls [59].

46.3.4.2 Isoflurane

Isoflurane may be used as a maintenance anesthetic agent in patients with TBI. Like the MAC of other volatile anesthetics, the MAC of isoflurane in children is relatively higher than that in adults. However, the difference in the MAC of isoflurane between adults and children is smaller than that of other anesthetics. Isoflurane preserves the heart rate, which is important in small children because their cardiac output is dependent on heart rate. Adolescents sometimes develop hypertension during anesthesia. Notably, coughing and laryngospasm often occur during the induction phase when using isoflurane, and the ICP may increase as a result [30]. For isoflurane, a MAC of 1.1 increases the CBF by 19 % and reduces the $CMRO_2$ by 45 %; these results are similar to those obtained using sevoflurane in an animal study [34]. The direct effect of isoflurane on the cerebral vasculature is much stronger than that of sevoflurane and desflurane. This is why isoflurane increases the CBF, while sevoflurane and desflurane do not. However, which anesthetics are superior to others in children with TBI remains unclear.

46.3.4.3 Desflurane

The MAC of desflurane is much higher in pediatric than in adult patients. It is reportedly 9.2 % for neonates, 9.4 % for infants <6 months of age, 9.9 % for infants 6–12 months of age, 8.7 % for children 1–3 years of age, and 8 % for children 5–12 years old [60]. Unfortunately, laryngospasm is one of the most important and unfavorable occurrences, but the most frequent event, in pediatric anesthesia with desflurane; the incidence may be as high as 50 % [61]. Additionally, the highest incidence of emergence agitation is associated with desflurane in children, although pediatric patients with TBI may require mechanical ventilation and thus continuous sedation in the ICU after surgery [62].

The CBF and $CMRO_2$ are higher in patients anesthetized with desflurane than in awake, nonanesthetized patients. In one study, the CBF decreased by 22 % and the $CMRO_2$ by 35 % [63]. This is why desflurane may be used as a maintenance agent in children with TBI.

46.3.5 Intravenous Anesthetic Agents

46.3.5.1 Propofol

Propofol can be used as a maintenance anesthetic agent in patients with TBI. As previously described in the section describing induction agents, propofol is associated with a significantly lower CBV than is sevoflurane [29]. In one study, propofol was given by target-controlled infusion (average concentration, 3.7 μg/mL), and sevoflurane was administered at 1.5 %; the target bispectral index for both agents

was 40. Both agents benefit the CBF and $CMRO_2$. Thus, propofol-based anesthesia can contribute to a reduction in the CBV and possibly the ICP.

However, several important issues are associated with total intravenous anesthesia using propofol in pediatric patients. Significantly larger doses are required in pediatric patients to maintain the plasma concentration of the drug. A loading of 2.5 mg/kg followed by continuous infusion of 15.0, 13.0, 11.0, and 9.0 mg/kg/h (infusion rate is decreased every 10–30 min) allows for the maintenance of a target concentration of 3.0 μg/mL in children 3–11 years of age [64]. Target-controlled infusion can be applied in children, but a specially designed pump is needed; this pump is not available in Japan, but in the United Kingdom (Paedfusor®) [65, 66]. Conversely, propofol infusion syndrome (PRIS) is considered to be a serious complication [67]. PRIS was first described in 1992 in the pediatric ICU setting where propofol was administered to pediatric patients for several days [68]. Thus, the Federal Drug Administration and product documents in Japan have prohibited continuous propofol infusion in children in the ICU. Only two pediatric cases of PRIS after several hours of propofol anesthesia have been reported [69, 70]. However, they are suspected to have occurred secondary to a fatty acid oxidation disorder or mitochondrial respiratory chain enzyme deficiency, and these conditions may help to explain the mechanism of PRIS [71]. The serum lactate level may be a sensitive marker of PRIS and should be evaluated [72].

46.3.6 Respiratory Management

Hyperventilation produces hypocapnia-induced cerebral vasoconstriction, which reduces the CBF. This explains why the ICP is reduced by hyperventilation. In the 1970s, hyperventilation was a common practice for managing severe TBI in children. The pathophysiology of pediatric TBI was not correctly understood until it was proven that cerebral hyperemia is uncommon [73]. Moreover, hyperventilation aiming to achieve a PCO_2 of 25 mmHg reportedly resulted in worse neurological outcomes at 3 and 6 months after TBI than those obtained with normal ventilation (PCO_2 of 35 mmHg) [74]. An increased risk of cerebral ischemia is observed in pediatric patients with TBI managed by hyperventilation [75]. This study indicates that hyperventilation aiming to achieve a PCO_2 of <35 mmHg increases the incidence of cerebral regional ischemia. A recent large cohort study including 464 patients investigated the association between hyperventilation and outcomes at hospital discharge and demonstrated a strong association between hypocarbia and poor neurological outcomes [76]. Furthermore, prophylactic hyperventilation (PCO_2 of ≤ 25 mmHg) is not recommended according to recent adult guidelines [77]. Thus, hypocarbia characterized by a PCO_2 of <25 mmHg should be avoided when treating children with TBI.

46.3.7 Temperature Management

Many efforts have been made toward demonstrating the benefit of hypothermia after TBI. Although a number of single-center preliminary studies have demonstrated a trend toward lower ICP and improved outcomes, Clifton et al. performed a large randomized trial and reported the lack of effectiveness of hypothermia in adult patients with TBI [78]. Therapeutic hypothermia after TBI in children commenced as early as the 1950s [79]. There were no beneficial effects of mild to moderate hypothermia on mortality or neurological outcomes in children with TBI, although therapeutic hypothermia significantly decreased the ICP or improved intracranial hypertension [80, 81]. Although most outcome measurements did not reach statistical significance, one phase II trial demonstrated that hypothermia may be beneficial in reducing the ICP, but not mortality [82]. The authors defined moderate hypothermia as 32.0 °C to 33.0 °C and normothermia as 36.5° to 37.5 °C. One multicenter, multinational trial failed to show any beneficial effects of hypothermia in pediatric patients with TBI [83]. Mortality tended to be worse in the hypothermia group than in the normothermia group, although the difference did not reach statistical difference. Hypothermic patients had a significantly lower ICP than did normothermic patients. However, more patients in the hypothermia than normothermia group developed rebound intracranial hypertension during the rewarming period. A recent randomized controlled trial (the Cool Kids trial, a phase III trial of a previous study) [82] also failed to demonstrate any benefits of hypothermia in pediatric patients with TBI [84]. That study was terminated earlier than expected after the first interim data analysis because of futility. In both trials, therapeutic hypothermia was initiated in the hypothermia group within 8 h after the occurrence of TBI. However, the duration of hypothermia was shorter in the Hutchinson trial than in the Cool Kids trial (24 vs. 48–72 h, respectively), and the rate of rewarming was higher (0.5 °C every 2 h vs. 0.5 °C–1.0 °C every 12 h, respectively) (Table 46.2). In all cases, hyperthermia (defined as a body temperature of >38 °C) was associated with worse neurological outcomes in the early phase of pediatric TBI [85, 86]. If hypothermia were applied to patients, it would be appropriate to initiate hypothermia therapy during surgical procedures performed in the very early phase of hospital admission. However, hyperthermia during anesthesia must be avoided.

46.3.8 Fluid and Cerebral Perfusion Pressure

46.3.8.1 Cerebral Perfusion Pressure

The CPP, defined as the mean arterial pressure minus the ICP, is a marker of the CBF. Autoregulation of CBF is usually maintained in healthy patients even during anesthesia or sedation. However, this phenomenon may be impaired after TBI, and

Table 46.2 Summary of hypothermia trials in children with TBI

Trial	Patients	Target temperature	Therapy initiated	Rate rewarming	Mortality	Neurological outcome	ICP
Hypothermia pediatric [83]	225	Hypo: 32–33 °C Normo:36.5–37.5 °C	Within 8 h after injury	0.5 °C every 2 h	NS	NS	Lower in hypo group
Cool Kids [84]	77 early termination	Hypo: 32–33 °C Normo:36.5–37.5 °C	Within 8 h after injury	0.5–1.0 °C every 12 h	NS	NS	NS

TBI traumatic brain injury, *Hypo* hypothermia treatment group, *Normo* normothermia treatment group, *NS* not significant, *ICP* intracranial pressure

a reduction in the CPP may therefore lead to cerebral ischemia and a poor neurological outcome. Many studies have reported the association between low CPP and poor outcomes. Because there are age-related normal mean arterial pressures, the optimal CPP should be carefully determined in each age group. A randomized controlled trial involving post-hoc analysis of hypothermia [82] demonstrated that the 5-day average CPP was higher in patients with good neurological outcomes than in patients with poor neurological outcomes (69 vs. 56 mmHg, respectively) and that the duration of time with a CPP of >50 mmHg was higher in patients with good neurological outcomes. The average patient age was 7 years in their study. Figaji et al. reported that among 52 children aged 9 months to 14 years (mean, 6.5 years), the lowest median CPP was higher in patients with favorable outcomes than in patients with unfavorable outcomes (44 vs. 29 mmHg, respectively) [87]. Two other studies of moderate quality also demonstrated an association between a CPP of <40 mmHg and poor outcomes; the average age was 9.1 years in one study [88] and 7.4 years in the other [89]. Thus, to date, a CPP of <40 mmHg may be a critical index in treating pediatric TBI, although age-related differences in CPP may exist. Conversely, blood pressure is commonly calibrated to the right atrium and ICP to the level of the foramen of Monro; thus, CPP may be underestimated when the patient's bed is elevated [90].

46.3.8.2 Fluids

Maintenance of the circulating blood volume is quite important to ensure adequate hemodynamics and prevent cerebral ischemia. Which fluid is optimal in the treatment of children with TBI is unclear. However, studies of adult patients with TBI have examined the effects of albumin administration [91, 92]. Higher mortality rates were observed in patients who were given albumin, but the pathophysiology associated with this phenomenon remains unclear. One possible mechanism involves intracranial hypertension, which was suggested in one article, although the reason for the association between high ICP and albumin administration is unknown [93]. Whether albumin administration can be applied to the treatment of children with TBI is also unknown.

Blood transfusion is another important issue. Transfusion increases the brain tissue oxygen tension, although this is a transient effect [94]. In one study, no difference in patient outcomes was seen between restricted and liberal transfusion strategies in a pediatric critical care setting involving children with TBI [95]. However, post-hoc analyses do not have enough statistical power to provide definitive conclusions regarding this issue. Current evidence shows that children with a hemoglobin level of <7 g/dL will benefit from transfusion and that children with a hemoglobin of >10 will not require transfusion if they have stable hemodynamics. Whether blood transfusion benefits children with TBI remains unclear. One systematic review did not obtain a concrete conclusion regarding the effects of transfusion in neurocritically ill patients [96].

46.3.9 Electrolytes and Other Agents

46.3.9.1 Sodium and Osmolar Management

In patients with TBI, hyponatremia results in hypoosmotic pressure, which causes cerebral edema and a subsequent increase in ICP. Sodium rarely penetrates the blood–brain barrier and may thus exhibit an osmolar gradient [97]. Moreover, sodium restores the cell membrane, maintains the cell volume, stimulates natriuretic peptide hormone release, prevents cell inflammation, and maintains cardiac output [98]. A recent large-scale randomized trial of the effect of hypertonic saline in adult patients with TBI was stopped owing to futility after enrollment of about 1,000 participants [99]. However, whether hyperosmolar therapy leads to good neurological outcomes in pediatric patients remains unclear. In the early 1990s, the effects of 3 % hypertonic saline (513 mEq/L, 1,027 mOsm/L) were compared with those of 0.9 % saline in children (mean age, 8 years). Hypertonic saline infusion at 6.5 mL/kg decreased the ICP 2 h after administration, although this treatment was also associated with a 7-mEq/L increase in the serum sodium concentration [100]. Furthermore, a small randomized trial in which 1.7 % hypertonic saline (268 mEq/L, 598 mOsm/L) was compared with lactated Ringer's solution (131 mEq/L, 277 mOsm/L) in pediatric patients showed less frequent mannitol use, shorter duration of mechanical ventilation, shorter ICU stays, and fewer complications in the hypertonic saline group [101]. Two additional studies demonstrated the beneficial effects of 3 % hypertonic saline [102, 103]. In both studies, hypertonic saline infusion was commenced when the ICP exceeded 20 mmHg. The latter study recommended a maximal rate of increase in the serum sodium level of 15 mEq/L/day and maximal decrease in the serum sodium level of 10 mEq/L/day. These studies also found that a high serum osmolarity of up to 360 mOsm/L can be tolerated with the administration of hypertonic saline in pediatric patients, although renal impairment can be suspected when the serum sodium level reaches >160 mEq/L [104]. Cerebral salt wasting sometimes develops in patients with TBI, complicating the management of serum osmolarity. Cerebral salt wasting causes hyponatremia, which results in cerebral edema. Although the syndrome of inappropriate antidiuretic hormone causes hyponatremia, the pathophysiology and treatment of this syndrome differ from those of cerebral salt wasting.

Another frequently used hyperosmolar agent is mannitol. Mannitol administered at 1 g/kg has been shown to decrease the ICP. Although many centers commonly use mannitol to maintain the ICP in patients with TBI [105, 106], no randomized trials have compared mannitol with other agents for treatment of intracranial hypertension in the pediatric population. On the other hand, mannitol may accumulate in injured brain tissues, thus possibly causing increased ICP by a reverse osmotic shift of fluid [107]. This phenomenon may occur when mannitol is administered for long periods [108]. Moreover, mannitol is associated with a risk of acute kidney injury caused by acute tubular necrosis because it is excreted unchanged into

the urine. Administration of mannitol after confirmation of a serum osmolarity of <320 mOsm/L was recommended in a study of adult patients [109].

46.3.9.2 Glucose

No maximal serum glucose level has been established in pediatric patients with TBI because no study has determined the association between glucose levels and late outcomes. A retrospective analysis by Michaud et al. found that the mean admission glucose level in children who died or remained severely disabled was significantly higher than that in children with more favorable outcomes (288 vs. 194 mg/dL, respectively) [110]. Similarly, Cochran et al. investigated the association between the admission glucose level and patient outcomes at hospital discharge. Worse outcomes were associated with higher serum glucose levels [111]. However, the above two studies only assessed the admission glucose levels. In contrast, glucose levels were measured at the time of hospital admission and twice daily in a study by Chiaretti et al.; they showed that a serum glucose concentration of >150 mg/dL was a risk factor for an adverse neurologic outcome [112]. High glucose levels should be avoided to reduce the risk of unfavorable neurological outcomes.

46.4 Postoperative Management

Children with TBI should be continuously treated in the ICU after undergoing certain surgical procedures. As described earlier, the treatment targets in the ICU should be consistent with those for intraoperative management in terms of the carbon dioxide level, body temperature, sodium level, and CPP. Additionally, adequate sedation must be given during mechanical ventilation in the ICU. If indicated, hypothermia may be maintained for 24–72 h after the injury. Other important issues are listed below.

46.4.1 Specific Medications

46.4.1.1 Barbiturates

According to most reports, the most frequently used barbiturate agents are pentobarbital and thiopental. High-dose barbiturates lower the ICP by reducing cerebral metabolism, including oxygen consumption, and decrease the CBF [113]. Hypotension is very common with high-dose barbiturate therapy, because these agents have negative inotropic effects on the cardiovascular system. Thus, barbiturate therapy for intractable intracranial hypertension is not a first-line treatment and is usually applied when ICP remains uncontrolled after attempting several treatments such as

hyperventilation, steroid administration, and osmolar therapy using mannitol. This is why it is difficult to determine the efficacy of high-dose barbiturate therapy in children with TBI based on information in published articles. No randomized controlled trials have investigated the prophylactic effects of barbiturates on mortality or neurological outcomes in children with TBI. In one study, when pentobarbital was administered at 5 mg/kg and subsequently infused at 1–2 mg/kg/h, 14 of 27 (52 %) children achieved an ICP of <20 mmHg. Moreover, children with refractory intracranial hypertension during high-dose barbiturate therapy exhibited high mortality rates and poor neurological outcomes as assessed by the Glasgow Outcome Scale at 6 months and 1 year after TBI [114]. Various side effects of high-dose barbiturates have also been reported. When pentobarbital was administered at 4–7 mg/kg followed by continuous infusion at 1–4 mg/kg/h, 91 % of children receiving barbiturates required dopamine to maintain adequate blood pressure, and 82 % of these patients developed hypotension [115]. Thiopental can be administered as an initial bolus of 2–5 mg/kg followed by continuous infusion at 1–5 mg/kg/h [37]. It also reduces the ICP in children with TBI after only a 5-mg/kg bolus [27]. Two randomized trials involving adult patients with TBI were performed to identify the favorable effects of barbiturates in such patients, but neither study showed any clinical benefits [116, 117]. A Cochrane review of published data also found no evidence for beneficial effects of barbiturates in patients with TBI [118].

46.4.1.2 Corticosteroids

The potential beneficial effects of corticosteroids in patients with TBI include restoration of altered vascular permeability [119], decreased edema [120], and reduced cerebrospinal fluid (CSF) production [121]. Two randomized trials investigated the effects of corticosteroids in children with TBI. Both trials used dexamethasone, but no other corticosteroids such as methylprednisolone or prednisolone. Neither trial found any differences in mortality or ICP between placebo and 1 mg/kg/day of dexamethasone [122, 123]. Moreover, dexamethasone treatment resulted in a trend toward an increased incidence of bacterial infection. Recent guidelines for adults with TBI stated that the administration of corticosteroids for this purpose should be avoided because such treatment does not improve ICP, mortality, or neurological outcomes [124]. Such treatment may even increase mortality. Overall, it is not strongly recommended to use steroids in pediatric patients with TBI. One trial showed significant suppression of the endogenous cortisol level in such patients [123], although more severe hyperemia and more diffuse swelling are observed after TBI in children than in adults [125].

46.4.1.3 Anticonvulsants

Whether phenytoin as an anticonvulsant reduces posttraumatic seizures (PTS) has also been investigated. PTS are categorized as immediate (within 24 h), early

(within 7 days), or late (8 days or later) [126]. Guidelines for adults with TBI strongly recommend the prophylactic use of anticonvulsants for early PTS [127, 128]. The incidence of PTS in pediatric patients with TBI varies among studies. One prospective observational study of pediatric patients found a 10 % incidence of late PTS [129], and most of the seizures (79 %) were generalized. Another retrospective study that investigated children <16 years of age with TBI found that 149 (8.4 %) of 1,785 patients developed PTS [130]. Furthermore, in a randomized trial of a pediatric population, patients in the intervention group received 18 mg/kg of phenytoin followed by 2 mg/kg every 8 h for 2 days [131]. No significant differences in the incidence of PTS or the mortality rate were found between the intervention and placebo groups, although approximately 30 % of the participants were lost to follow-up. Finally, a retrospective cohort study of 194 pediatric patients demonstrated that prophylactic phenytoin treatment significantly reduced the incidence of PTS [132]. The rate of PTS in that study was 9.3 %. Because children with PTS usually have poor outcomes, including the development of various disabilities [133], prevention of PTS in patients with TBI is critical. A few studies have evaluated phenytoin levels in blood samples. The level of unbound phenytoin is high in patients with TBI who develop PTS because their hepatic metabolism is high and the protein binding of drugs is low [134]. Thus, studies assessing the association between the clinical effects and serum levels of phenytoin are needed.

46.4.2 Cerebrospinal Fluid Drainage

The role of CSF drainage is to reduce the intracranial fluid volume and thereby reduce the ICP. Drainage can be achieved using an external ventricular drain, lumbar drain, and ventricular drain. Drainage may be continuous or intermittent [135]. Previous studies, although poor in quality, have shown the beneficial effects of CSF drainage to reduce the ICP [6, 8, 136, 137]. Most of these studies considered the threshold of initiation of drainage to be an ICP of >20 mmHg. However, CSF drainage can result in complications such as hemorrhage and drain malpositioning [138]. Future trials that assess the effectiveness of CSF drainage are warranted due to the lack of well-designed studies on this critical issue.

46.5 Summary

- No anesthetic agent is superior to others in the management of anesthesia for children with TBI.
- Although propofol may be beneficial, the potential for PRIS should be noted.
- ICP monitoring is useful in the management of children with TBI.
- Hyperventilation (PCO_2 of <25 mmHg) should be avoided.

- Hyperthermia must be avoided. Hypothermia (32–33 °C) followed by rapid rewarming (0.5 °C every 2 h) is not recommended.
- CPP of <40 mmHg is critical.
- Hypertonic saline may be used to prevent hyponatremia. The maximum acceptable sodium level is 160 mEq/L.
- Hyperglycemia (>200 mg/dL) should be avoided.
- Sedation may be continued in the ICU. Paralyzation can be induced if indicated.
- Corticosteroid administration is not recommended.
- Barbiturates reduce the ICP. However, evidence of their association with improve outcomes is not strong.
- Phenytoin may be used to prevent PTS.
- CSF drainage reduces the ICP.

Appendix

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Chapter 47
Anesthesia During Surgery for Meningomyelocele

Toshimi Horiki

Abstract Meningomyelocele develops secondary to failure of closure of the posterior neural tube. Most children with this disease present for primary closure of the defect during the neonatal period to minimize the risk of infection. Therefore, a thorough understanding of neonatal anesthesia management is required. Particular problems with anesthesia for patients with meningomyelocele are the prone position, the position of the tracheal tube, and maintaining body temperature. Anesthesia should be continued with inhalational anesthetic agents or opioids with controlled ventilation. Remifentanil is the newest in the family of synthetic opioids. It has an extremely short context-sensitive half-life and rapid recovery from drug effect. However, the side effects are similar to those of other opioids. These patients are also at high future risk for latex sensitivity and possibly anaphylaxis, secondary to repeated exposure to latex products encountered during frequent bladder catheterizations and multiple surgical procedures.

Keywords Neonates • Chiari malformation • Latex sensitivity

47.1 Introduction

Meningomyelocele develops secondary to failure of closure of the posterior neural tube, resulting in malformation of the vertebral column and spinal cord and other CNS anomalies. Currently, aggressive physical, medical, and surgical therapies have lowered the mortality in patients with meningomyelocele to approximately 10 %. Cognitive development is normal in up to 80 % of patients. Most children with this disease present for primary closure of the defect during the neonatal period to minimize the risk of infection; therefore, a thorough understanding of neonatal anesthesia management is necessary.

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This chapter reviews the embryology (the process of neural tube defects), pathophysiology (hydrocephalus and Chiari type II), surgical procedures, neonatal anesthesia management, and the high risk for latex sensitivity in the future.

47.2 Embryology and Anatomy

47.2.1 Spinal Cord Development

By approximately the 20th day of gestation, the ectoderm on the dorsum of the trilaminar embryonic disk develops midline thickening with cranial and caudal ends known as the neural plate (Fig. 47.1a) [1].

A central groove runs the length of the neural plate, with a neural fold that grows higher along each side. The neural folds eventually begin to fuse in the midcervical region, and the fusion continues upward and downward. This process is known as neurulation and forms the neural tube (Fig. 47.1b) [1].

The neural tube detaches from the adjacent ectoderm, which closes over the dorsum of the neural tube (Fig. 47.1c) [1].

47.2.2 Neural Tube Defects

Neural tube defects result from failure of the neural plate in 3–4-week-old embryos (Fig. 47.2). Spina bifida involves the neural tube of the spinal cord and has two different types: spina bifida occulta and spina bifida cystica. Meningomyelocele is included in the latter type [2].

47.3 Pathophysiology

Most patients with meningomyelocele have hydrocephalus and Chiari type II malformation, and a ventriculoperitoneal shunt may be inserted a few days following primary closure for meningomyelocele [3]. Chiari type II malformation is one of several types of Chiari malformation. This defect consists of a bony abnormality in the posterior fossa and upper cervical spine with caudal displacement of the cerebellar vermis, forth ventricle, and lower brainstem below the plane of the foramen magnum; therefore, medullary cervical cord compression can occur. Vocal cord paralysis with stridor and respiratory distress, apnea, abnormal swallowing and pulmonary aspiration, opisthotonos, and cranial nerve deficits may be associated with the Arnold-Chiari malformation and usually manifests

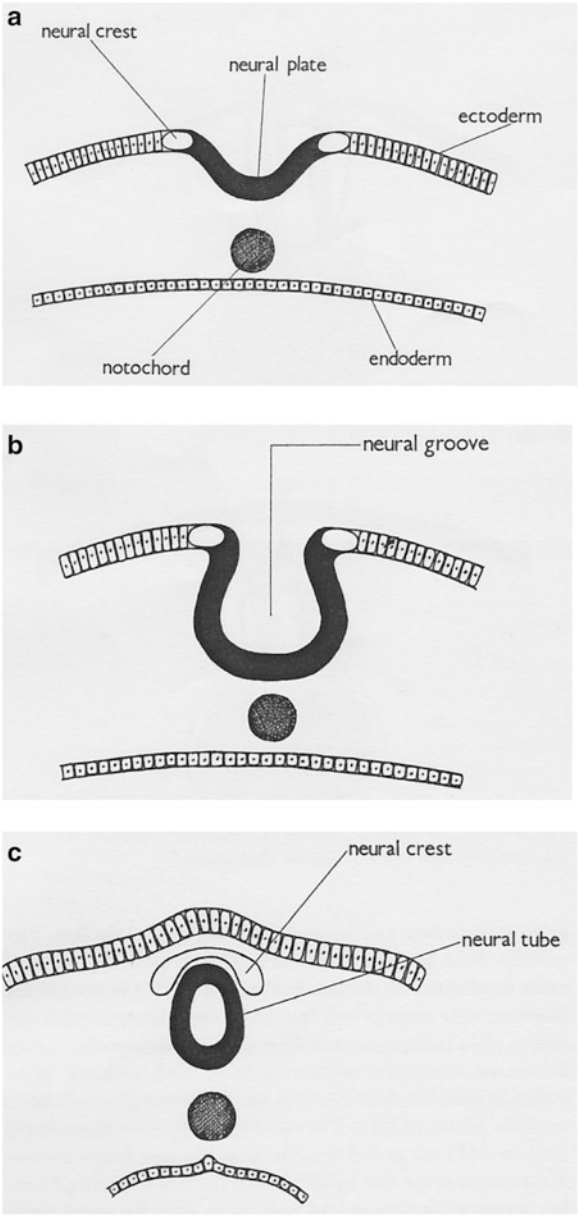

Fig. 47.1 Development of the neural tube 1. (**a**) Cross-section of the embryo showing the midline ectodermal thickening of the neural plate. (**b**) The neural plate thickens, folds, and sinks into the underlying mesoderm as the first step in the formation of the neural tube, which extends along the dorsal midline. (**c**) The neural folds fuse to form the neural tube, and the neural tube is the precursor of the brain and spinal cord (This article was published in Pediatric Surgery, volume two, Fifth edition Peacock WJ, Management of Spina Bifida, Hydrocephalus, Central Nervous System Infections, and Intractable Epilepsy, p1850, Copyright Elsevier 1998)

during infancy. The presence of these conditions should be considered when planning the anesthesia management for patients with meningomyelocele.

Non-neurologic findings in patients with meningomyelocele are as follows: hip dislocation, clubfeet, kyphoscoliosis, chest wall malformation, hydronephrosis,

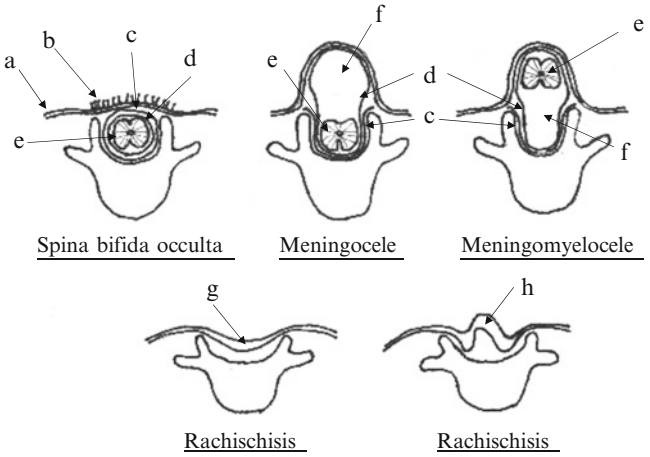

Fig. 47.2 Neural tube defects: (**a**) skin, (**b**) hairs, (**c**) dura, (**d**) arachnoid, (**e**) spinal cord, (**f**) subarachnoid space, (**g**) neural tissue, and (**h**) folded neural tissue

hydroureter, horseshoe kidney, undescended testes, hydrocele, malrotation, omphalocele, Meckel's diverticulum, and inguinal hernia [3].

47.4 Surgical Procedures

Immediately after birth, the exposed neural tissue must be covered with a sterile, saline-soaked gauze, and the infant should be positioned on his or her abdomen to reduce trauma to the exposed neural tissue (Fig. 47.3).

Most children with a meningomyelocele present for primary closure of the defect within the first 24, 48, or 72 h of life to minimize the risk of infection [3, 4]. However, many cases are now scheduled for elective prenatal repair before birth because the defect is usually apparent on prenatal ultrasonography. Most patients with meningomyelocele have hydrocephalus, and a ventriculoperitoneal shunt may be inserted a few days following primary closure. Shunt malfunction can be caused by any clinical deterioration, with signs of raised ICP (headache and nausea) to subtle changes in behavior, tone, or bowel habits. Therefore, shunt function should always be assessed before considering other treatments for clinical deterioration.

47.5 Management of Anesthesia

Most children with this disease present for primary closure of the defect during the neonatal period, with special precautions necessary for the neonate.

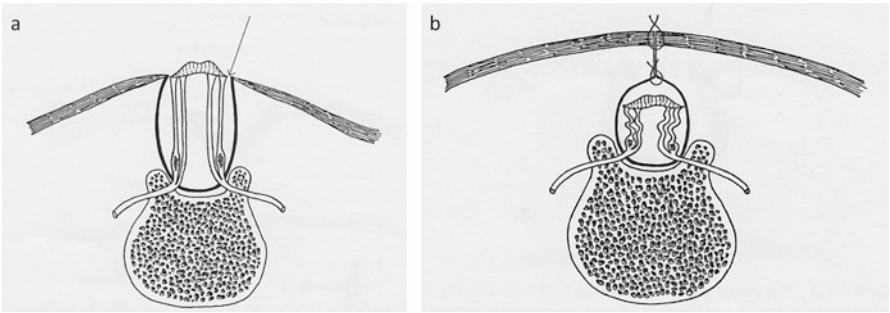

Fig. 47.3 The repair of a myelomeningocele. (**a**) The first step in the repair of a meningomyelocele is to carefully free the neural plaque from its attachment to the wall of the sac. (**b**) The neural plaque is allowed to drop back into the dural sac in the spinal canal. A circumferential incision is made in the dura, and the incision is closed in a watertight fashion. The subcutaneous layer and the skin are then sutured (This article was published in Pediatric Surgery, volume two, Fifth edition Peacock WJ, Management of Spina Bifida, Hydrocephalus, Central Nervous System Infections, and Intractable Epilepsy, p1851, Copyright Elsevier 1998)

The lesion should be kept covered with sterile dressing, and the operation room should be warmed by using radiant warming units and forced-air heating pads and adding humidity to the inspired gases in the ventilator circuits. The neonatal body habitus favors heat loss. The source of heat loss is 39 % radiation, 37 % convection, 21 % evaporation, and 3 % conduction [4]. Monitoring is required, including routine noninvasive monitoring or neuromuscular blockade monitoring. If an extensive procedure is necessary, an arterial catheter should be inserted for direct blood pressure measurement and to provide for intermittent blood gas analysis when required. Red blood cell-containing components, fresh frozen plasma, and platelets should be available for possible blood loss.

Intravenous induction is usually selected, and awake intubation is selected for unusual positioning or an anticipated difficult airway. However, an international consensus group and others have cautioned against awake intubation unless there is a life-threatening situation [4]. Before giving neuromuscular blocking agents, it should be ascertained whether the surgeon wishes to use a nerve stimulator to identify nerve roots. A short trachea has been described in association with meningomyelocele; therefore, it is imperative that the endotracheal tube is not in an endobronchial location. There may be difficulty in positioning the child for intubation because placing the defect in the middle of a “doughnut” not only causes pressure on the open defect but also necessitates additional padding beneath the shoulders and head (Fig. 47.4) [5]. During the prone position for surgery, all pressure points should be adequately padded and the eyes protected. The position of the endotracheal tube should be carefully checked.

Anesthesia should be continued with inhalational anesthetic agents or opioids with controlled ventilation. Fentanyl is often administered as part of an opioid-based technique. A common loading dose is 5–10 μg/kg, with a dose of 2–5 μg/kg/h usually adequate for maintenance [4]. However, in neonates, hepatic enzyme

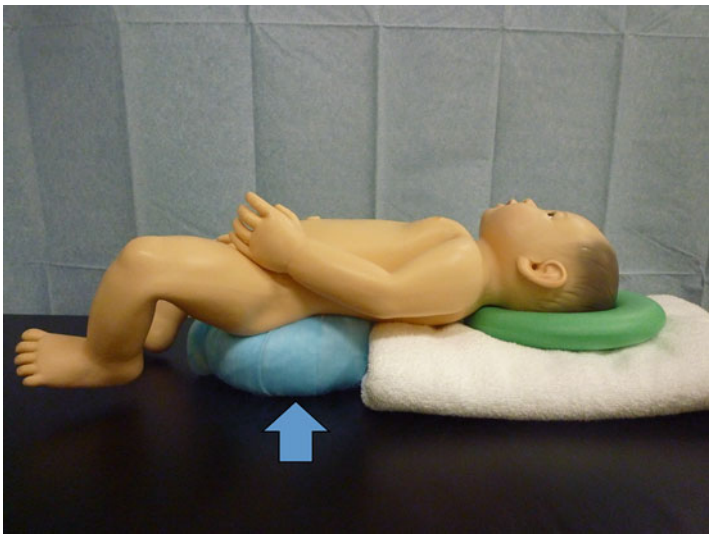

Fig. 47.4 Supine positioning for meningomyelocele induction. A cushion is formed and placed under the back

function, decreased hepatic blood flow secondary to increased intra-abdominal pressure, and potent inhaled anesthetics may influence fentanyl clearance [6]. As a result, extremely prolonged ventilatory depression may occur after fentanyl anesthesia [7]. Remifentanil is the newest in the family of synthetic opioids. It has a rapid onset, small volume of distribution, rapid clearance, and a brief half-time (1.0–1.5 min) for equilibration between plasma and the effect compartment. Its extremely short context-sensitive half-life (3–5 min) and rapid recovery from drug effect are the hallmarks of remifentanil's unicity [8]. The IV loading dose is 0.5–2 μg/kg and the IV infusion is 0.05–0.3 μg/kg/h. The side effects are similar to those of other opioids and include bradycardia, apnea, chest wall rigidity, and vomiting [5]. Respiratory depression is concentration dependent. Because of the rapid offset of the analgesic effect, anesthesia with remifentanil must include a transition to some other form of analgesia, including another longer acting opioid or a regional block.

Blood loss is difficult to accurately measure. The amount of bleeding should be estimated, and atrial systolic pressure and hematocrit should be monitored as a guide to replacement.

Hydrocephalus occurs in 80 % of infants with meningomyelocele, and these infants will return to the operating room within several days for placement of a ventriculoperitoneal shunt.

Postoperatively, respiratory status should be carefully assessed because breathing difficulties may occur after a tight skin closure, and the ventilator responses to hypoxia and hypercarbia may be diminished or absent when hydrocephalus and Chiari malformation coexist.

47.6 Latex Sensitivity

Children with myelodysplasia are at high risk for latex sensitivity and possibly anaphylaxis [4]. This likely results from repeated exposure to latex products encountered during bladder catheterizations and multiple (usually more than five) surgical procedures, during which latex gloves have been in contact with large mucosal surfaces.

Children with a risk for latex sensitivity and possibly anaphylaxis should be managed in a latex-free environment and if signs and symptoms of anaphylaxis develop during surgery, latex allergy should be suspected. Suspected anaphylaxis should be treated with intravenous epinephrine at a dose of 1–10 μ/kg, as required.

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Chapter 48
Anesthesia During Surgery for Vascular Anomalies

Toshimi Horiki

Abstract This chapter reviews arteriovenous malformations (AVMs), including vein of Galen malformation and moyamoya disease as vascular anomalies. The method of choice in diagnosing suspected AVMs in infants and children is MRI, and angiography is necessary to analyze the blood vessel anatomy. Infants and children with AVMs require sedation or general anesthesia for these examinations. The most effective technique for anesthetic maintenance in MRI is a continuous infusion of propofol. It is ideal, and in most circumstances, careful titration of the infusion rate produces an immobile patient with well-maintained spontaneous ventilation, and its rapid recovery time also allows discharge much sooner than with other techniques. Dexmedetomidine is the most recent addition to the list of sedative drugs used in pediatrics, and it is currently approved for the sedation of unintubated patients during non-stimulating or nonpainful procedures.

Moyamoya disease appears to be more common among children of Japanese ancestry, and this disease may be precipitated by hyperventilation. Therefore, careful and continuous monitoring of end-tidal CO_2 partial pressure is essential in anesthesia management. The main goals during anesthesia are the maintenance of normotension, normovolemia, normo- or mild hypercapnia, and normothermia. Postoperative pain control is also important because crying and hyperventilation secondary to inadequate analgesia can lead to cerebral ischemia.

Keywords Vein of Galen • "Off-site" anesthesia • Moyamoya disease • End-tidal CO_2

48.1 Introduction

AVMs in the pediatric neurosurgery field are classified as skull or spinal cord types. Most AVMs are found in the skull and classified as brain AVMs, vein of Galen aneurysmal malformation (VGAM), and dural arteriovenous fistula.

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MRI and angiography are useful in the diagnosis of suspected AVMs. Infants and children with AVMs require sedation or general anesthesia for these examinations. Moyamoya disease appears to be more common among children of Japanese ancestry, and this disease may be precipitated by hyperventilation. Therefore, careful and continuous monitoring of end-tidal CO_2 partial pressure is essential in anesthesia management.

This chapter reviews the management of "off-site" anesthesia and the special anesthesia problems associated with moyamoya disease.

48.2 Arteriovenous Malformations (AVMs), Including the Vein of Galen

48.2.1 Classification

AVMs in the pediatric neurosurgery field are classified as either skull or spinal cord types. Most AVMs are found in the skull and classified as brain AVMs, vein of Galen aneurysmal malformation (VGAM), and dural arteriovenous fistula (AVF) (Table.48.1) [1].

VGAM occurs in the subarachnoid space of the choroid fissure. This is the result of an anomalous connection between the arteries of the posterior cerebral circulation and an enlarged vein of Galen (Fig. 48.1). VGAM is classified into two types: choroidal and mural. The choroidal type is involved in serious neonatal failure, and the mural type is involved in hydrovenous disorders of the infant.

48.2.2 Diagnosis and Treatment

The first choice diagnostic examination for infants and children with suspected AVM is MRI [1]. VGAM is distinguishable from brain AVM and dural AVF by MRI.

Table 48.1 AVMs in the skull of infants and children

Part of the skull	Disease
Subpial	Brain AVM
	Pial AVM
	Pial AVF
Subarachnoid	VGAM
	Choroidal type
	Mural type
Dural	Dural AVF
	DSM
	Infantile type
	Adult type

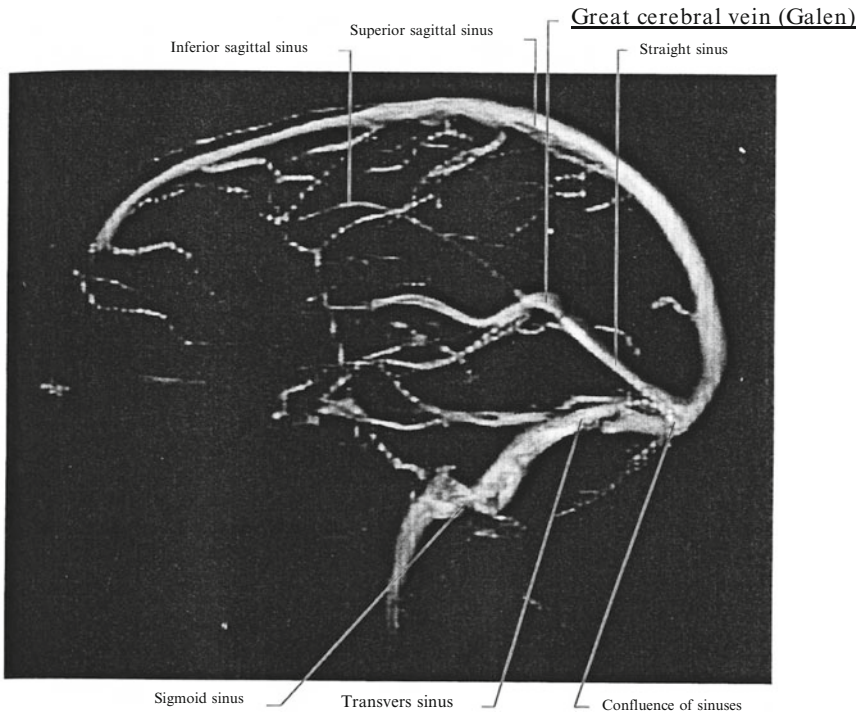

Fig. 48.1 Lateral projection from a magnetic resonance venogram using time-of-flight method (This article was published in Gray's Anatomy, Thirty-nine edition Standing S, Crossman AR, Management of Spina Bifida, Vascular supply of the brain, p 305, Copyright Elsevier 2005)

CT is useful for examining the size and calcification of the brain, and angiography is necessary for analyzing the blood vessel anatomy. When these examinations involve infants and children, they require sedation or general anesthesia.

Treatment for VGAM consists of occlusion of inflow (arterial) feeders followed by embolization of the venous side, which can be accomplished by interventional radiology under general anesthesia. Multidisciplinary efforts are directed at interventional radiology procedures as the initial intervention and control of high-output congestive heart failure (CHF). The open surgical approach typically involves access through a subtemporal, midline, or lateral occipital craniotomy, and a burr hole at the confluence of the venous sinuses permits an approach to the venous side of the malformation in a retrograde manner.

48.2.3 Management of Anesthesia

The management of anesthesia in MRI is one of the "off-site" anesthesia. Interventional procedures using MRI are dependent on the equipment that cannot be moved

into the operating room; therefore, any infant or child might require anesthetic outside of the surgical suite.

Off-site anesthetics are generally administered to two broadly defined groups of children: those who require immobilization for non-stimulating procedures and those who are undergoing a painful invasive procedure in a location distant from the operation room. Nearly all children younger than 3 years of age will require some type of sedation or anesthesia [2].

Equipment brought into the magnetic room must function safely in a high magnetic field environment and not emit radiofrequency noise that can interfere with the scan. Therefore, several manufacturers are required for MRI-compatible anesthesia machines, monitors, and infusion pumps. Laryngoscopes that are made of plastic or nonferromagnetic metals are available. Plastic stethoscopes and scissors must also be used.

The most effective technique for anesthetic maintenance in MRI is a continuous infusion of propofol. Because the anesthetic goal for MRI is immobilization without the need for analgesia, propofol is ideal, and in most circumstances, careful titration of the infusion rate produces an immobile patient with well-maintained spontaneous ventilation. The rapid recovery time also allows discharge much sooner than with other techniques. Frankville et al. studied children who received an infusion of propofol at the rate of 50, 75, or 100 μg/kg/min with tracheal intubation during MRI. They found that following induction of anesthesia with halothane, nitrous oxide, and a 2 mg/kg loading dose of propofol, a propofol infusion at a rate of 100 μg/kg/min effectively prevented children from moving during MRI [3]. Machata et al. assessed airway patency in spontaneously breathing infants and children by measuring upper airway size and configuration with MRI. Their maintenance of anesthesia was as follows. After the patients received midazolam 0.1 mg/kg intravenously, they were moved into the MRI. Then, nalbuphine 0.1 mg/kg, followed by a loading dose of propofol 1 mg/kg, was administered. Supplemental doses of propofol 0.5 mg/kg were administered until adequate sedation was achieved. Supplemental oxygen was provided by pediatric face mask with a gas flow rate of 2 l/min, and sedation was maintained with propofol 5 mg/kg/h using syringe pumps suitable for MRI. They observed that airway patency was maintained in all infants and children sedated with this propofol-based sedation regimen [4].

Dexmedetomidine is the most recent addition to the list of sedative drugs used in pediatrics [5]. It is currently approved for the sedation of unintubated patients during non-stimulating or nonpainful procedures. Infants and children 5 months to 16 years of age who were sedated with dexmedetomidine for nonpainful procedures showed minimal effects on respiration. In the case of sedation for MRI, a loading dose of 3 μg/kg dexmedetomidine administered over 10 min IV followed by an infusion of 2 μg/kg/h minimized the need for rescue with pentobarbital. An alternative approach included a loading dose of 1 μg/kg dexmedetomidine over 10 min followed by an infusion of 0.5 μg/kg/min plus a 0.1 mg/kg bolus of midazolam after sevoflurane inhalational induction for IV placement.

After a cerebral angiogram, pediatric patients must lie flat for several hours to avoid bleeding from the femoral arterial after removing the sheath. The presence of parents can help reassure and distract an older or more cooperative child. Narcotics or α-2 agonists can help deep extubation or a period of quiet sleep in the recovery room for younger or less cooperative children [5].

Embolization of an AVM can occur ether under a single anesthetic or in separate sessions. When a patient is going to be embolized and resected in one session, they are likely to transport under anesthesia from the interventional radiology suite to the operating room. Transport should be performed with attention to the support of the airway and control of hemodynamics, making sure that a patient's level of sedation does not decrease to the point where blood pressure spikes can occur [5].

The anesthesia goals for open surgery are similar to those of other open cranial procedures. Operative concerns are airway control, prone positioning, precautions for massive blood loss, and typical concerns for surgery on newborns.

48.3 Moyamoya Disease

48.3.1 Background

Moyamoya disease is an anomaly that results in progressive and life-threatening occlusion of intracranial vessels, primarily the internal carotid arteries near the circle of Willis [2]. An abnormal vascular network of collaterals develops at the base of the brain, and the appearance of these many small vessels on angiography was originally described by the Japanese name "moyamoya." This disease appears to be more common among children of Japanese ancestry. Associated intracranial aneurysms are rare in children but may occur in more than 10 % of affected adult patients [1].

48.3.2 Symptoms, Diagnosis, and Treatment of Moyamoya Disease

Moyamoya disease usually manifests as transient ischemic attacks progressing to strokes and fixed neurological defects in children [2]. The attack may be precipitated by hyperventilation that results from blowing on hot food, playing a flute, singing a song, or crying. If moyamoya disease is suspected, MRI/MRA should be performed.

Medical management consists of antiplatelet therapy, such as aspirin, or calcium channel blockers, and surgical management is often recommended for children who have experienced repeated or progressive attacks [2]. Techniques to bypass stenosis of the internal carotid artery and middle cerebral artery have been used with some

success in selected patients. Other techniques have been developed to take advantage of the ischemic brain's tendency by attempting to augment blood flow through the development of collaterals.

48.3.3 Management of Anesthesia

Surgery for the condition of moyamoya disease is often complicated by cerebral ischemia, so the goal in perioperative management is to maintain the balance between oxygen supply and demand in the brain [5]. Hypocapnia, hypercapnia, hypotension, and hypovolemia during surgery have all been identified as risk factors for ischemic complications.

Careful and continuous monitoring of end-tidal CO_2 partial pressure is essential in the management of anesthesia. Before tracheal intubation, percutaneous CO_2 monitoring is useful (Fig. 48.2). Children with moyamoya disease have reduced hemispheric blood flow bilaterally, and hyperventilation may further reduce regional blood flow and cause significant EEG and neurological changes. Normocapnia must be maintained throughout all phases of the procedure, including induction of anesthesia.

Volatile anesthetics and nitrous oxide can cause cerebral vasodilation, and this may result in intracerebral steal [6]. To address this, several previous studies reported excellent results with total intravenous anesthesia (TIVA) for revascularization procedures on the basis of regional blood flow [7]. Fentanyl is often

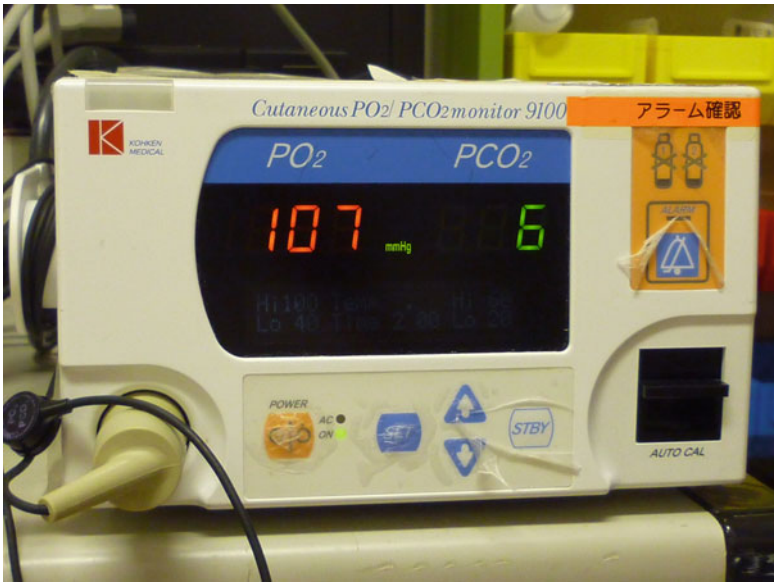

Fig. 48.2 Percutaneous end-tidal CO_2 monitor

administered as part of an opioid-based technique because it is easily titratable with minimal adverse effects. A common loading dose is 5–10 μg/kg, with a dose of 2–5 μg/kg/h usually adequate for maintenance [8]. Remifentanil is a useful opioid when used with propofol for TIVA with benefits that include rapid recovery, reduced nausea, vomiting, and postoperative delirium [9]. If a loading dose of remifentanil is 0.5 μg/kg/min for 3 min and maintenance infusion is 0.25 μg/kg/min, blood concentration becomes 50–200 ng/mL as a result. A common loading dose of propofol is 1 mg/kg, and maintenance infusion is 10 mg/kg/h for 10 min, then 8 mg/kg/h for 10 min, and then 6 mg/kg/h for 10 min. However, when this regimen is modeled for pediatric patients, the blood concentration achieved is approximately 2 μg/mL (3 μg/mL for adults) [8].

Adequate hydration and maintenance of baseline blood pressure are essential. Most of these children have an intravenous catheter inserted the night before surgery and are given sufficient fluids to avoid dehydration during the perioperative period. Lee et al. studied to determine whether the NIRS-derived indices could identify blood pressure ranges that optimize autoregulation for seven pediatric patients with moyamoya disease [10]. In their study, NIRS-derived autoregulation indices, the cerebral oximetry index, and the hemoglobin volume index were calculated intraoperatively, and optimal mean arterial blood pressure and the lower limit of autoregulation were identified. From their results, the NIRS-derived measures of autoregulation could become useful clinical monitors in pediatric patients with moyamoya disease.

Normothermia is maintained, particularly at the end of the procedure, to avoid postoperative shivering and the stress response. A smooth extubation without hypertension or crying is desirable because most complications occur postoperatively and are associated with dehydration and crying. Postoperative pain control is also important because crying and hyperventilation secondary to inadequate analgesia can lead to cerebral ischemia [2].

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Chapter 49
Anesthesia for Pediatric Cardiac Surgery and Brain Protection

Kazuyoshi Shimizu

Abstract In the past decades, dramatic advances in medical and surgical treatments have improved the short-term outcomes and early postoperative morbidities and mortalities for neonates, infants, and children with congenital heart disease undergoing cardiac surgeries. Recently, the attention has been focused on the quality of functional recovery resulting from perioperative care, because the problem of neurologic insults has been raised, and acute brain injury possibly affects neurodevelopmental outcomes. The causes of brain injury are multifactorial; however, perioperative management including anesthesia, hypothermia, cardiopulmonary bypass, and surgical techniques could be a contributing factor. Various techniques to minimize the neurologic damage in pediatric cardiac surgery have facilitated complex heart surgery, including pharmacologic and non-pharmacologic interventions. Current expected indices are neuroprotective techniques of cardiopulmonary bypass (deep hypothermic circulatory arrest and regional cerebral perfusion) and neuromonitoring (near-infrared spectroscopy). A number of studies on these approaches in animal models have been investigated. Clinical trials regarding the association between long-term neurological outcomes and brain protection strategies have been increasing; however, high-quality protocols based on large, multicenter, randomized, controlled studies are still insufficient to provide the obvious evidence in this field. We have to identify the current problems and continuously explore these in depth in pediatric cardiac operations.

Keywords Brain protection • Pediatric cardiac surgery • Cardiopulmonary bypass

49.1 Introduction

Recent advances in perioperative management in pediatric cardiac surgery have improved outcome of patients with congenital heart disease (CHD). Some morbidities, however, still remain a concern. In particular, neurologic injury, which is an

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important factor to patients' life, has been focused on patients following cardiac surgery. The incidence of acute brain injury is falling from up to 25 % [1] to 1–2 % [2] by the improvement of techniques over the last years. However, the causes of neurologic impairment are variable, multifactorial, and complex. Some approaches are necessary from multi-views of management in the perioperative period. Brain injury is mainly influenced by hypoxic/ischemic/reperfusion injury and is additionally modified by influence of inflammatory changes associated with cardiopulmonary bypass (CPB) and also drugs including anesthetic agents. The vulnerable areas, particularly cerebral white matter, to acute changes in perfusion and oxygenation in the developing brain exists, and also white matter injury prior to CPB and anesthetic exposure is further exacerbated postoperatively [3].

This chapter introduces neuroprotective methods and neuromonitoring in pediatric cardiac surgery, especially in neonates and infants.

49.2 Neuroprotection

For adults, some data shows the evidence-based approach regarding improved neurologic outcomes [4]. In pediatric field, a systematic review regarding brain protection and neuromonitoring strategies during heart surgery was recently published [5]. This systematic review demonstrates that data supporting use of various techniques as below are limited and their effectiveness is uncertain. Among them, the only intervention with sufficient evidence to recommend was avoidance of extreme hemodilution during CPB.

A number of researches have been published; however, the apparent evidence of pharmacological and non-pharmacological approaches supporting sufficient neuroprotection in children undergoing cardiac surgery under CPB is difficult to demonstrate.

49.2.1 Pharmacologic Interventions

49.2.1.1 Corticosteroids

Inflammatory response to CPB is one of the contributing factors for brain injury during the cardiac procedure; however, the consistent role of anti-inflammatory agents for neuroprotection is still controversial. Corticosteroids, an anti-inflammatory drug, are widely used pre- and intraoperatively in pediatric cardiac surgery. Prophylactic steroids during the perioperative period could provide the improvement of clinical course and the reduction of the incidence of adverse events associated with CPB. However, these human studies were not designed to investigate the neuroprotective effects of steroids. In experimental models, systemic preoperative high-dose (30 mg/kg) methylprednisolone significantly decreased

systemic manifestation of inflammatory response and brain damage in piglets with deep hypothermic circulatory arrest (DHCA) [6, 7].

Currently, few studies indicating the direct efficacy of corticosteroid for neuroprotection in children undergoing cardiac surgery with CPB exist.

49.2.1.2 Anesthetic Agents

Administration of anesthetic agents possibly results in neural apoptosis and cell death related to altered expression of ion channels and disturbance to intracellular calcium homeostasis [8], and these dose and duration seem to be contributing factors to neural damage leading to neurodevelopmental delay [9]. Recently, anesthetic neurotoxicity has been investigated in the developing brain [10]. The subunit composition of N-methyl-D-aspartate (NMDA) receptors, opioid receptors, and γ-aminobutyric acid (GABA) receptors changes during development [11]; however, commonly used anesthetic drugs cause NMDA receptor inhibition and GABA receptor excitation in the developing brain [12]. Therefore, the use of antagonists to excitatory neurotransmitters in clinical practice has probably been desirable from the viewpoint of neuroprotection.

Volatile agents, isoflurane, sevoflurane, and desflurane, have been widely studied on the neuroprotective effects in animals and have demonstrated neuroprotective effects [13]. In particular, desflurane conferred significant neurologic protection in experimental models with CPB [14, 15]. The mechanism is thought to be a slowing of neural metabolism and apoptosis.

Ketamine is a non-competitive antagosist of NMDA receptors and has well-documented neuroprotective effects [16]; however, ketamine did not reduce central nervous system injury during CPB in children [17], and there is no evidence on the effects of clinical doses of ketamine on neuronal structure or neurocognitive functions in children [18].

Dexmedetomidine, an alpha 2 receptor antagonist, does not have a neurotoxic effect in the developing brain, and animal studies demonstrate neuroprotective effect [19]. The exact mechanisms are not fully investigated.

At present, because the applicability of animal data to clinical anesthesia practice remains uncertain, available data do not support the choice of any one anesthetic drug over the others and also the optimal blood level of these, particularly during DHCA, under CPB in children undergoing cardiac surgery.

49.2.1.3 Erythropoietin (Epo)

Epo has been focused on for the last few years in terms of its neuroprotective effect [20]. In neonates who suffered from hypoxic/ischemic encephalopathy, Epo improved the neurologic outcome [21]. Many mechanisms have been pointed out, including neurotrophic effect, antiapoptotic effect, anti-inflammation effect, and also vasodilative effect to the injured tissue. Clinically, the high-dose Epo is needed

to as the neuroprotective dose range (1,000–30,000 U/kg) because only small amounts of Epo can cross the blood–brain barrier. Recently, a clinical study, which investigated the safety and efficacy of Epo treatment for neonate undergoing cardiac surgery, has been published [22]. This trial showed that neurodevelopmental outcomes were not different between Epo group and placebo group; however, a larger trial will be necessary.

Currently, there is little evidence that pharmacological approach has the potential to improve neurological outcome in pediatric cardiac surgery.

49.2.2 Non-Pharmacologic Interventions

49.2.2.1 CPB Management

CPB Flow Management

Full flow of CPB, which has been used 150 ml/kg/min, was associated with both of good short-term and long-term neurologic outcomes in neonates [23]. Besides, other CPB flow strategies including DHCA, regional cerebral perfusion (RCP)/antegrade cerebral perfusion (ACP), and low flow cardiopulmonary bypass (LFCPB) have been applied in various complex corrections for complex CHD.

Cerebral blood flow (CBF) is, however, basically maintained under individual autoregulation; this system does not become well functioned under deeper hypothermia on CPB. Generally, cerebral autoregulation is preserved at levels of moderate hypothermia. Subsequently, CBF becomes pressure passive [24].

DHCA has been indicated to keep bloodless surgical field, especially aortic arch reconstruction. Hypothermia to 16–18 °C provided adequate neuroprotection for 30–45 min in the experimental study [25].

In the meantime, disadvantages of DHCA have been indicated. Pediatric patients requiring DHCA have a higher incident of postoperative neurological disturbance and delayed motor development compared to those in whom LFCPB is used [26]. Longer duration of DHCA was associated with an increasing risk of seizures and also worse neurodevelopmental outcomes [27, 28]. A circulatory arrest time of 41 min or longer contributed to increased risk for neurodevelopmental outcomes in the clinical setting [29, 30].

The exact mechanisms of neural damage following DHCA are unclear. Subsequent impairment in CBF and cerebral oxygen metabolism ($CMRO_2$) is thought to be involved in cerebral edema following DHCA [31].

Thus, RCP/ACP have been described as a neuroprotective alternative to DHCA [32]. The benefit of RCP is definitely reduction of circulatory arrest time with maintaining continuous cerebral blood flow and oxygenation during CPB. RCP provides selective perfusion of the carotid artery via aortic cannulation of either the innominate or subclavian artery with a polytetrafluoroethylene (PTFE) graft. The perfusion to the opposite side of the cerebral hemisphere is supplied through the

circle of Willis. As for the flow rate of RCP, approximately 20–30 ml/kg/min at 20–25 °C is used [33, 34]. Conversely, some data pointed out that RCP flow of less than 40 ml/kg/min is inadequate [35]. Andropoulos DB et al. demonstrated that RCP flow of a median of 64 ml/kg/min was necessary to achieve adequate perfusion to the brain with neuromonitoring including transcranial doppler ultrasound (TCD) and near-infrared spectroscopy (NIRS).

Recently, several randomized trials regarding the impact of RCP over DHCA have been published on the neurodevelopmental outcomes. However, a single-center randomized trial demonstrated no improvement in later developmental outcome [36, 37], and another study suggested that RCP may cause worse brain magnetic resonance imaging (MRI) outcomes [38]. The cause of these results indicating failure to show the superiority of RCP could be inadequate flow [39].

There is still controversy on the superiority of DHCA, LFCPB, or RCP/ACP from the insights of neurological outcomes in pediatric heart operation. At least, adequate monitoring of cerebral perfusion is essential in pediatric cardiac surgery using CPB, especially DHCA and low flow approach in order to assess the optimal supply to the brain.

Acid–Base Management

Two strategies, the pH stat and the alpha stat, have been widely available during hypothermic CPB. The alpha-stat strategy maintains the temperature-uncorrected arterial PCO_2 and pH at normothermic values. In contrast, the pH stat maintains the temperature-corrected pH and $PaCO_2$ at the normal values at different body temperatures. A pH-stat management might be preferable to use in infants undergoing cardiac operation with DHCA because it allows for greater CBF during hypothermia, increasing oxygen availability and maintaining uniformity of brain cooling [4].

In animal models, neurological outcome using pH-stat method was improved during DHCA [40]. Some of the human reports have shown shorter recovery time to Electroencephalogram activity for infants managed with pH stat [41], and others did not show any differences in long-term neurological outcome in children with different strategies [42, 43].

Currently, pH-stat strategy is widely applied throughout CPB in pediatric cardiac surgery.

Hemodilution Management

Hemodilution during CPB has been used for several decades. The advantages of hemodilution are thought to decrease blood viscosity from cooling, reduce blood products use, and improve microcirculatory flow. On the other hand, hemodilution might reduce perfusion pressure, increase cerebral flow leading to microemboli, and decrease oxygen-carrying capacity.

Some studies have demonstrated that lower hematocrit (Ht) during CPB was associated with worse neurocognitive outcomes [44, 45]. Jonas RA et al. reported that the lower-Ht (21 %) group had worse neurocognitive outcomes at age 1 year, compared with the higher-Ht (28 %) group. Later, the same team has demonstrated that the neurologic outcomes in the higher-Ht (35 %) group were similar with those in the lower-Ht (25 %) group [46].

Therefore, there is still unclear, but hematocrit level of 25 % or greater during the hypothermic CPB might improve neurodevelopmental outcomes in pediatric cardiac surgery.

Temperature Control

Temperature control has been one of the essential treatments during the perioperative period in pediatric heart operation.

Induced hypothermia during CPB has been applied for neuroprotection with decreasing metabolic demand [47] and been able to reduce CPB flow to have bloodless operating field, as discussed above. In contrast, hyperthermia associated with CPB-induced systemic inflammation is frequently observed in cardiac surgery and leads to worse neurodevelopmental outcome [48]. Recently, some studies have been reported on the efficacy of normothermic CPB in adults [49] and pediatrics [50]; however, it is unclear whether the safety margin of brain preservation is high with normothermic approach.

In animal model, mild hypothermia in the post CPB period significantly reduced neuronal cell death [51]. However, clinical data is little from the insight of neurodevelopmental outcome in pediatric cardiac surgery. Cottrell SM et al. showed that neurodevelopmental outcome at 1 and 4 years after pediatric cardiac surgery was not associated with early postoperative temperature profile on targeting normothermia strategy [52].

There is no obvious data that the temperature control results in the favorable neurologic outcome. At least, temperature is perioperatively avoided to be hyperthermia.

Glucose Management

Several manuscripts have been published regarding the association between glucose management and postoperative outcomes in pediatrics. Vlasselaers et al. demonstrated morbidity and mortality benefits to critically ill children from strict glycemic control. However, the occurrence of hypoglycemia in the intensive insulin therapy (IIT) group (target blood glucose 50–79 mg/dl for children <1 year old and 70–101 mg/dl for those 1–16 years old) was approximately 25 % [53]. Recently, the efficacy of tight glycemic control for children tends to be questionable [54]. From the viewpoint of the neurologic outcome in pediatric patients, the tendency is also similar. Some reports demonstrated that

hyperglycemia was not associated with worse neurodevelopmental outcomes and hypoglycemia increased electroencephalographic seizure activity and delay electroencephalogram recovery [30, 55]. The maturity of the brain might contribute to the difference of influence of high glucose concentration to brain damage between children and adult.

There is uncertainty whether tight glycemic control leads to favorable neurologic outcome in children undergoing cardiac surgery. At least, hypoglycemia should be avoided in terms of safety management during the perioperative period.

In summary, minimize use of DHCA and consider RCP/ACP if possible. If RCP/ACP is used, a target flow rate is aimed to 25 % of full flow, approximately 40 ml/kg/min. If DHCA is necessary, the longer duration of cooling on CPB, pH-stat strategy, maintenance of hematocrit 25–35 % on CPB and shorter than 40 min circulatory arrest time need to be used during the CPB in pediatric cardiac surgery.

49.3 Neuromonitoring

Despite the existence of several modalities of neurologic monitoring, the standard of care applying widely still remains uncertain.

49.3.1 Near-Infrared Spectroscopy (NIRS)

NIRS has been used as a noninvasive and real-time technology to monitor cerebral tissue oxygenation with transcutaneous measurement of oxyhemoglobin and deoxyhemoglobin concentrations having different absorption spectra. When the probes are placed on patients' forehead, NIRS values reflect CBF on the frontal site. Although the value assumes that the volume of blood within the light path is approximately 75 % venous and 25 % arterial, the actual ratio in children widely varies and averages 85 % venous and 15 % arterial [56]. Baseline value of NIRS, which has a measurable range of 15–95 %, is reported around 70 % in patients with acyanotic congenital heart disease and 40–60 % in cyanotic patients.

The balance of cerebral oxygen supply and demand results in variability in NIRS, in which many factors (CPB flow pattern, temperature, and so on) can involve [57]. Preop, intraop, and postop values of NIRS somehow correlate with neurodevelopmental outcomes.

In animal studies, Kurth et al. demonstrate that any EEG changes occurred below 42 % of cerebral oxygen saturation in hypoxic–ischemic piglets [58], and another study shows that the brain functions are seriously abnormal, and there is serious morphological impairment when the rSO_2 is less than 30 % in newborn pigs [59].

Some clinical reports suggest a correlation between low cerebral oxygen saturation and neurologic outcome and also demonstrate any improvements provided by interventions based on low rSO_2 [60]. In 51 HLHS patients with low to abnormal visual-motor integration (VMI), the perioperative stage 1 palliation rSO_2 was significantly lower (63.6 ± 8.1 vs. 67.8 ± 8.1). Nonlinear relationships of rSO_2 to the neurodevelopmental measures found rSO_2 thresholds of 49–62 %. The hours at a rSO_2 less than 45 and 55 % were related to low visual-motor integration and neurodevelopmental index scores [61]. Dent et al. reported that new postoperative MRI lesions, typically abnormalities of the white matter, were correlated with a prolonged low rSO_2 (<45 % for >180 min) in 15 neonates with perioperative NIRS monitoring undergoing the Norwood procedure [62]. Another report, targeting interventions perioperatively to maintain cerebral $rSO_2 > 50$ %, documented no association between new MRI findings and cerebral rSO_2 [63]. Kussman et al. reported the correlation between an intraoperative rSO_2 and the neurologic outcome (development assessment and MRI findings) at 1 year in 104 infants who underwent biventricular repair without aortic arch obstruction. The primary NIRS variable was the integrated rSO_2 for $rSO_2 < 45$ %. Lower Psychomotor Development Index scores were associated with lower rSO_2 during the 60mins period following CPB [64].

On the other hand, a systematic review on the use of NIRS alone does not demonstrate improvement in neurologic outcome [65]. Additionally, NIRS can detect aortic cannula malposition and venous obstruction [66, 67].

The major limitations reported are as follows: (1) the precise contribution of various vascular beds and stability in NIRS values, (2) the size of the area explored, (3) the lack of a direct reference against which to correlate values, and (4) the influence of hemoglobin values and $PaCO_2$. The increase in arterial saturation is likely to increase rSO_2; in contrast, hemodilution and a decrease in $PaCO_2$ are likely to decrease rSO_2 [68].

When using NIRS monitoring, the thresholds of decline could be clinically applied >20 % from baseline and/or <50 % in absolute changes. If so, treatment to increase oxygen delivery to the brain (increase FiO_2, $PaCO_2$, cardiac output, depth of anesthesia, CPB flow, and hemoglobin) and/or decrease oxygen consumption (decrease temperature) should be established because low rSO_2 may eventually lead to hypoxic brain injury.

49.3.2 Electroencephalography (EEG)/Bispectral (BIS) Index

Continuous EEG provides a real-time picture of the brain's surface electrical activity and therefore offers a time-sensitive method of detecting brain injury [69]. Perioperative amplitude-integrated electroencephalography (aEEG) monitoring has been used in pediatric cardiac surgery. It has been reported that using aEEG,

background activity was largely suppressed in infants during DHCA [70]. Time to recovery of aEEG background correlated with neurologic outcome in hypoxic asphyxia [71] and infants undergoing cardiac operation [72, 73]. Gunn JK et al. demonstrated that failure of aEEG background to recover to a continuous pattern within 48 h after CPB was highly correlated with increased mortality and worse motor development at 2 years of age.

Bispectral (BIS) index monitor has been widely applied for the monitoring of the depth of anesthesia during the operations. BIS sensor probe is located on the forehead and temple and is easy to use without any calibration. BIS index, calculated with bispectral analysis based on the algorithm, ranges from 0 (isoelectric) to 100 (fully awake). Increasing the anesthetic depth can provide the reduction of the BIS value; however, the accuracy of the BIS index during hypothermia remains unclear. During CPB in cardiac surgery, BIS falls as cooling and subsequently arises as rewarming [74]. BIS is reported to detect cerebral hypoperfusion. Hayashida M et al. demonstrated the combination of BIS and NIRS could detect cerebral ischemia [75]. Fewer intraoperative hemodynamic adverse events were reported when BIS monitoring was applied [76]; however, the significant association between BIS and neurologic outcome in children undergoing cardiac surgery is unclear.

So far, there is insufficient data to demonstrate the recovery time for the aEEG pattern to normalize and the exact thresholds of BIS to guide the optimal hemodynamic management in pediatric cardiac operation.

49.3.3 Transcranial Doppler Ultrasound (TCD)

TCD sonography can measure cerebral blood flow velocities (CBFV) by a real-time, noninvasive method. The transducer probe is placed on the temporal window to display the middle and anterior cerebral arteries. As prescribed in the previous paragraph, "CPB management," Taylor RH et al. reported that the change of CBF autoregulation system depending on temperature during the CPB was detectable by TCD [24]. According to a systematic review on TCD, it suggests a good correlation between changes in CBF and mean cerebral artery (MCA) blood flow velocity, and also TCD can help to significantly improve neurological outcome after cardiac surgery in neonates and pediatric patients [77]. TCD in combination with NIRS can be used to assess the effectiveness of cerebral perfusion in LFCPB with or without antegrade cerebral perfusion (ACP) to help guide bypass flow rates. The margin of safety represented by a minimum flow of 30 ml/kg/min is required to reliably assure the presence of detectable middle cerebral artery perfusion [78]. In terms of the association between TCD and neurodevelopmental outcomes, the first manuscript reported by Cheng HH et al. demonstrated that postoperative CBFV in infants undergoing biventricular repair with CPB was related to neurodevelopmental outcome at 1 year old [79].

49.3.4 Multimodal Strategies

Although these available monitors/devices have limitations as above, multimodal approach of these could provide improved neurologic outcomes.

Austin EH et al. demonstrated the role of an interventional algorithm with multiple neuromonitoring during the pediatric cardiac surgery on neurologic outcomes. In 250 infants and children undergoing cardiac surgery with CPB, acute postoperative neurological events were detected in 26 % of children who had monitoring including NIRS, TCD, and EEG event. The active intervention resulted in a reduction of acute neurological events up to 7 %; the same incidence is observed when no low rSO_2 occurred [80]. Similar to strategies in adults for particular situations, goal-directed therapy (GDT) subsequently might be adapted in pediatric cardiac field in the future [81].

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Chapter 50
Anesthesia for Diagnostic and Perioperative MRI

Hiroshi Otake

Keywords Pediatric anesthesia • MRI • Safety • Sedation

50.1 Introduction

Providing anesthesia or sedation for children outside of the operation room (OR) is one of the most stressful jobs for the anesthesiologist. The demand for anesthesiologists or other medical professionals to administer anesthesia/sedation for pediatric diagnostic imaging using modalities such as computerized tomography or magnetic resonance imaging (MRI) has increased greatly over the last decade [1, 2]. Providing pediatric anesthesia/sedation outside of the OR requires more clinical and administrative resources than when done inside the OR. This poses many challenges for the anesthesiologist, including the long-distance transportation of patients, a long turnover time between cases, insufficient anesthesia apparatus and equipment, and an unfamiliar environment in which to work. In addition, new MRI procedures can require a longer time to perform and generate a greater level of noise, both of which serve as stressors to the child. In achieving the optimal level of sedation, however, adverse events such as hypoxemia can sometimes occur. When anesthesia is conducted in an MRI suite, there are three important things to be avoided: (1) materials and equipment that will be attracted to the MRI machine, (2) devices that will interfere with the function of the MRI machine, and (3) MRI interference with the patient or the functioning of materials and devices used for anesthesia [3, 4]. Taking all of this into consideration, anesthesia for diagnostic and perioperative MRI is one of the toughest jobs for the anesthesiologist.

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50.2 Special Considerations for Anesthesia or Sedation at MRI Units

Anesthesia departments are responsible for ensuring the safe and effective delivery of anesthesia or sedation, irrespective of location or personnel dictates to the effect that anesthesiologists should provide oversight and credentialing of practices [5, 6].

The application of MRI involves the use of a superconducting magnet, which creates a variety of safety issues not seen in other clinical areas. The strength of the magnetic field is measured in tesla (T), and 1T is the equivalent of 10,000 gauss (G). In most MRI machines, this field is 1.5–3 T (15,000–30,000 G) in strength, while the earth's magnetic field is 0.5 G. Thus, any ferromagnetic material brought near the machine becomes a major hazard, as it can be turned into a projectile by the strong attractive force created by the magnet. Chen reported the death of a 6-year-old child undergoing MRI due to a skull fracture and intracranial hemorrhage after an oxygen tank that had been brought into the room was pulled into the machine at high speed [7]. Chaljub et al. reported five incidents at MRI units involving oxygen or nitrous oxide tanks, one of which caused facial fractures [8]. To prevent such tragedies, Landrigan [9] suggested using metal detectors prior to MRI examination. The unexpected incidence reported by Zimmer et al. [3] proved that even weak ferromagnetic objects, undetectable by routine testing, could pose a hazard in MRI suites. Therefore, Miyasaka et al. [4] strongly suggested building anesthesia-compatible MRI units for patient safety.

Additional patient injury can occur from implanted metal devices such as cardiac pacemakers, central or vagus nerve stimulators, and electronic insulin pumps or ventriculoperitoneal shunts. As these devices may be affected by the magnet of the MRI machine, special MRI-compatible or MRI-safe equipment should be used. Screening of patients and employees should be carried out before they are allowed to enter the scanning room.

Monitors should be MRI-compatible as burns or thermal injury can occur from coiled or frayed monitor cables or pads in contact with the skin. Normal cables (sometimes even MRI-safe ones) heat up during the scanning process. Artifacts may appear on images with some non-MRI-compatible monitors, and MRI machines can interfere with monitoring such as of EKG waves, for example. It is important that monitors used for pulse oximetry and capnometry be MRI-compatible, especially when used for sedated or anesthetized patients. If you do not have MRI-compatible monitors, creating a hole in the console wall to thread the necessary tubing from outside the scanner to the patient is one option. In total, about 9–10 m of tubing will be required for suction, infusion of medication, end-tidal carbon dioxide ($ETCO_2$), and ventilator circuits [10–12].

The loud knocking noise generated by the MRI machine can be a hazard, so everybody, including the patient, remaining in the scanning room should use earplugs or headphones while the machine is running.

50.3 Clinical Considerations

50.3.1 Goals and the Process

Safety is the priority in delivering anesthesia at MRI units, especially as MRI itself is not the treatment. Anesthesiologists should aim not only to deliver the anesthesia safely but also minimize anxiety, pain, and discomfort for the patient and their family. The process of delivering anesthesia outside the OR involves four tasks: (1) making the anesthesia-conduction site safe and comfortable, (2) thoroughly evaluating the patient preprocedurally, (3) providing safe anesthesia and keeping records, and (4) facilitating smooth emergence and recovery.

Each institution should have a uniform set of standards for sedation [5]. Those standards include standardized documentation, fasting guidelines, and informed consent procedures and hold regardless of the location of the procedure or the practitioner. The sedation personnel, monitoring equipment, and recovery facilities must be uniform within an institution, as well as the quality improvement process [13]. Ideally, in addition to providing anesthesia, the anesthesia department should demonstrate leadership and a clear model of responsibility in the delivery of sedation [6]. Hospitals are required to develop protocols for patients receiving all levels of sedation. From time to time, anesthetic and sedation outcomes both in and outside the OR should be reviewed for quality improvement [13].

50.3.2 Site Settings

In order to provide a safe environment for patients, there are several key points to be checked beforehand.

Space You should check whether you have enough space to provide the anesthesia, especially when the anesthesia machines are to be located in the scanning room. Check the space you can use in the event of an emergency, which will normally be located just outside the scanning room. You should secure enough space outside the scanning room in the event that the patient needs to be resuscitated.

Infrastructure and Piping for Anesthesia Delivery In addition, you should make sure that oxygen and suction are available in the scanning room. The anesthesia machine should be connected to the gas piping, gas scavenger system, and power source, as in the OR. Make sure the infusion pumps are set up properly in terms of location and fixation.

Devices and Drugs Make sure of the location of the devices and drugs you may need. Make sure of the contents of the emergency cart. If something is missing, you should bring it prior to commencement of the examination.

Care Providers' Role You may not be familiar with the environment or staff of the MRI suite. There should be at least one medical professional present to observe the patient and keep records. The procedure provider cannot be the observer. It is important to determine who will play what role prior to commencement of the procedure in case of an emergency.

50.3.3 Patient Evaluation and Preparation

A complete evaluation of the patient is paramount in conducting procedures safely. Thorough preparation is necessary since the anesthesiologist outside the OR encounters limitations of space and access to ancillary services such as pharmaceuticals. Patient evaluation should include a medical history, clinical condition, family history, and airway evaluation, which should take into account various factors such as Mallampati class, snoring, and sleep apnea.

Informed consent should be obtained only after information on the management plans, potential risks of anesthesia or sedation, and clinical benefits have been explained. The potential need to deepen sedation, induce general anesthesia, and place an airway device should also be made clear at this point.

Many sets of guidelines [14–22] such as those of the American Society of Anesthesiologists (ASA) [16] suggest fasting in preparation for MRI, as a nil per os (NPO) status is thought to bear on the likelihood of aspiration or pulmonary complications. Suggested NPOs are 2 h for clear liquid, 4 h for breast milk, and 6 h for a light meal or infant formula. These are the same as for general anesthesia.

The Universal Protocol must also be followed at sites outside of the OR, including preprocedure verification, site marking, and time-out as mandated by the Joint Commission [5, 6].

50.3.4 Patient Observation and Keeping Records

The patient should be observed by someone other than the one conducting the procedure, and vital signs and events should be recorded on anesthetic charts.

50.3.5 Post-MRI Anesthesia

As in the OR, careful observation and monitoring of the patient should continue into the recovery phase after MRI anesthesia. Emergence agitation, respiratory events, and unstable hemodynamics should be managed in a safe environment and under the vigilance of skilled personnel. Close attention should be paid to the patient's medical condition, which may pose a risk after sedation/anesthesia. Anticipated

time of recovery must be communicated to the recovery phase nursing team, the responsible medical or surgical team, and the parents. Children scheduled for outpatient MRI should meet strict discharge criteria to eliminate risk. Patients with obstructive sleep apnea or infants at risk for postanesthesia apnea may require extended stay or hospitalization. Inpatient care should be considered in patients with unstable hemodynamics or in whom acute respiratory events requiring intubation occur.

50.3.6 Resuscitation

Medical personnel in MRI suites are less prepared to apply resuscitation than those in the OR, so the leadership of the anesthesiologist is very important in this event. In addition, the magnetic field of MRI machines may bring about secondary dangers. Therefore, cardiopulmonary resuscitation should be initiated after the patient has been quickly removed from the scanning room. The patient should then be transferred to a previously designated location near the MRI equipped for monitoring and resuscitation.

50.4 Guidelines

While MRI itself poses little risk to children, the administration of sedation or anesthesia may add substantial risk. In contrast to anesthesia in the OR, the approach to providing sedation and anesthesia outside of the OR varies among institutions and even among different providers within the same institution [2, 15, 19, 23–25]. To improve the quality of care, academic societies have published guidelines in many countries. However, those guidelines are not consistent [5, 6, 10, 14–22]. Therefore, the big challenge facing anesthesiologists is the need to balance the delivery of safe and effective sedation while adhering to the sedation guidelines of one's society. To enhance the safety of children, it is important to establish a global consensus across specialties, countries, and authorities in terms of pediatric anesthesia/sedation for MRI.

50.5 Incidence and Related Factors

Cravero et al. [2] reported incidence of complications associated with pediatric sedation/anesthesia for diagnostic and therapeutic procedures. Investigating 30,037 records, they found no deaths and only one case of cardiac arrest. The incidences per 10,000 of total adverse events, cardiac arrest, aspiration, laryngospasm, vomiting, and desaturation were 339.6, 0.3, 0.3, 4.3, 47.2, and 156.5, respectively.

Unexpected intubation was required for 9.7 per 10,000 cases. In 88.9 per 10,000 cases (1 per 338 cases), procedures could not be completed due to inadequate sedation. In another study, Cravero [24] analyzed 49,386 cases in which propofol was used for sedation/anesthesia for procedures and found that the incidences of cardiac arrest, aspiration, laryngospasm, vomiting, and desaturation were 0.4, 0.9, 20.7, 10.6, and 154.4, respectively. Procedures could not be completed in 59.5 per 10,000 cases due to inadequate sedation. Sedation provided by a non-anesthesiologist, a higher ASA status, an NPO of less than 8 h for solid food, and opioids were all factors showing a significant correlation with adverse events. Recently, Couloures et al. [26] reported an analysis of 131,751 procedural sedations and found no difference in the rates of major complications among different pediatric specialists administering procedural sedation.

Cote et al. [27] conducted a retrospective analysis of adverse events during sedation for procedures. Permanent neurologic injury or death occurred more frequently in a nonhospital-based facility. Inadequate resuscitation was also associated with a nonhospital-based setting. Inadequate and inconsistent physiologic monitoring was another major factor contributing to poor outcome at all venues. Other related factors included inadequate pre-sedation medical evaluation, lack of an independent observer, medication errors, and inadequate recovery procedures. In another retrospective analysis, Cote et al. [28] also investigated the medication used for sedation. Adverse sedation events were frequently associated with drug overdoses and drug interactions, particularly when three or more drugs were used. Patients receiving medications with long plasma half-lives such as chloral hydrate, pentobarbital, promazine, promethazine, and chlorpromazine may benefit from a prolonged period of post-sedation observation.

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Part XI
Anesthetic Management: Cardiovascular Surgery and Cerebrospinal Protection

Chapter 51
Cardiovascular Surgical Technique Under Cardiopulmonary Bypass and Cerebrospinal Protection

Hitoshi Ogino

Abstract Brain and spinal cord injuries are some of the most troublesome sequelae during perioperative periods of cardiovascular surgery, which decrease the patient quality of life in the long term and can subsequently lead to serious morbidity and mortality. In cardiac surgery, one cause of perioperative cerebral complications is cardiopulmonary bypass (CPB). Off-pump coronary artery bypass grafting, particularly with a non-touch aortic technique, has been developed for preventing cerebral deficits. Other crucial issues are intraoperative examination of the ascending aorta with epiaortic echo and appropriate selection of alternative CPB cannulation sites such as the axillary or femoral arteries. On the other hand, in a variety of recently advanced endovascular aortic repair techniques, protection of the central nervous system is of greater concern, because the perfusion vessels of the brain, spinal cord, or both are involved in the surgical repairs. Hypothermia is still the underlying principle for cerebrospinal protection methods, because of the increased safety margin for preventing ischemic injury. Based on mild to moderate hypothermia, several kinds of antegrade and retrograde perfusion modalities are used for more secure protection. However, since they do not always provide complete cerebrospinal protection, several technical or pharmacological adjuncts should be added. These include precise preoperative examination of aortic and arterial lesions including identification of the Adamkiewicz artery, perioperative neuromonitoring with regional cerebral oxygenation and motor-evoked potentials, and various pharmacological methods.

Keywords Brain protection • Spinal cord protection • Cardiac surgery • Aortic surgery • Hypothermia

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51.1 Introduction

Although cardiovascular surgery has recently made great progress, with lower mortality rates, some patients still develop serious perioperative complications of the central nervous system, such as stroke. In particular, during coronary artery bypass grafting and aortic surgery for atherosclerotic cardiovascular diseases, the incidence increases. In this chapter, neurological sequelae during cardio-aortic surgery, their treatment, and their prevention are described.

51.2 Brain Protection During Cardiac Surgery

Neurologic complications potentially occur during cardiac surgery at certain instances, acting as an Achilles heel [1, 2]. Stroke is the most common complication, in most cases related to the adverse effects of cardiopulmonary bypass (CPB). These include embolism due to ascending aortic cannulation or retrograde femoral perfusion, other microemboli produced by CPB itself, and hypoperfusion due to hypotension with non-pulsatile flows of CPB with lower perfusion pressure. Watershed-type strokes result from hypoperfusion, particularly in patients at high risk for cerebral involvement having significant intracranial arterial diseases or carotid arterial diseases. Cerebral embolisms are rather more serious sequelae, resulting from manipulation of the ascending aorta, such as by cannulation and clamping. In addition, recent analyses demonstrated some deterioration of the neurological cognitive functions after cardiac surgery, presumably due to cerebral hypoperfusion or microemboli from CPB, even without a significant stroke [3, 4]. The reported independent predictors of neurological deficits during cardiac surgery are symptomatic cerebrovascular disease, advanced age, type of surgery, and atheroma in the ascending aortic aorta [5]. Particularly, in coronary artery bypass grafting (CABG) with the highest frequency, the incidence of stroke is also higher than in other surgical procedures, because the etiology of coronary artery disease is similar to other atherosclerotic diseases such as carotid and intracranial arterial diseases and ascending aortic diseases [6].

51.2.1 Off-Pump Coronary Artery Bypass Grafting (OPCAB)

For preventing such cerebral complications, CABG without CPB (i.e., OPCAB) has been developed for high-risk patients with atherosclerotic aortic and arterial diseases [7, 8]. In particular, the “no-touch aorta technique” in conjunction with OPCAB using total arterial grafts is the most promising procedure for preventing neurological complications [9–11].

51.2.2 Epiaortic Echo and Alternative Cannulation Site

Other considerable sources of intraoperative stroke are atheromatous and calcified plaques in the ascending aorta [12]. Intraoperative examination with epiaortic echo is therefore absolutely imperative [13]. In cases of a diseased ascending aorta, an alternative option for CPB cannulation site, including the axillary artery or femoral artery, is required [14]. Gentle aortic cross-clamping is also inevitable. It goes without saying that anesthetists need to care for the maintenance of sufficient systemic blood pressure in high-risk patients with cerebral hypoperfusion due to either intracranial or carotid arterial lesions. Care for the systemic temperature is also important. Mild hypothermia potentially has a protective effect on cerebral function, in particular, neurocognitive functions [15].

51.2.3 Prevention of Embolism Due to Atrial Fibrillation

Care for reducing potential risks of embolism caused by atrial fibrillation is required during the postoperative period. Regimens consisting of a beta-blocker alone or a beta-blocker in combination with amiodarone are recommended for preventing postoperative atrial fibrillation [16].

51.3 Brain Protection During Aortic Surgery

Brain protection is one of the key issues in aortic surgery, particularly in aortic arch repairs requiring the adequate preservation of sufficient cerebral function even with some adverse manipulations of the cerebral circulation. Deep to moderate hypothermia is the mainstream of the three major brain protection techniques, namely, hypothermic circulatory arrest (HCA), selective cerebral perfusion (SCP), and retrograde cerebral perfusion (RCP), because normal circulation is completely interrupted despite decreased but continuous oxygen consumption by the brain.

51.3.1 Hypothermic Circulatory Arrest (HCA)

This is still the simplest and most fundamental technique for brain protection. The history of cardiac surgery began in conjunction with this technique [17–20]. However, it can only be used alone safely within a 40-min period with deep or profound hypothermia of less than 20 °C. Griepp et al. first used this technique successfully in total aortic arch replacement in 1975 [21]. Since then, deep or profound hypothermia has been a routine and reliable technique for brain protection during cardiac

and aortic surgery. However, the cerebral safety margin is limited to within 40 min. At more than 65 min, patients tended to develop some cerebral deficits after the surgery [22]. Another disadvantage is the requirement for substantial additional periods of CPB for core cooling and rewarming. Hypothermia-induced coagulopathy is also a problem, particularly in aortic surgery.

51.3.2 Selective Cerebral Perfusion

This reliable technique is the current preference for meticulous brain protection during aortic arch surgery, because of its physiologic perfusion in conjunction with deep to moderate hypothermia [23–29] (Fig. 51.1). The shortcoming is the necessity of arch-vessel manipulations, such as cannulation or clamping, which might result in cerebral embolization [24, 25, 29]. However, these should be overcome by sufficient cautions, that is, safe and gentle cannulation into the less atherosclerotic portions of the arch vessels [26, 29–31]. In some circumstances, the left subclavian artery is diseased and thus cannulation should be avoided in conjunction with deep hypothermia for cerebral and spinal safety. This reliable SCP technique has been refined and standardized so that the current focus is the use of moderate to mild hypothermia in conjunction with SCP [28, 29, 32]. The outcomes were satisfactory

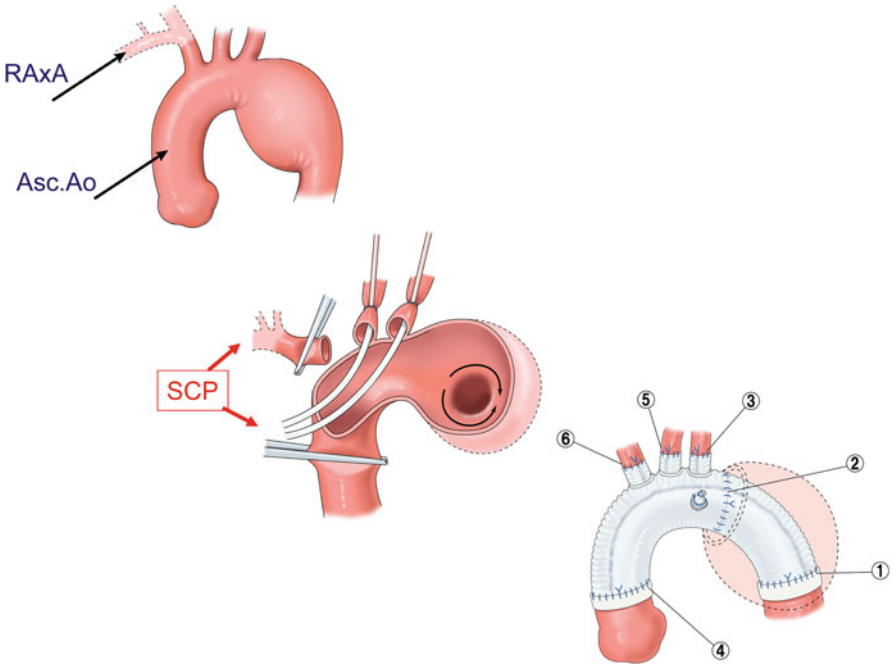

Fig. 51.1 Total arch replacement with selective cerebral perfusion. *RAxA* right axillary artery, *Asc.Ao* ascending aorta, *SCP* selective cerebral perfusion

and revealed the cerebral safety of the technique. However, one question has emerged, that is, how long would the spinal safety be during the hypothermic circulatory arrest for the distal anastomosis in total arch replacement. In a previous report from Hannover in Germany, the incidence of spinal cord injury increased in the patients requiring more than 60 min of hypothermia circulatory arrest at moderate hypothermia [33]. The animal experiment using pigs by Griepp et al. demonstrated that the safety margin of the HCA for the distal anastomosis is within 90 min at 28 °C [34]. Consequently, the safety margin of the spinal cord should be within 60 min during the total aortic arch repair at moderate hypothermia. In cases with more than 60 min of HCA, distal perfusion from a perfusion catheter into the descending aorta or the femoral artery is required, with the descending aorta balloon occluded [35]. For neuromonitoring, continuous readings of the regional cerebral oxygenation with near-infrared spectroscopy are applied.

51.3.3 Retrograde Cerebral Perfusion

The limitations of HCA, the impact of widespread retrograde cardioplegia infusion, and the historical use of RCP for massive air embolism had contributed to the clinical application of RCP for brain protection during aortic arch repair in the 1990s [36–42]. However, the necessity of deep hypothermia, the limitations of the cerebral safety margin, and the rather adverse effects of RCP, such as brain edema, have limited the current application of this technique [43–45].

51.4 Spinal Cord Protection During Aortic Surgery

Complications resulting from spinal cord injuries such as paraplegia and paraparesis are still the most devastating complications of surgical treatment for descending (dTAA) or thoracoabdominal aortic aneurysm (TAAA). During the open aortic repair of dTAA and TAAA, these sequelae still occur reportedly at the incidence between 5 and 15 % [46–51]. The independent predictors are extensive aortic lesions (extent I and II TAAA), emergency surgery, prolonged aortic cross-clamp time, bleeding, chronic renal failure, old age, severe atherosclerosis, impaired cardiac function, hypotension, history of abdominal aortic repair, and occlusion of the left subclavian artery or internal iliac arteries. Even in the recently advanced thoracic endovascular aortic repair (TEVAR), neurological sequelae develop at an incidence of approximately 5 % [52], particularly in patients requiring a longer coverage of the aortic lesions, including the closure of the arteria radicularis magna (Adamkiewicz artery, AKA) with a stent graft [53, 54]. Consequently, appropriate protection of the spinal cord is still a great concern in the critical arguments regarding dTAA and TAAA repairs, including TEVARs and hybrid procedures.

Since DeBakey first carried out TAAA repair with an aortic homograft using a temporary arterial shunt in 1956 [55], multidisciplinary approaches have been

directed toward minimizing spinal cord ischemia in dTAA and TAAA surgical repairs. Some multiple etiologies of spinal cord ischemic injuries are as follows: (1) perfusion abnormality of the spinal cord feeding arteries, including the AKA; (2) perfusion abnormality of the other intercostal and lumbar arteries; (3) perfusion abnormality of the left subclavian artery (vertebral artery), the iliac arteries, the visceral arteries, and the other collateral arteries; (4) interruption of perfusion by cross-clamping of the aorta and the aortic branches; (5) hemodynamics change due to CPB or bleeding; (6) embolism; (7) occlusion of reconstructed intercostal arteries; (8) increase in cerebrospinal fluid pressure; and (9) reperfusion injury of the spinal cord, including edema and subsequent compartment phenomena. Consequently, to prevent serious spinal cord injuries, the author's principal modalities are multidisciplinary, as listed below:

1. Preoperative demonstration of the AKA by magnetic resonance imaging (MRI) or computed tomographic scans (CT scans) (Fig. 51.2)
2. Intraoperative monitoring of spinal cord ischemia with transcranial motor-evoked potentials (MEPs) or somatosensory-evoked potentials (SEPs)
3. Distal aortic perfusion with left heart bypass or partial CPB during the aortic cross-clamping (Fig. 51.3)
4. Application of mild hypothermia between 28 and 32 °C (Fig. 51.4)
5. Occasional use of deep hypothermia for open aortic anastomosis

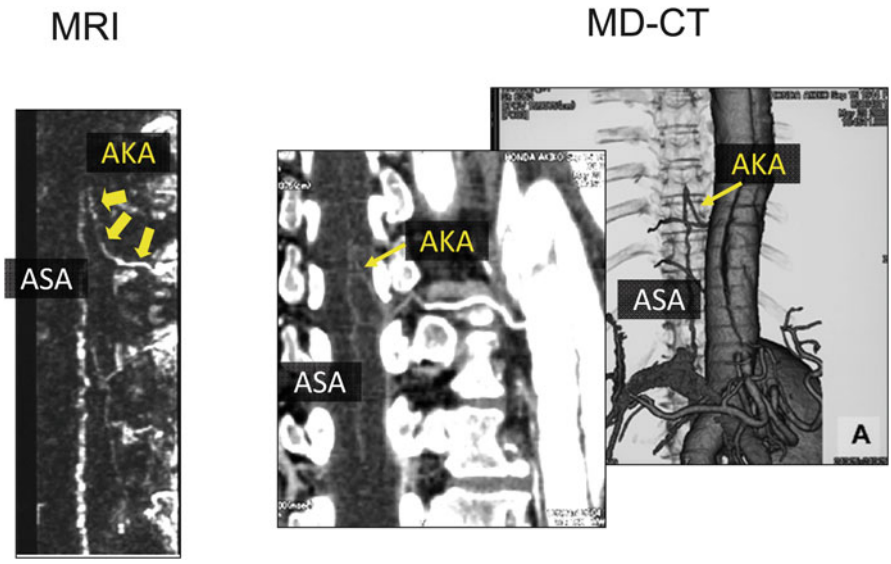

Fig. 51.2 Preoperative identification of the Adamkiewicz artery. The MRI demonstrates the Adamkiewicz artery (AKA, *large yellow arrows*) ascending to the anterior midsagittal surface of the spinal cord from the radicular-medullary artery originating from the dorsal branch of the intercostal or lumbar artery. It is continuous with the anterior spinal artery (ASA), with a hairpin turn in the early phase (*left*). The Adamkiewicz artery (AKA) can be visualized clearly by multidetector CT scans as well (*right*)

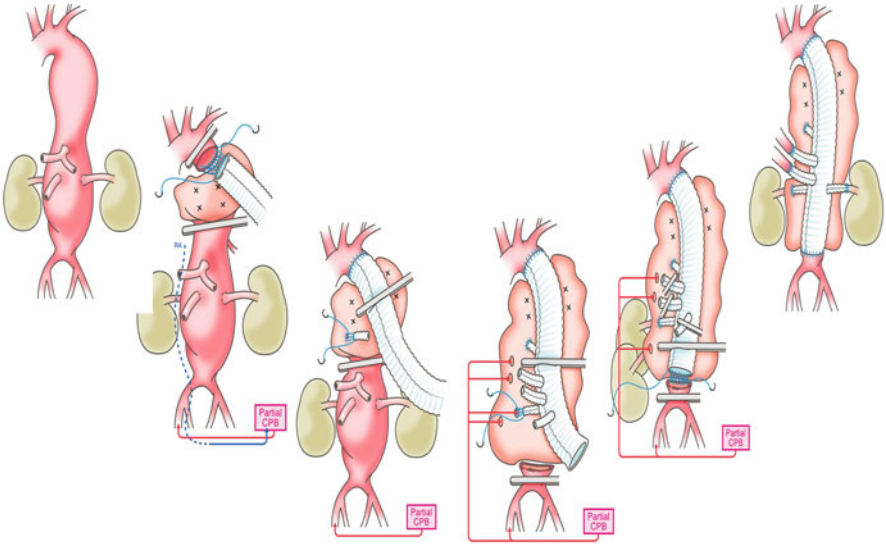

Fig. 51.3 Open repair of thoracoabdominal aortic aneurysm (extent II) using a partial cardiopulmonary bypass with mild hypothermia. *CPB* cardiopulmonary bypass, *RA* right atrium

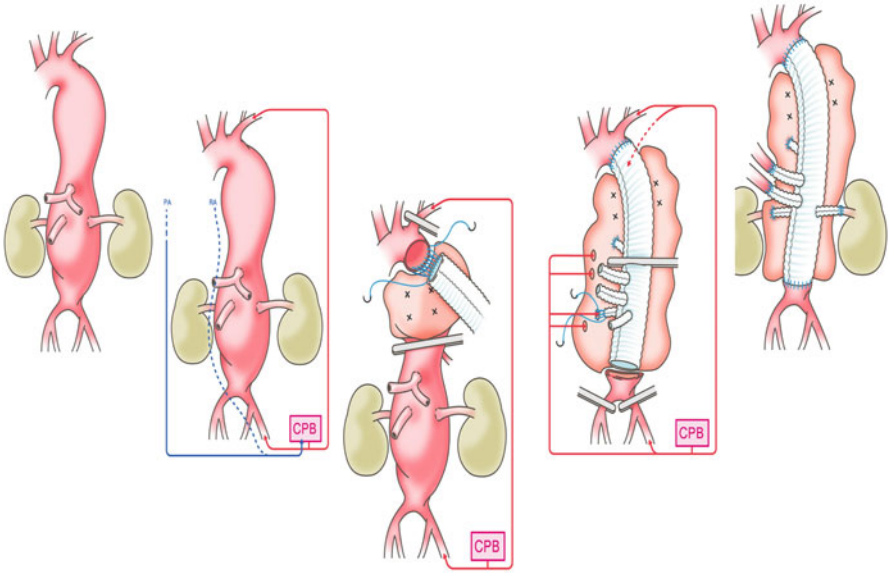

Fig. 51.4 Open repair of thoracoabdominal aortic aneurysm (extent II) using a total cardiopulmonary bypass with deep hypothermia. *CPB* cardiopulmonary bypass, *RA* right atrium, *PA* pulmonary artery

6. Sequential (segmental) aortic clamp technique to reduce the spinal cord ischemic time
7. Increase in the collateral flow by controlling the back-bleeding of the patent intercostal and lumbar arteries
8. Perfusion of the patent intercostal arteries
9. Reattachment of the responsible intercostal and lumbar arteries
10. Higher cardiac output and arterial pressures
11. Cerebrospinal fluid drainage (CSFD)
12. Increase in ischemic tolerance with pharmacological adjuncts, including naloxone, steroids, or barbiturates

Preoperative knowledge of the target arteries requiring reconstruction or preservation is a great advantage. Yamada et al. first demonstrated the feasibility of preoperative detection of the AKA using noninvasive contrast MRI [56]. Yoshioka et al. developed a new technique using CT scans to demonstrate the AKA and the collateral arteries to the spinal artery [57, 58]. The AKA demonstration by CT scans is less time consuming than contrast MRI and enables visualization of the origin of the intercostal artery connecting to the AKA more clearly, with three-dimensional views. However, CT scans have the disadvantages of not being able to exclude the interfering effects of the spine on the image of the AKA and not being able to differentiate the AKA from the anterior radicular vein, which also has a similar hairpin curve. The identification rate of the AKA is reportedly about 90 % [57]. Preoperative knowledge of the AKA also aids preoperative planning of surgical strategy. The safest segmental cross-clamp site can be determined, as can the appropriate range of aortic lesions to be repaired or replaced or associated vessels to be vascularized, based on preoperative anatomical assessment of the AKA. In addition to the AKA, the existence of a complex network of blood supply to the spinal cord (including sources from the intercostal or lumbar arteries as well as the left vertebral artery, internal thoracic artery, and internal iliac arteries) has been addressed. Consequently, the preservation of these collateral flows perioperatively is also important.

On the other hand, monitoring of MEPs can provide important, precise information on adequate blood supply to the spinal cord in real time during surgery [59]. The efficacy of monitoring MEPs has been extensively discussed [60, 61]. However, the monitoring of MEPs is affected by peripheral ischemia, anesthesia (including neuromuscular blockade), and systemic hypothermia. Such monitoring is unable to prevent all spinal cord complications. Therefore, together with monitoring of the MEPs, it is advantageous to use a map of the target vessel connecting to the spinal cord as demonstrated by MRA, to obtain more reliable protection for the spinal cord [50]. The information obtained from the anatomical assessment provides a map of the relevant intercostal or lumbar artery suitable for reconstruction or for preservation of the blood supply to the spinal cord, whereas the subsequent functional monitoring provides a precise and real-time guide ensuring spinal cord safety without ischemic deficits and without delays during surgery. Occasionally, with a significant change in MEPs, rapid revascularization of the spinal cord should be performed, even for other intercostal arteries apart from the

AKA. Even if the identified AKA has already been reconstructed, revascularization of the other relevant arteries should be carried out until the MEPs are restored [50, 60, 61].

Mild hypothermia of approximately 32 °C is also widely used in conjunction with distal perfusion of partial CPB [50, 62–66] at a distal pressure of more than 60 mmHg, because the spinal cord perfusion might be insufficient in these settings. MEPs are used perioperatively to monitor spinal cord ischemia continuously. Some intercostal arteries responsible for the spinal cord ischemia are aggressively reattached according to the preoperative demonstration of the AKA by MRI or CT scans [67], while controlling back-bleeding from the other intercostal arteries without delay [68, 69]. On the other hand, Kouchoukos et al. employed systemic deep hypothermia for protection of the spinal cord as well as the brain in dTAA and TAAA repair in 1995 [70]. In selected high-risk patients having a Crawford extent I and II TAAA or a dissecting dTAA and a TAAA, deep hypothermic surgery at approximately 20 °C with total CPB appears to ensure more rigorous spinal safety [71–73]. Even in this setting, MEPs can be recorded above 25 °C with adjusted anesthetics. Early rewarming after the proximal anastomosis has been another refinement for minimizing some adverse effects of systemic hypothermia by reducing the time of ventricular fibrillation and CPB. Obviously, systemic hypothermia has some drawbacks, such as coagulopathy, pulmonary dysfunction, cardiac arrhythmia leading to cardiac arrest or ventricular fibrillation, and systemic edema from fluid shift, in part due to prolonged CPB. To eliminate these shortcomings, the usefulness of regional cooling of the spinal cord is addressed in surgery for the dTAA and TAAA. Davison et al. and Cambria et al. first adopted this technique clinically during dTAA and TAAA resection [48, 74–76]. Tabayashi et al. also described the impact of epidural cooling on spinal cord protection [77, 78]. Epidural cooling also has some drawbacks, including a sharp rise in the CSF pressure and uncertain homogenous cooling of the spinal cord. Recently, as a solution for these adverse phenomena, a countercurrent closed-lumen epidural catheter was developed [79, 80].

The standard surgical techniques are described as follows. The aneurysm is approached through a left thoracic or thoracoabdominal incision. During aortic cross-clamping, distal aortic perfusion is maintained by a partial CPB, consisting of a femoro-femoral circuit with mild hypothermia at 32 °C [50, 62–66]. Anastomoses are performed using a segmental (sequential) clamp technique to reduce spinal ischemic time [64, 81]. In cases with extended lesions including the visceral arteries, visceral perfusion is added, using 10–14-Fr branched balloon-chipped tubes of the CPB circuit [82]. Cerebrospinal fluid drainage is performed, particularly, for high-risk patients with Crawford type II TAAA [83–86]. In each case, a surgical strategy for reconstructing or preserving the relevant intercostal arteries or lumbar arteries is devised, based on the preoperative anatomical assessment of the AKA identified by CT or MRI. Revascularization of the intercostal or lumbar arteries is guided by the monitoring of MEPs. Subsequently, the Adamkiewicz artery and other relevant intercostal and lumbar arteries, predominantly those between T8 and L1, are revascularized or preserved by beveling techniques. The critical intercostal or lumbar arteries and visceral arteries are selectively

reconstructed using a graft interposition technique with an 8–10-mm tube graft, while en bloc reconstruction (island technique) is performed. With critical reduction of the amplitude of the MEPs, rapid revascularization of the spinal cord blood supply is performed. In addition, the distal perfusion flow is increased to raise the distal pressure above 80 mmHg. The blood pressure of the upper body is also increased with the use of catecholamine or transfusion, or both. There is the other option of perfusion of the responsible intercostal and lumbar arteries [87].

Theoretically, there are some pharmacological adjuncts, such as naloxone and steroids, to reduce the ischemic or reperfusion injuries of the spinal cord, although no evidence of efficacy has been demonstrated [88, 89].

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Chapter 52
Brain Protection and Anesthetic Management During Cardiac Surgery

Kazuto Miyata and Hiroyuki Uchino

Abstract Brain injury after cardiac surgery is associated with significantly reduced prognosis. The ability to predict and prevent neurological complications during the perioperative period is thus important. Two types of brain damage after cardiac surgery can be categorized as follows: type I includes focal neurological deficits, coma, and stupor and type II includes decline in intellectual function and memory impairment. These types show frequencies of 3.1 % and 3.0 %, respectively. With both types, mortality rates are increased. Important risk factors for brain injury after cardiovascular surgery include age, atherosclerosis of the central artery, intra-aortic balloon pumping (IABP), diabetes mellitus, lung disease, and alcohol abuse.

Cardiopulmonary bypass (CPB) can induce brain injury after cardiovascular surgery, as CPB can evoke embolization, low perfusion rates, and inflammatory responses. As off-pump coronary artery bypass graft (OPCAB) significantly inhibits embolization and inflammatory responses, we consider OPCAB to protect against brain injury after surgery. However, many reports suggest that these considerations are insufficient.

In addition to classical preanesthetic evaluation, attention should be paid to register elements that may influence the risk-benefit balance of the procedure. Specific preoperative evaluation of patients scheduled for cardiac surgery includes intracranial, carotid, and ascending aorta arteriosclerotic lesions.

To avoid neurological complications, early prediction of the development of neurological complications using several monitors is essential. Management during cardiopulmonary bypass (tightly controlling perfusion pressure, hematocrit, and blood glucose levels) is considered to be the most important factor to prevent neurological complications following cardiac surgery.

Keywords Neurological complications • Cardiopulmonary bypass (CPB) • Emboli • Hypoperfusion • Inflammatory reaction

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52.1 Introduction

Brain injury after cardiac surgery is associated with significantly reduced prognosis. The ability to predict and prevent neurological complications during the perioperative period is thus important.

Two types of brain damage after cardiac surgery can be categorized as follows: type I includes focal neurological deficits, coma, and stupor and type II includes decline in intellectual function and memory impairment. With both types, mortality rates are increased. To avoid neurological complications, early prediction of the development of neurological complications using several monitors is essential.

Important risk factors for brain injury after cardiovascular surgery include age, atherosclerosis of the central artery, intra-aortic balloon pumping (IABP), cardiopulmonary bypass (CPB), diabetes mellitus, lung disease, and alcohol abuse.

This chapter reviews the types of brain injury which can occur after cardiac surgery, particularly CPB, the mechanisms of these brain injuries, and the preoperative evaluation and anesthetic management to avoid neurological complications.

52.2 Types of Brain Injury and Risk Factors After Cardiac Surgery

Various types of brain injury can occur after cardiac surgery, including focal neurological injury that remains due to focal brain ischemia and impaired consciousness that develops due to global brain ischemia after extensive exposure to low oxygen and hypoperfusion (Fig. 52.1).

Roach et al. [1] reported a study in which 2,108 patients with postoperative brain injury who underwent planned coronary artery bypass surgery were classified into two types and subsequently compared. Type I brain injury patients were defined as those who died due to stroke or hypoxic encephalopathy, experienced nonfatal stroke or transient ischemic attack, or developed stupor or coma at the time of discharge. Type II brain injury was defined as a new deterioration in intellectual function, confusion, restlessness, disorientation, declined memory, or seizure without evidence of focal neurological injury. The results of this study showed that the frequency of brain injury increased with increasing age in both types I and II, with frequencies of 3.1 % and 3 %, respectively. In both types, mortality was significantly greater in patients who experienced brain injury than in those who did not, and the durations of stay in the intensive care unit (ICU) and hospitalization were also significantly increased. In addition, this study also investigated preoperative risk factors for postoperative brain injury. Odds ratios for the preoperative risk factors are shown in Fig. 52.2. Combined with other reports [2, 3], the preoperative risk factors that are particularly important include age, proximal aortic atherosclerosis, use of intra-aortic balloon pumping (IABP), diabetes, pulmonary disease, and history of excessive alcohol consumption.

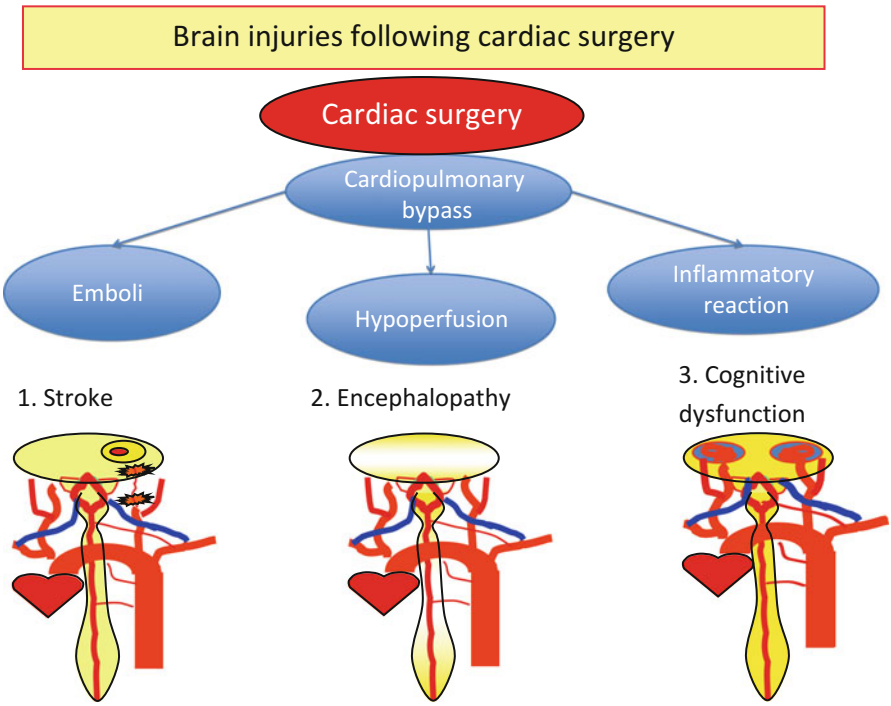

Fig. 52.1 Brain injuries following cardiac surgery

	Type I	Type II
Proximal aortic atherosclerosis	4.52	
History of neurological disease	3.19	
Use of IABP	2.60	
Diabetes mellitus	2.59	
Hypertension	2.31	
Pulmonary disease	2.09	2.37
Age	1.75	
Blood pressure > 180 mmHg on admission		3.47
History of excessive alcohol consumption		2.64
History of CABG		2.18
Arrhythmia on day of surgery		1.97
Antihypertensive therapy		1.78

Fig. 52.2 Preoperative risk factors Roach et al. [1]

52.3 Mechanisms of Brain Injury Development After Cardiac Surgery

The major causes of brain injury after cardiac and large vessel surgery are as follows: (1) emboli, (2) hypoperfusion, and (3) inflammatory reaction [4]. These conditions can easily lead to an ischemic environment, particularly during cardiac surgery using cardiopulmonary bypass.

52.3.1 Emboli

Emboli are classified into two types: macroemboli (≥200 μm) and microemboli (<200 μm). A particularly high risk of emboli is seen with surgery that uses cardiopulmonary bypass. Substances that could cause emboli during cardiopulmonary bypass are listed in Fig. 52.3. Macroemboli often occur due to rupture of the arteriosclerotic plaque during aortic clamping or cannulation of the returning blood and can potentially cause stroke. In contrast, microemboli can be caused by air, fat, or aggregations of platelets and occur at the retinal or subcortical end artery [6].

In a study that investigated 1-week postoperative cerebral infarction rates, the severity of atherosclerosis of the descending aorta was evaluated using transesophageal echocardiography (TEE) [7]. This study reported that Katz classification grade 3, 4, and 5 cerebral infarction developed at the rates of 5.5 %, 10.5 %, and 45.5 %, respectively, showing that postoperative cerebral infarction development can be predicted by evaluating atherosclerosis of the descending aorta.

Fat droplets can cause microemboli, thus requiring careful attention. The fat weight in blood reportedly decreases with the usage of cell saver compared with the direct return of blood to the cardiopulmonary bypass circuit [8], indicating that the

Biological	Nonbiological	Gaseous
Atheroma	Polyvinyl chloride fragments	Air
Calcium	Aluminum debris	Oxygen
Fibrin	Silicone	Nitrogen
Platelet aggregates	Bone wax	Carbon dioxide
Red cell aggregates	Glove powder	Nitrous oxide
Neutrophil aggregates	Cotton fiber	
Chylomicrons		
Lipids		

Fig. 52.3 Types and classification of emboli reported during cardiopulmonary bypass Robert et al. [5]

usage of cell saver can prevent emboli caused by fat droplets. In addition, retained intracardiac air can cause emboli. To prevent this, it is important to spray the surgical site with carbon dioxide, which is heavier than air and more soluble in blood, and to detect retained air using TEE and subsequently conduct sufficient de-airing.

52.3.2 Hypoperfusion

Perfusion pressure decreases due to hemodilution and decreased vascular resistance during surgery under cardiopulmonary bypass. In terms of the degree of perfusion pressure during cardiopulmonary bypass, many facilities have determined to maintain a level of 50–60 mmHg, since autoregulation of cerebral blood flow maintains a mean blood pressure of 50–150 mmHg [9].

In a randomized controlled study ($n = 248$) of patients undergoing coronary artery bypass surgery comparing patients with low perfusion pressure (50–60 mmHg) and high perfusion pressure (80–100 mmHg) during cardiopulmonary bypass [10], the frequencies of postoperative cardiac and neurological complications were 12.9 % and 4.8 %, respectively, showing a significant decrease in complication rates in the group with high perfusion pressure. However, no significant differences were seen between groups in the development of neurological complications alone. Later, an additional randomized controlled study ($n = 412$) was conducted on patients undergoing coronary artery bypass surgery [11], but no significant differences were seen between the two groups in terms of frequencies of cardiac and neurological complications or postoperative cognitive dysfunction.

Currently, no clear evidence is available on the appropriate perfusion pressure to apply during cardiopulmonary bypass. However, since an upward shift in autoregulation is seen in high-risk groups such as elderly patients [12] and patients with progressed arteriosclerosis [7] or diabetes [13], a higher perfusion pressure is considered desirable.

52.3.3 Inflammatory Reaction

The release of inflammatory mediators is induced by cardiopulmonary bypass and contact with blood, and subsequently neurons such as astrocytes and microglia are activated. The release of inflammatory mediators is further promoted by these neurons, inducing postoperative cognitive dysfunction [14].

While cardiopulmonary bypass-related brain injuries do not have to be considered with off-pump coronary artery bypass graft (OPCABG) procedures, blood pressure may be decreased when locating on the posterior surface of the heart, and brain perfusion pressure may be decreased with elevated venous pressure.

In the randomized controlled Octopus study ($n = 281$) [15], low-risk patients were divided into off-pump CABG (OPCAB) and on-pump CABG groups to

investigate postoperative cognitive function. No significant differences between groups were seen in cognitive function 3 and 12 months postoperatively. However, at 3 months postoperatively, the degree of improvement in cognitive function was significantly greater in the OPCAB group. Five years after the Octopus study, follow-up results were reported [16]. No significant differences between groups were identified in terms of the decrease in postoperative cognitive function, frequencies of cardiovascular events, or quality of life. Postoperative changes in cognitive function due to differences in surgical procedure (OPCAB or on-pump CABG) were not observed in the low-risk groups of patients from these studies.

A meta-analysis performed by Wijeysundera et al. assessed the effect of OPCAB on mortality and morbidity and included 37 randomized controlled trails and 22 risk-adjusted observational studies. While observational studies showed OPCAB to be associated with a reduced stroke rate, the randomized controlled trials did not show a statistically significant reduction [17]. As brain-protective effects by OPCAB are not yet clear, further studies are required.

52.4 Preoperative Evaluation

Peripheral blood, biochemical, and respiratory function tests are performed similarly to general anesthetic management tests. At the medical inquiry, exercise tolerance is always evaluated along with cardiac function tests, including electrocardiography and echocardiography. In patients with tolerance under 4 METs, it is important to pay careful attention as the risks of perioperative and long-term cardiovascular complications are greater.

Since prognostic improvement in the central nervous system is one of the most important challenges, head computed tomography (CT), magnetic resonance imaging (MRI), and carotid ultrasonography examinations are actively performed in elderly patients, in patients with severe arteriosclerotic lesions, or prior to cardiac surgery that uses cardiopulmonary bypass. In patients with significant calcified lesions in the ascending aorta established by thoracic CT, epicardial echocardiography is actively performed to determine the clamping site and whether clamping is appropriate.

52.5 Anesthetic Management for Cardiac Surgery to Avoid Neurological Complications

Five-lead electrocardiography and pulse oximetry, as well as both noninvasive and invasive arterial pressure measurements, are conducted as monitoring methods. During cardiac anesthesia, the depth of anesthesia has a tendency to be shallow since circulatory care is prioritized during cardiac anesthesia, leading to a higher

risk of intraoperative awakening. For this reason, the use of a bispectral index (BIS) monitor is essential. In addition, the onset of severe neurological complications can be determined early by recording the degree of regional cerebral tissue oxygen saturation before anesthesia induction using near-infrared spectroscopy (NIRS) [18].

Administration of 100 % oxygen is started, followed by the gradual administration of 1–2 μg/kg of fentanyl. After 2–3 min of oxygen administration, an invasive arterial pressure line is inserted under local anesthesia. Administration of remifentanil at 0.2–0.3 μg/kg/min is subsequently started, and the patient is put under [consider "sedated"] with 0.1 mg/kg of midazolam, a drug known to have weak circulatory suppression effects. After confirming that manual ventilation is possible, 0.9 mg/kg of rocuronium is administered to obtain muscular relaxation. Tracheal intubation is subsequently performed following stabilization of hemodynamics. If blood pressure increases or the patient experiences tachycardia, remifentanil is increased to 0.5 μg/kg/min. Transesophageal echocardiography is inserted after tracheal intubation, and a central venous catheter is inserted from the right internal jugular vein, along with a pulmonary artery catheter if there is low left ventricular function. Cardiac function is examined using transesophageal echocardiography. In addition, aortic atherosclerosis from the aortic arch to the descending aorta is also evaluated. Blood pressure can decrease after tracheal intubation, and in that case, transfusion loading, administration of 0.1 mg of phenylephrine, or decreasing the dosage or discontinuation of remifentanil is conducted as a countermeasure.

Propofol 1–2 μg/mL and remifentanil 0.2–0.5 μg/kg/min are concomitantly used for anesthetic maintenance. Even for invasive procedures such as median sternotomy, remifentanil is not given as a single dosage but is fundamentally administered as a continuous dose. Heparin is administered at 300 U/kg and activated clotting time (ACT) is set at $\geq$ 400 s. ACT is measured every 30 min, and additional heparin is administered as necessary.

When ACT becomes $\geq$ 300 s, cannulae to return and remove blood are inserted. Caution should be exercised at the beginning of cardiopulmonary bypass since perfusion pressure has a tendency to decrease at the time of initial drop. Oxygen-carrying capacity is also decreased with decreased hemoglobin due to hemodilution. Low hematocrit (15–17 %) reportedly leads to a greater incidence of complications and mortality [19, 20]; therefore, the target hematocrit should be about 27 %. Regarding optimal perfusion pressure during cardiopulmonary bypass, 50–80 mmHg is generally the target. However, as described earlier, perfusion pressure should be maintained at a higher level in elderly patients and patients with severe arteriosclerotic lesions or diabetes [7, 12, 13].

Atherosclerosis in the ascending aorta is verified with epicardial echocardiography prior to aortic clamping, and the clamp site is noted carefully. For suction during cardiopulmonary bypass, cell saver is used instead to decrease fat droplets.

Patients often become hyperglycemic due to the influx of myocardial protection fluid during cardiopulmonary bypass. Hyperglycemia (blood glucose $>$ 140 mg/dL) in patients with cerebral infarction reportedly worsens the neurological prognosis

[21]. In a study that assessed patients who were admitted to the surgical ICU, mortality improved when glucose levels were controlled with intensive insulin therapy (blood glucose, 80–110 mg/dL) vs. conventional therapy (blood glucose, > 215 mg/dL) [22]. However, later reports showed no significant differences in mortality with intensive insulin therapy in patients admitted to a medical or surgical ICU [23–25]. For these reasons, glycemic control of postoperative ICU patients is currently set at 140–180 mg. However, as these reports concern postoperative patients, further investigation is necessary, as no clear standards for optimal glycemic control during cardiac surgery currently exist.

No conclusion has been reached whether α stat or pH stat should be utilized for acid-base management during cardiopulmonary bypass. Alpha stat is a method that neutrally maintains the acid-base balance at 37 °C under hypothermic conditions without loading carbon dioxide. This method is normally used for management during cardiopulmonary bypass. Conversely, pH stat loads carbon dioxide during hypothermic conditions which leads to acidosis at 37 °C; blood gas measurements after correcting the temperature to actual body temperature show a neutral acid-base balance. By loading carbon dioxide, cerebral blood flow increases due to cerebrovascular dilatory actions. In surgery for pediatric congenital heart disease, pH stat is used for cardiopulmonary bypass management, and decreased occurrence of complications and earlier recovery of electroencephalographic activity have been reported [26]. However, another report claimed that neurodevelopment is no different 1 year postoperatively [27]. In cardiac surgery for adults that requires hypothermic conditions, the incidence of brain injuries is reportedly increased with pH stat [18], and no conclusion on whether α stat or pH stat is superior has been established.

After removing the aortic clamp, cardiac function and postoperative evaluations are conducted using transesophageal echocardiography. Whether sufficient intracardiac de-airing has been attained should also be verified. The apex, right pulmonary vein, left atrium, left atrial appendage, and right coronary artery inlet often retain air, thus sufficient de-airing should be performed by changing the body position or compressing the lung.

Cardiopulmonary bypass is withdrawn with care after cardiac function has recovered adequately. Adjustments of catecholamines or additional fentanyl administrations are performed as necessary, noting the hemodynamics. From the perspective of early extubation, the total dose of fentanyl should not exceed 10 μg/kg.

52.6 Summary

We provided an overview of anesthetic management from the perspective of brain protection during cardiac anesthesia. To reduce neurological complications during cardiac anesthesia, investigation of the origins of the complications and determination of prevention strategies are extremely important. Once developed, brain

injuries are very difficult to treat. Early prediction of the development of neurological complications using monitors such as NIRS, BIS, and transesophageal echocardiography is essential. Management during cardiopulmonary bypass is considered to be the most important factor to prevent neurological complications following cardiac surgery. However, although approximate standards for the optimal amount of perfusion and hemoglobin levels have been established, a conclusion has yet to be determined regarding the management of glycemic control and acid-base balance. Further investigations are necessary in the future.

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Chapter 53
Anesthesia for Adult Vascular Surgery and Cerebrospinal Protection

Takayasu Kakinuma

Abstract Paraplegia is a significant complication of cardiovascular surgery, especially aortic aneurysm surgery. The patient management of cardiovascular surgery to prevent the occurrence of paraplegia caused by spinal cord injury is important during the perioperative period. Motor-evoked potentials are effective for intraoperative spinal cord monitoring, while Adamkiewicz artery identification and reconstruction, distal aortic perfusion, and cerebrospinal fluid drainage are effective for spinal cord perfusion pressure management. In addition, the pharmacological actions of anesthesia on the spinal cord are critical, and ischemic tolerance is also attracting attention. Here, we discuss the possibilities for spinal cord protection during the perioperative period.

Keywords Cardiovascular surgery • Cerebrospinal protection • Spinal ischemia

53.1 Introduction

In cardiovascular surgery, the most significant complication is paraplegia accompanying reperfusion injury or ischemic spinal cord injury. Paraplegias primarily develop after thoracoabdominal aortic aneurysm surgery. Since the spinal cord is constructed with complex blood flow control, its management is affected by a variety of factors. In addition, monitoring of spinal cord ischemia is crucial for the early detection of paraplegia. Since anesthesia affects the spinal cord in many different ways, careful selection of anesthesia is essential. Furthermore, in the perioperative period, procedures such as Adamkiewicz artery identification and reconstruction, spinal cord ischemia monitoring, spinal cord perfusion pressure management, cerebrospinal drainage, spinal epidural cooling, and pharmacotherapy are important for spinal cord protection. In this chapter, we would like to describe the anesthetic management for cardiovascular surgery and perspectives for cerebrospinal protection.

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53.2 Blood Flow in the Spinal Cord

The spinal cord is supplied by the vertebral and subclavian arteries, thoracoabdominal aorta, and segmental arteries from the internal iliac artery. The segmental arteries anastomose in the vertical direction to form the anterior spinal artery and posterior spinal artery. The anterior spinal artery continuously passes along the ventral side of the spinal cord from the basilar artery to the filum terminale, while the posterior spinal arteries are thin and discontinuous and traverse bilaterally on the dorsal side of the spinal cord. Furthermore, the pial arterial plexus forms a network of vessels that covers the surface of the spinal cord. The cervical spinal cord is supplied by the vertebral, ascending cervical, and deep cervical arteries. The anterior spinal artery of the thoracic spinal cord is supplied by the radicular arteries, which originate directly from the highest intercostal artery and dorsal aorta (1–2 arteries from the cervical spinal cord, 2–3 arteries from the thoracic spinal cord, and 1–2 arteries from the lumbar spinal cord). The largest of these is called the great radicular artery, or Adamkiewicz artery, which arises primarily on the left side, and is known to originate between T9 and T12 and between T12 and L3 in 75–80 % and 83.9 % of cases, respectively [1]. The lumbar spinal cord is supplied by the lumbar artery, whereas the sacral spinal cord is supplied by the anastomosis of the lateral sacral, median sacral, and iliolumbar arteries. Magnetic resonance angiography and multidetector-row computed tomography are utilized to identify these arteries and the blood supply (Fig. 53.1). Animal studies have found that paraplegia occurs 70 % of the time when the great radicular artery is ligated. There is a large amount of individual variation in the arteries that supply the spinal cord, and this phenomenon leads to complicated perioperative management. The “collateral network concept” of blood flow in the spinal cord proposed by Griepp et al. (Fig. 53.2) states that the spinal cord does not solely depend on the great radicular artery but is involved in a complex system of collateral pathways [2]. In addition, similarly to cerebral blood flow, spinal blood flow involves autoregulation, which is lost under conditions of hypoxemia and hypercapnia [3].

53.3 Causes of Spinal Cord Ischemia

Ischemic spinal cord injury may occur in cardiovascular surgery, particularly in thoracoabdominal aortic aneurysm surgery. The most significant complication of spinal cord ischemia is paraplegia, with incidence rates of 0.5–1.5 % in aortic stenosis repair, 0–10 % in thoracic aortic aneurysm surgery, 10–20 % in thoracoabdominal aortic surgery, and about 40 % in extensive dissecting thoracoabdominal aortic aneurysm surgery [4]. In addition, paraplegia is also reported to occur 0.25 % of the time in lower renal artery aortic aneurysm surgery [5]. In particular, the incidence of spinal cord injury is reported to be approximately

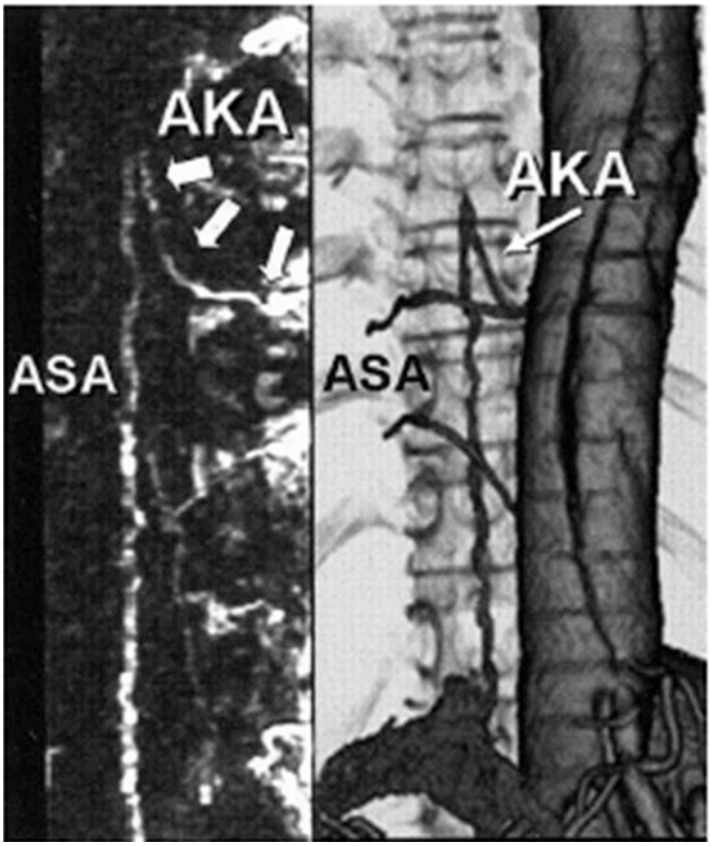

Fig. 53.1 The Adamkiewicz artery (MRA). Magnetic resonance angiography demonstrates the Adamkiewicz artery (AKA [*large white arrows*]) ascending to the anterior midsagittal surface of the spinal cord from the radicular-medullary artery originating from the dorsal branch of the intercostal or lumbar artery. It is continuous with the anterior spinal artery (ASA), with a hairpin turn in the early phase (*left*). The Adamkiewicz artery (*white arrow*) can be visualized clearly by multidetector computed tomography scans as well (*right*). Ann Thorac Surg 2006;82:592–6

20 % with vascular prosthesis implantation for Crawford II thoracoabdominal aortic aneurysms [6]. There are several causes of spinal cord ischemia, including hypertension proximal to aortic cross clamping, hypotension distal to cross clamping, elevated cerebrospinal fluid (CSF) pressure, blockage of blood flow in the intercostal and lumbar arteries, extended duration of aortic cross clamping, extensive aortic lesions, aortic dissection, and emergency surgery. Injury to the gray and white matter of the spinal cord and late-onset cell death of motor neurons are characteristically known to be caused by ischemia. Regarding mechanisms for these ischemic spinal cord injuries, glutamic acid-Ca^{2+} imbalance similar to that of the brain [7], glial cell activation after ischemia, and mitochondrial dysfunction may be involved [8].

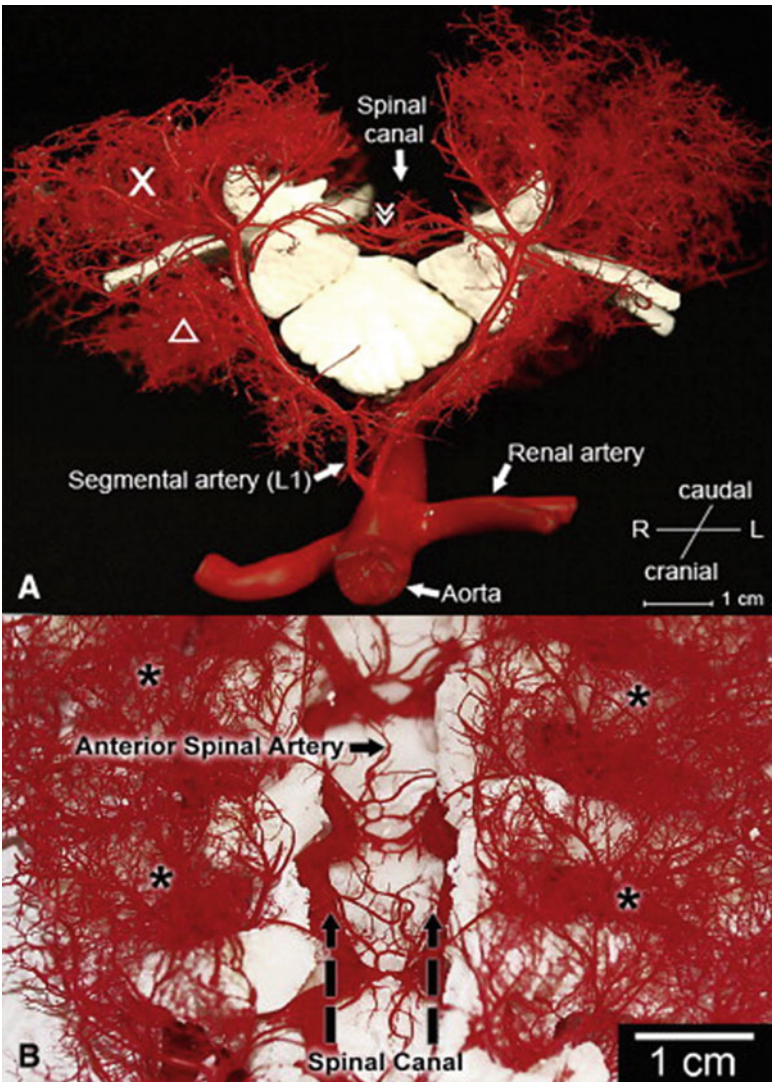

Fig. 53.2 The collateral network. Spinal cord perfusion and protection during descending thoracic and thoracoabdominal aortic surgery: the collateral network concept. Ann Thorac Surg: 83: 865–869, 2007

53.4 Intraoperative Spinal Cord Ischemia Monitoring

Several methods, such as measurements of somatosensory-evoked potential (SEP) and motor-evoked potential (MEP), are available for spinal cord ischemia monitoring. SEP monitoring detects ischemia of the sensory regions at the posterior and lateral funiculus but does not show ischemia of the motor regions at the anterior

horn of the spinal cord. A large prospective study of thoracoabdominal aortic aneurysm cases reported that this monitoring does not improve neurological prognosis, as shown by a 13 % false-negative rate and a 67 % false-positive rate [9]. In MEP monitoring, spinal cord α-motor neurons are stimulated by transcranial electrical stimulation of the cerebral motor cortex, and evoked electromyograms from the upper and lower limb muscles are monitored. Since MEP monitoring reacts early to ischemia of the anterior horn of the spinal cord with corticospinal tract monitoring, it is useful for verifying the intercostal arteries that supply blood to the spinal cord, as well as for evaluating intercostal artery blood flow reconstruction or perfusion distal to aortic cross clamping. In addition, because a body temperature of 28–30 °C is known to have very little effect on MEP, it can also be used in surgery performed under hypothermic conditions. If there is a decrease in MEP in both lower and upper limbs, minimizing the effects of anesthetics is essential, because the decrease in MEP could be due to anesthetic agents. If the unilateral decrease in MEP in the lower limb is on the side supplied by the femoral artery, transient ischemic changes may occur in the periphery. In particular, if there is a decrease in MEP only in the lower limbs and not in the upper limbs, spinal cord ischemia may be involved (Fig. 53.3).

53.5 Anesthetic Management

Anesthetics that only have a small effect on MEP measurements are chosen when monitoring spinal cord ischemia. It is necessary to exercise care in the selection of anesthetic agents, since monitoring precision decreases with the use of muscle relaxants and the amplitude of muscular MEP decreases with the inhibition of synaptic conduction caused by nitrous oxide, desflurane, sevoflurane, and isoflurane. While propofol and midazolam are known to have less effect compared to inhalation anesthetics, they also possess inhibitory effects against MEP at high concentrations.

Remifentanil, fentanyl, and ketamine have very little effect on MEP and so are useful in surgery that requires spinal cord ischemia monitoring. Muscle relaxants should either not be used at all after anesthesia induction or used minimally under muscle relaxation monitoring. Barbiturates are reported to reduce spinal cord injury caused by aortic cross clamping [10]. Drugs such as morphine that act on μ-opioid receptors can exacerbate spinal cord motor neuropathy after spinal cord ischemia, so caution is necessary. Naloxone antagonizes the exacerbating action of morphine on spinal cord motor neuropathy and is known to be effective in patients where spinal cord ischemia is suspected [11]. Administration of fentanyl can be harmful when spinal cord ischemia is suspected. Buprenorphine and pentazocine are used in animal studies, since they are known to not worsen ischemic spinal cord injuries [12]. Ketamine is an NMDA receptor antagonist that has been reported to reduce ischemic spinal cord injuries [13]. Ketamine can also be used postoperatively due to the analgesic effects of its metabolite norketamine and its lack of damaging effects

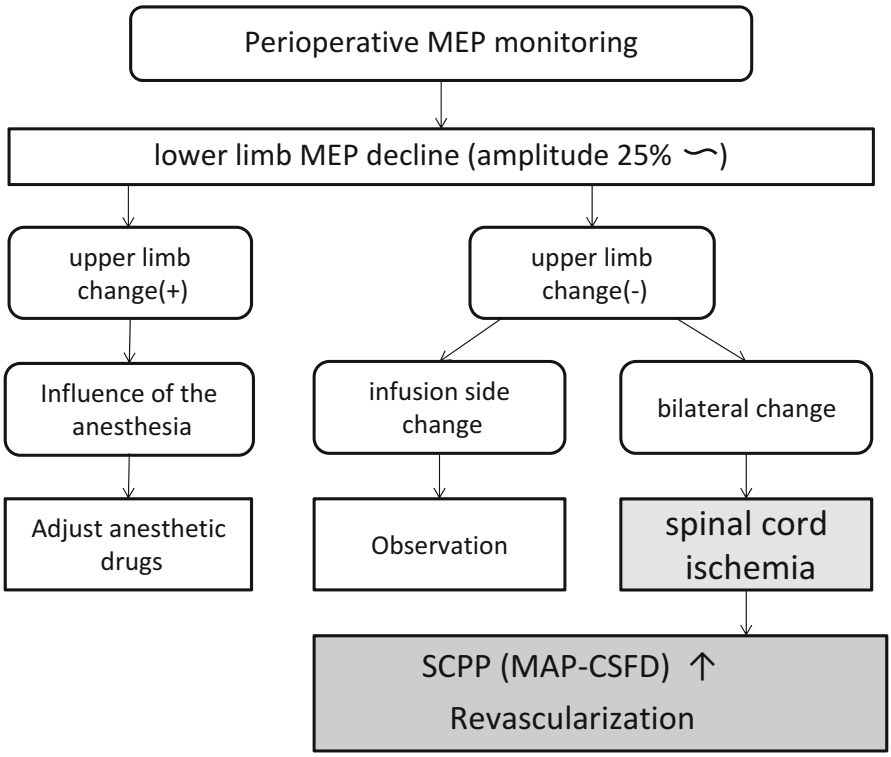

Fig. 53.3 Strategy of spinal cord ischemia protection

on the spinal cord. In addition, continuous administration of local anesthetics to the intercostal nerve block or wound area is also effective. Furthermore, dexmedetomidine has been reported to possess a spinal motor cell protective effect in animal studies, indicating its potential usefulness [14]. Ischemic preconditioning is known to be important in cardioplegia and has been reported in animal studies to possibly be effective in achieving spinal cord protection [15]. We have summarized spinal cord protection and multiple-facility clinical trials involving cerebroprotective medicines (Table 53.1).

Standard ASA monitors and an arterial line, namely, a central line to measure central venous pressure (CVP) and determine volume status, are important. A PAC may be useful to help manage hemodynamics and volume status in certain patients but is not routinely indicated. A bispectral index monitor is placed before induction. Total intravenous anesthetic technique including propofol and fentanyl infusion is often selected for general anesthesia. The infusion dose of propofol (150–250 mcg/kg/h or target-controlled infusion 3–4 mcg/mL) is titrated to effect according to BIS (bispectral index monitoring). (40–60). Remifentanil is administered at 0.2–0.5 μg/kg/min. Patients who present with cardiovascular disease often have coronary artery disease, hypertension, lung disease, diabetes, or renal disease. In order to

Table 53.1 As a result of spinal cord protection and many facilities, the clinical trial of the cerebroprotection medicine

Ca^{2+} channel blocker	*No benefit*	NMDA antagonist	Dizocilpine: protective
		Noncompetitive	Dextrorphan: protective
Na^{+} channel blocker	Riluzole: protective	Competitive NMDA antagonist	No benefit
GABA agonist	Clomethiazole: protective	Polyamine receptor antagonist	Eliprodil: not investigated
	DHEA: protective		
Free radical scavenger	Edaravone: protective	Glycine antagonist	ACEA1021: not investigated
			Gavestinel: not investigated
Neurotrophic factor	NGF: protective	AMPA/KA receptor antagonist	NBQX: protective
	BDNF: not investigated		YM872: not investigated
Ganglioside	*Modest benefit*	Metabotropic receptor antagonist	Not investigated
$MgSO_4$	Protective	Others	Piracetam: not investigated
Steroid	*Methylprednisolone: modest benefit*	Hormone	TRH: no benefit
Opioid receptor antagonist	No benefit	Mannitol	No benefit

The Journal of Japan Society for Clinical Anesthesia vol. 30 2010 Controversy for Cardiac anesthesia spinal protection: current drug therapy and its future

avoid a blood pressure drop, the induction must be performed extremely carefully in advanced cardiac dysfunction. Rocuronium bromide (0.6–0.9 mg/kg body weight), or vecuronium bromide (0.08–0.1 mg/kg body weight), or succinylcholine (1.5 mg/kg body weight) is used to facilitate intubation. These are used only at the time of anesthesia induction. Otherwise, muscle relaxants are used at the minimum concentrations required under the monitoring of the muscle relaxation level during the operation.

Weaning from cardiopulmonary bypass (CPB) may require either a change in anesthetic technique or an adjustment in dose delivery. During the rewarming process from hypothermia during CPB, there is likely to be insufficient anesthesia. Regardless of the exact nature of this change, it is vital that anesthesia is properly maintained and this should be confirmed by the operation team members.

As Schreiber reported, a meta-analysis showed that the positive effects of the designated techniques (positive airway pressure, low-volume ventilation, or vital capacity maneuvers during CPB) are probably short-lived with a questionable impact on the long-term clinical outcome of the treated patients [16]. Based on

the available data, it might be impossible to advise an optimal or best-evidence strategy of lung preservation during CPB.

53.6 Prevention of Spinal Cord Ischemia

Katz et al. reported that spinal cord ischemia can occur 71 % of the time when aortic cross clamping continues for ≥30 min [17]. In this case, performing distal aortic perfusion (left heart bypass or femoral artery bypass) to increase spinal cord perfusion is known to be effective [18, 19]. Jex et al. reported that the risk of spinal cord ischemia decreases from 44 to 8 % when distal aortic perfusion is performed [6]. In addition, CSF drainage (CSFD) is known to be effective in spinal cord ischemia. Spinal cord perfusion pressure decreases when CSF pressure elevates after aortic cross clamping, leading to an increased risk of spinal cord ischemia. CSFD thus holds a valuable potential for treating spinal cord ischemia and is used frequently [20]. In general, CSF pressure is managed with a target of 10 cm H_2O. However, since there can be severe complications such as epidural hematoma and subdural hematoma, proper attention must be given to the properties and volume of drainage. Under hypothermic conditions, the oxygen requirement of the central nervous system is known to decrease by 6–7 % for every 1 °C decrease in body temperature. Such decreases are also known to lower tissue metabolism and suppress membrane stabilization and excitatory neurotransmitter release, validating the protective effect of the reperfusion phase. Spinal epidural cooling is a method that lowers the temperature of the local spinal cord with a cool perfusion solution and has been reported to reduce nerve damage [21]. One study reported that a combination of CSFD and spinal epidural cooling decreased the incidence of paraplegia from 23.9 to 2.9 % [22].

53.7 Treatment and Management During Spinal Cord Ischemia

When spinal cord ischemia is suspected following reduced or lost MEP, procedures such as sustained perfusion pressure, confirmation of blood supply status, management of CSFD, reconstruction of an intercostal artery, or selective perfusion are performed to increase spinal cord blood flow. If this occurs during CPB, perfusion pressure is increased by raising the flow rate and blood pressure distal to cross clamping, and selective intercostal artery perfusion is performed, if possible, with the goal of achieving MEP recovery.

53.8 Postoperative Management

About 20–40 % of postoperative paraplegia is thought to be of late-onset development; therefore, sustaining spinal cord perfusion pressure in postoperative management is necessary and extremely important. When CSFD and blood pressure are raised to increase perfusion pressure, paraplegia may improve. Risk factors for spinal cord ischemia include hypotension (blood pressure $\leq$60 mmHg), anemia (hemoglobin $\leq$10 g/dL), and low cardiac output ($\leq$2.0 L/min) [23]. In addition, Etz et al. reported that CVP was higher and mean blood pressure was significantly lower in patients who experienced late-onset paraplegia [24]. Management of the patient's general condition that focuses on spinal cord perfusion pressure throughout the perioperative period is therefore necessary. Since the duration of postoperative sedation can be long and discovery can be delayed, monitoring spinal cord function in the intensive care unit is also considered critical.

53.9 Conclusion

In cardiovascular surgery, ischemic spinal cord injury is a significant complication. Since the spinal cord is under complex blood flow control, circulation management that focuses on spinal cord perfusion pressure is crucial. In addition, anesthesia should be selected with consideration of its pharmacological actions on the spinal cord, as well as monitoring the spinal cord. MEP is considered to be useful when monitoring for spinal cord ischemia, and the management of spinal cord perfusion pressure and revascularization together with early diagnosis are essential. For spinal cord protection, the combination of methods such as CSFD and spinal epidural cooling is also effective. Furthermore, postoperative management is a key factor, since patients can develop late-onset spinal cord injuries.

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Chapter 54
Postoperative Cognitive Dysfunction After Cardiac Surgery and Neuroprotection

Kengo Maekawa

Abstract Postoperative cognitive dysfunction (POCD) after cardiac surgery is growing in importance as the aging of the population advances. Highly sensitive neuropsychological testing is required to detect POCD, and a well-matched control group is useful in analyzing and interpreting the results. Pathophysiology studies of cognitive change after cardiac surgery focused on the role of cardiopulmonary bypass, intraoperative microemboli, hypoperfusion, and inflammatory response as possible causes of POCD. Long-term, follow-up studies that compared patients who underwent on- or off-pump coronary artery bypass surgery failed to demonstrate a significant reduction in the incidence of POCD. Therefore, the focus of research is shifting from cardiopulmonary bypass to patient-related risk factors. There is growing evidence that patient-related risk factors such as the extent of preexisting cerebrovascular disease play an important role in the pathogenesis of both short- and long-term POCD. Establishing the degree of functionally significant vascular disease in the brain preoperatively should be an essential part of patient evaluation.

Keywords Postoperative cognitive dysfunction • Cardiac surgery • Cardiopulmonary bypass • Cerebrovascular disease

54.1 Introduction

Advances in surgical techniques, perfusion systems, and perioperative management have reduced the mortality associated with cardiac surgery. However, postoperative cognitive dysfunction (POCD) remains a common outcome with potential to adversely impact quality of life. The mechanisms underlying POCD may include microemboli, hypoperfusion, and inflammatory response. Complications involving the brain are increasing substantially because older patients with advanced atherosclerotic vascular disease now undergo surgery. The objectives of this chapter are to

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review the manifestations and mechanisms of POCD after cardiac surgery and suggest an approach to neuroprotection during surgery.

54.2 Assessment of Cognitive Dysfunction

The rising number of patients of advanced age who are undergoing cardiac surgery and who have comorbid medical conditions underscores the importance of complications in overall patient outcomes. Anesthetists and surgeons have suspected for many years that some elderly patients suffer a decline in cognitive function after surgery, the so-called POCD. As noted by Shaw and colleagues in 1987, it manifests far more commonly than stroke, with 79 % of patients experiencing cognitive decline in the early period after cardiac surgery [1]. Due to the subtle nature of POCD, many physicians fail to notice when a patient's cognition declines after surgery. In many cases, it is not detected until the patient's relatives discover difficulties with normal activities at home or at work [2]. This condition is characterized by a decline in cognitive functions such as memory, ability to concentrate, and information processing. These changes can be detected in neuropsychological tests and present clinically as deficits in cognition and memory representing a significant change from the patient's previous level of functioning [3].

A consensus meeting held in 1994 encouraged a more standardized and comparable methodology of assessing POCD [4]. It was recommended that neurological and neuropsychological state be tested before surgery to provide accurate baseline information. A second important recommendation was that analyses should be based on the change in performance in an individual from baseline to a specific time after surgery. The recommended core neuropsychological battery should include: (1) the Rey Auditory Verbal Learning Test to assess memory, in which patients are asked to recall as many words as possible immediately upon viewing a list of 15 words and again after 15–25 min; (2) the Trail-Making Tests A and B, in which participants connect numbered and then alternately numbered and lettered dots in order under timed conditions to assess attention and mental flexibility; and (3) the Grooved Pegboard Test, which involves inserting notched pegs into specific holes in a shallow box to test fine motor dexterity.

It is essential to consider the many pitfalls associated with repeated neuropsychological testing of surgical patients such as the practice, floor (i.e., poor initial performance that cannot decline any further), and ceiling (i.e., excellent initial performance which cannot improve) effects [5]. Other important challenges arise with obtaining a reliable assessment of preoperative performance and defining deficits in meaningful statistical analysis. Analytic criteria used commonly are percentage change from the baseline for a defined number of tests and absolute decline from baseline scores greater than a defined proportion of the standard deviation of two or more tests [6]. These statistical methods, however, do not relate cognitive decline with data from age-matched healthy controls and thus fail to account for practice effects, normal variability, and the cognitive decline that

occurs in a healthy population. Therefore, contemporary studies have included control groups such as patients who have undergone percutaneous coronary intervention [7], off-pump surgery [8], and noncardiac surgery [9]. However, no generally agreed diagnostic criteria have been published, and several quite different definitions of POCD are found in the literature.

54.3 Preoperative Cognitive Status

From clinical psychiatry it is known well that depression is associated with cognitive deterioration. Depression is not unusual before surgery, but no clear association has been established between depression and POCD [10]. However, there is evidence that a considerable proportion of cardiac surgery patients may have significantly lower cognitive performance before surgery [11–13]. As is commonly known, aging is associated with structural cerebral changes, including vascular disease of the brain and impaired cognition [14]. In a study from Japan by Goto and colleagues in which cerebral magnetic resonance images (MRI) were obtained before cardiac artery bypass graft (CABG) in 421 patients, 30 % had small cerebral infarcts and 20 % had multiple cerebral infarcts (Table 54.1) [15]. Thus, one-half of this cohort had evidence of ischemic brain abnormalities before surgery.

Chronic cerebral infarcts, and even new deficits on diffusion-weighted MRI, have been identified in 4.5 % of patients, probably due to recent cardiac catheterization (Fig. 54.1) [16]. In addition, patients with such existing abnormalities had lower baseline cognitive performance and showed a worse postoperative neuropsychological test performance than those with normal preoperative findings. These limitations should be taken into account in choosing methods of analyzing and interpreting results.

54.4 Short-Term Cognitive Changes

While short-term cognitive change after cardiac surgery typically refers to changes observed in cognitive performance, cognitive decline in the immediate perioperative period could be related to adverse effects of anesthetic drugs, narcotics for pain control, and other clinical issues. Therefore, some investigators have chosen to defer follow-up testing until at least 3–4 weeks after surgery. The incidences reported, however, have varied enormously. In the brief period after cardiac surgery, the incidence of POCD varied from 22 to 79 % among different studies, depending on how the deficit was defined, the test methods applied, the composition of the target population, and study design [1, 17]. There are also reports of POCD after noncardiac surgery performed while the patient was under general anesthesia, suggesting that even if short-term cognitive change does occur after cardiac surgery, it is not specific to the use of cardiopulmonary bypass [8].

Table 54.1 MRI of the brain and POCD in patients undergoing coronary artery bypass grafting

	Overall ($n = 421$)	Small infarctions ($n = 126$; 30 %)	Multiple infarctions ($n = 83$; 20 %)
Age (years)	70.0 ± 5.4	70.3 ± 5.2	70.9 ± 5.9
Carotid arteries stenosis (>75 %)	28 (7 %)	8 (6 %)	12 (15 %)
Cerebral arteries stenosis (occluded)	14 (3 %)	3 (2 %)	9 (11 %)
Aortic atheroma (≥3 mm)	73 (17 %)	23 (18 %)	19 (23 %)
POCD	49 (12 %)	17 (13 %)	17 (20 %)

Source: Adapted from Goto et al. [15] with permission

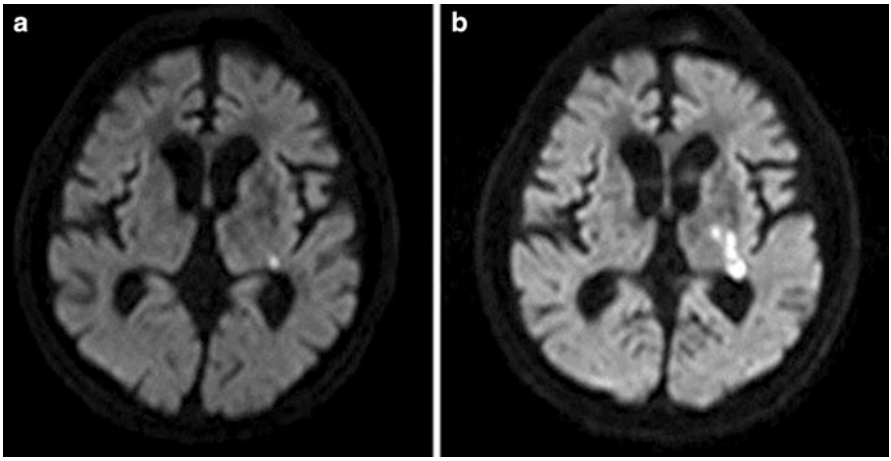

Fig. 54.1 Diffusion-weighted MRI of a 67-year-old man with no demonstrable neurologic deficits before off-pump CABG. (**a**) Preoperative MRI scan revealed small diffusion abnormality on the left posterior limb of the internal capsule. (**b**) Another scan performed 5 days after surgery demonstrated that size of diffusion restriction lesion had increased; the patient had dysarthria and right hemiparesis

54.4.1 Microemboli

The pathophysiology of short-term cognitive change after cardiac surgery remains poorly understood. The focus of most investigations has been on neurological injury secondary to microemboli, hypoperfusion, and systemic inflammatory response. The cardiopulmonary bypass circuit and the surgical field in cardiac surgery are sources of a variety of embolic particles such as thrombi, fat, and gas bubbles. In addition, emboli can be generated from disrupted aortic atherosclerotic plaques by aortic manipulation and cannulation. Some earlier studies have reported an association between embolic count and short-term cognitive outcome [18, 19], but other contemporary studies have not replicated these findings [20,

21]. Application of diffusion-weighted MRI indicates that about 50 % of patients who undergo cardiac surgery develop new discrete lesions suggestive of microembolic infarcts [22]. A number of studies have found associations between short-term cognitive change and new ischemic lesions on diffusion-weighted MRI [23, 24]. In contrast, no such correlation has been found by other studies in patients after cardiac surgery [25]. It has been hypothesized that the cognitive manifestations of microemboli may depend as much on patient-related risk factors such as the degree of preexisting cerebrovascular disease as on the quantity and size of the embolic load.

54.4.2 Hypoperfusion

Elderly patients and those with comorbid disease such as hypertension and diabetes may be vulnerable to the effects of hypoperfusion because they have altered autoregulation of cerebral blood flow. Certain regions of the brain, including the hippocampus, periventricular white matter areas, and watershed areas, may be particularly susceptible to the effects of hypoperfusion. However, the evidence that deranged cerebral hemodynamics are associated with neurological injury is weak and sometimes conflicting. Some evidence suggests that maintaining perfusion pressure at more physiological levels during cardiopulmonary bypass (80–90 mmHg) is associated with lower short-term POCD [26]. However, a study using single-photon positron-emission computed tomography failed to show a significant association between neuropsychological test performance and postoperative global or regional blood flow [27]. As discussed above, emboli and hypoperfusion may act synergistically, in that decreased flow during surgery may fail to wash out embolic materials from the brain, particularly in the watershed areas [28].

54.4.3 Systemic Inflammatory Response

Cardiac surgery is associated with a profound systemic inflammatory response, especially when cardiopulmonary bypass is used. It is known that a severe systemic inflammatory response can break down the blood–brain barrier, leading to a range of clinical consequences, including delirium and sepsis-mediated encephalopathy, with symptoms ranging from subtle cognitive deficit to coma. However, there are sparse data to support the inflammatory response alone as the causative factor. Several groups have measured biomarkers of neuronal injury such as neuron-specific enolase and S100β after cardiac surgery with cardiopulmonary bypass and have found elevated plasma levels but with varying correlations between these markers and cognitive function [29, 30]. Preclinical studies suggest that S100β may be involved in neuronal and glial growth, proliferation, and activation, thus facilitating its role as a marker to study inflammation and brain injury.

Unfortunately, it is important to note that serum S100β concentrations appear to be influenced by age, sex, on-pump or off-pump surgery, the use of cardiotomy suction or a cell saver, and the assay used [31–33]. Therefore, it is currently not possible to link these findings with pathophysiological processes.

54.5 Anesthesia

A number of studies have reported that clinically available opioids can be neurotoxic in rats [34, 35]. Fentanyl is associated with delirium [36], but there seems to be no clear relationship between dosage and the incidence of POCD at 3 or 12 months after CABG surgery [37]. Animal studies suggest that exposure to some halogenated anesthetics increases the production of the Alzheimer's amyloid peptide and vulnerability to neurodegeneration [38, 39], but these results are not always supported by clinical data [40]. Inflammation and stress responses might also contribute to cognitive decline induced by anesthesia [41]. Animal research and clinical trials are needed to establish whether anesthetic agents cause cognitive changes or if they affect aging-related cognitive decline.

54.6 Long-Term Cognitive Changes

Several studies suggest that, in addition to the immediate effects of POCD, long-term cognitive outcomes also are affected. A study by Newman and colleagues published in 2001 found that 5 years after on-pump CABG 42 % of patients available for follow-up had cognitive performance lower than at baseline [42]. This high percentage of patients with decline suggests that cardiopulmonary bypass accelerates cerebral aging and that the harmful effects of cardiopulmonary bypass become more apparent in the long term. In contrast, a 5-year follow-up by van Dijk et al. published in 2007 failed to show a difference in the frequency of POCD between patients who underwent surgery with or without cardiopulmonary bypass [43]. Interestingly, approximately 50 % of patients in both groups suffered cognitive decline, suggesting that late cognitive changes are related to factors other than cardiopulmonary bypass. Interpreting this study of cognitive outcomes after CABG has been difficult because of the lack of comparison groups, either with or without coronary artery disease. In 2009, Selnes and colleagues reported that, compared to those with no vascular disease risk factors, patients with coronary artery disease had lower baseline cognitive performance and greater decline during 6 years of follow-up [44]. Thus, vascular disease may impact cognitive performance.

Other possible causes of late cognitive decline in elderly patients include progression of subcortical small vessel disease, development of silent cerebral infarcts, and Alzheimer's disease during the follow-up period. There is evidence

from several epidemiological studies that cerebrovascular disease may be associated with accelerated cognitive decline, even without cardiac surgery. In a recent systematic review of 105 studies, silent cerebral infarcts defined on MRI were detected in 20 % of healthy elderly people [14]. Silent infarcts are associated with subtle deficits in physical and cognitive function. Moreover, the presence of silent infarcts more than doubles the risk of subsequent stroke and dementia. Given that many candidates for CABG have MRI evidence of cerebral infarct even before surgery [15], it is likely that the late cognitive decline reported previously in the literature is related to the progression of underlying cerebrovascular disease.

54.7 Cognitive Recovery After Surgery

Although several previous observations are of empirical importance to the phenomenon of cognitive decline, the studies that provided them did not identify which factors influenced recovery from POCD after cardiac surgery. A 2013 study by Fontes and colleagues reported that 45 % of patients undergoing cardiac surgery who experienced cognitive decline at 6 weeks returned to baseline cognitive function by 1 year [45]. The authors suggested that heightened instrumental activities of daily living performance at 6 weeks after surgery is associated with likelihood of cognitive recovery at 1 year. One hypothesis is that interventions that encourage better performance on instrumental activities immediately after surgery improve cognitive performance.

54.8 Neuroprotective Strategies

Because adverse neurological events after cardiac surgery represent a wide range of injuries, differentiating the individual causes of types of injuries becomes difficult (e.g., stroke, delirium, and POCD). Additionally, there is growing evidence that patient-related risk factors such as the extent of preexisting cerebrovascular disease have a greater impact on both short- and long-term cognitive declines than do procedural variables. Therefore, it is important to assess those risk factors that indicate a predisposition toward POCD such as cerebrovascular disease and then adapt the surgical approach to high-risk patients (Table 54.2). It will become more important to reduce late cognitive decline by controlling modifiable patient-related risk factors such as hypertension, diabetes, hyperlipidemia, and smoking.

Table 54.2 Neuroprotective strategies used in cardiac surgery

Timing	Issue	Intervention
Before surgery	Establish risk factors	Use neuropsychological testing to identify preoperative cognitive impairment
		Use MRI to identify preexisting cerebrovascular disease
During surgery	Aortic atheroma	Use epiaortic/TEE ultrasound to identify ascending and aortic arch disease [46, 47]
		Modify surgical procedures: avoid repeated aortic clamping, choose no-touch aortic techniques for high-grade atheroma, choose site, and assess risk of cannulation
	Hypoperfusion	Use higher blood pressures during cardiopulmonary bypass
		Use alpha-stat pH management (for adults) [48]
	Brain hyperthermia	Avoid rapid/excessive rewarming [49]
	Hyperglycemia	Avoid or treat hyperglycemia [50]
	Microemboli	Minimize cardiotomy suction and dissection of mediastinal fat [51]
After surgery	Diagnosis and identification of ischemic brain lesions	Perform diffusion-weighted MRI

TEE = transesophageal echocardiography

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Chapter 55
Postoperative Cognitive Dysfunction After Noncardiac Surgery and Neuroprotection

Ryoichi Miyashita

Abstract Many patients develop postoperative cognitive dysfunction (POCD) after administration of general anesthesia for major surgery. Symptoms of POCD include impairment of memory, concentration, and language comprehension and are especially common in older adults. However, the pathophysiology of POCD has not yet been fully elucidated. Furthermore, there are no internationally accepted criteria for defining POCD, and incidence rates are possibly overestimated. Anesthetists should be aware of the diagnosis, its risk factors, and possible approaches to preventing and treating POCD. Therefore, this article aims to summarize recent developments concerning the diagnosis, mechanism, and prevention of POCD.

Keywords POCD • Diagnosis • Mechanism • Prevention • Neuroinflammation

55.1 Introduction

After general anesthesia administered for major surgery, many patients develop postoperative cognitive dysfunction (POCD), which includes impairment of memory, concentration, and language comprehension. A serious complication, POCD is characterized by a functional decline that may persist for months [1]. Additionally, older adults are at a greater risk of developing POCD. One multicenter trial reported that, postoperatively, POCD was present in 25 % at 1 week and 10 % at 3 months in patients aged over 60 years [2]. Physiological changes due to aging result in a reduction in the body's ability to cope with the stress associated with surgery, anesthesia, and hospitalization in general. Furthermore, an increased prevalence of comorbidities and subsequent risk increase in the development of perioperative complications is frequently seen in older individuals. The last decade has seen an increase in interest in this subject, with the focus on the pathophysiology, prevalence, treatment, and prevention of this condition. The aim of this chapter is to

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summarize recent developments concerning the diagnosis, mechanism, and prevention of POCD.

55.2 Diagnosis

Postoperative cognitive dysfunction and delirium are often reported as being part of the same continuum of postoperative cognitive impairment [3]. However, they should be considered as two different entities. Delirium is most often a transient condition that develops acutely in the immediate postoperative period, with a marked fluctuation in attention and orientation [4]. In contrast, POCD is more subtle and can be long lasting [5].

The occurrence rate of POCD can be influenced by the age and number of survey subjects, type of surgery, survey period, examination method variability, and definition of dysfunction. Current definitions of POCD include cases where the postoperative value is lower by 1–2 times or more than the standard deviation of the preoperative value and cases where the postoperative value is lower by 20 % or more than the preoperative value. Moreover, tests in which 20 % of the results show a postoperative value that is lower by 20 % or more than the preoperative value are frequently used, because these tests show the highest frequency of occurrence [6]. A floor effect, in which the postoperative value does not go below the preoperative value, can occur in cases where there was a preoperative reduction in cognitive function. Many studies exclude cases with reduced preoperative cognitive function, for example, cases with scores of 23 points or less in the mini-mental status examination. However, studies that include such cases have shown high rates of POCD [7].

The *Rey auditory verbal learning test*, *trail making test A*, *trail making test B*, and *grooved pegboard test* are recommended neuropsychological tests for research on POCD [8]. *The Rey auditory verbal learning test* is a language memorization test in which a subject listens and then repeats a list of 15 words, 5 times. At the 6th repetition, the subject listens and repeats a different list of words. After this, the subject performs delayed recall. If the subject is able to recall the words after the intervention, he/she is considered to have anterograde amnesia. The *trail making tests A and B*, in which the subject connects numbers or alternating numbers and letters in order, are related to attention, concentration, and cognitive function. The *grooved pegboard test* examines visual–spatial functions and reflects parietal functions by having subjects insert pegs in randomly positioned slots.

Furthermore, neuroimaging has been used to elucidate the mechanism of POCD, with the results indicating that widespread cerebral ischemia causes cognitive functional disorder and severe focal ischemia reduced cognitive function [9, 10]. Elucidating the relationship between neuropsychological tests and neural functional imaging diagnostics such as single photon emission computed tomography and functional MRI performed immediately after surgery is expected to further reveal the mechanism behind POCD.

55.3 Mechanisms of POCD

Postoperative cognitive dysfunction is a major cause of morbidity after noncardiac surgery. The underlying mechanisms of POCD remain elusive, but possibly involve a combination of factors related to the patient, surgery, and anesthesia. Several pathways contributing to the development of POCD have been suggested. Surgical procedures cause systemic stress, which can lead to the release of neuroendocrine hormones and the initiation of an inflammatory response [11]. The release of cytokines during this process may contribute to changes in brain function and the development of POCD. Surgical trauma can also increase the level of inflammatory cytokines, such as interleukin (IL)-1β, IL-6, tumor necrosis factor-α (TNF-α), and C-reactive protein in the peripheral and central nervous system, subsequently leading to an impairment in cognitive function [12]. Several experiments using animal models have demonstrated that elevated levels of pro-inflammatory cytokines are closely associated with cognitive impairment [13]. In particular, microglia are attracting attention for their role in eliminating damaged cells in the brain. Microglia are quiescent under normal circumstances, but are activated when MHC class II and other markers on the cell surface react to the invasion of a foreign body by releasing cytokines; the microglia transform from a ramified form to an amoeboid form and migrate to the damaged area where they induce phagocytosis. Activated microglia then produce inflammatory cytokines (IL-1β, IL-8, and TNF-α) and thus contribute to inflammatory conditions. Aging and disease induce microglial priming, which can then be activated by infection or stress. Activated microglia maintain abnormal reactions and reduce cognitive function [14].

Several interesting findings on the mechanisms underlying inflammation control have recently been made. A type of neuronal acetylcholine receptor, the α7 subtype, is present on the surface of macrophages and functions as an inflammation control factor [15]. In mice, pre-administration of a selective α7 receptor agonist was shown to inhibit both surgically induced breakdown of the blood–brain barrier and macrophage infiltration within the hippocampus [16]. In cultured macrophages, an α7 receptor agonist was shown to inhibit the activation of NF-κB by TNF-α. These findings suggest that neuroinflammatory phenomena are either inhibited or enhanced by α7 acetylcholine receptor agonists and NF-κB, respectively, are closely associated with the appearance of POCD, and may contribute to the development of POCD via microglial activation and cytokine release (Fig. 55.1).

The role of general anesthetics in brain toxicity has been proposed as a possible pathogenic factor for POCD. Animal studies suggest that prolonged exposure to commonly used anesthetic agents causes neurodegeneration such as cell damage and apoptosis [17, 18]. In a recent study, older adult rat brains were equally (nitrous oxide) or more sensitive (ketamine with and without nitrous oxide) to anesthetic neurotoxicity [19]. Additionally, following 2 h of 1.2 % isoflurane with 70 % nitrous oxide administration, spatial memory in adult rats was impaired for 2 weeks, an effect that may have a genetic component [20]. Direct extrapolation of these findings to humans is not possible because different species have varying

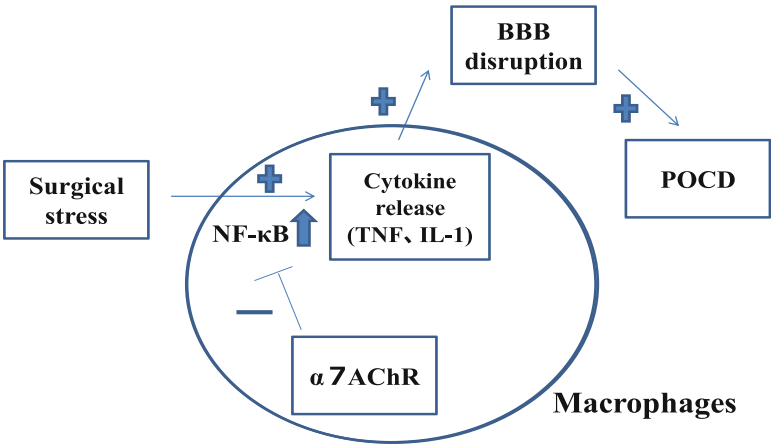

Fig. 55.1 Neuroinflammation and POCD. In mice, pre-administration of a selective α7 receptor agonist was shown to inhibit both surgically induced breakdown of the blood–brain barrier (BBB) and macrophage infiltration within the hippocampus. In cultured macrophages, an α7 receptor agonist was shown to inhibit the activation of NF-κB by TNF-α. α7AChR = α7 subtype of nicotinic acetylcholine receptor; NF-κB = nuclear factor-κB; TNF-α = tumor necrosis factor-α

windows of maximum vulnerability to the neurotoxic effects of general anesthetics, typically where synaptogenesis is at its peak [21].

55.4 Risk Factors

The cause of POCD is most likely multifactorial [22]. A number of risk factors leading to POCD have been identified (Table 55.1). First, older individuals are at increased risk of developing POCD. Environmental changes because of being hospitalized may be part of the multifactorial cause of cognitive alteration and deterioration and may explain why elderly patients are more susceptible to these changes. It is well established that geriatric patients are at higher risk of developing delirium upon hospitalization because of deviation from their everyday routines [23].

Interestingly, a relatively high incidence of POCD is seen after cardiac and orthopedic procedures. Overall, there is a higher risk in operations that are longer in duration with major invasiveness and significant blood loss than in surgical interventions that are less invasive, minor, and short. However, it is not clear whether POCD is triggered by surgery and/or anesthesia itself. One study compared differences in reaction to regional versus general anesthesia in 428 randomly selected patients undergoing major noncardiac surgery. No significant difference was found in the incidence of cognitive dysfunction after 3 months [24]. These findings suggest that POCD is less likely to be associated with the type of anesthesia used.

Table 55.1 Risk factors for POCD

Patient-related risk factors	Surgery-related risk factors
Increased age	Major and invasive surgery
History of alcohol abuse	Cardiac surgery
Preexisting POCD	Long operation duration
Low level of education	Long hospital stay
Change in environment	Postoperative complications

Several other patient-related factors have been associated with an increased risk of the development of POCD, including history of alcohol abuse, prior cerebral vascular accident, previous POCD, poor cognition, and/or a lower educational level [25]. A lower educational factor fits in with the threshold theory for cognitive decline, which states that a low level or lack of education leaves a patient more vulnerable to cognitive deterioration. Therefore, a small degeneration in cognition may result in significant impairment, while patients with a higher educational level might still retain normal cognitive functioning, even after a slight decline [26]. Alzheimer type dementia has also been a topic of research when searching for genetic causes of POCD. However, it possibly does not play an important role in the development of this condition [27]. Similarly, fentanyl dosage and different volatile anesthetics did not affect the occurrence of POCD [28, 29].

55.5 Prevention and Future Strategies

55.5.1 Preoperative

To begin with, it is important to recognize risk factors such as age, alcohol intake, and low level of education preoperatively. In cases where there is an increased risk of POCD, the use of multiple drugs such as benzodiazepines should be limited and short-acting options chosen [30]. A short period of fasting, social contact, and physiological day–night rhythm can also help reduce the incidence of POCD and other common postoperative impairment of cognition [22].

If preoperative mild cognitive decline is present, functional decline can be expected to accelerate after surgery. In other words, the identification of high-risk patients by simple preoperative higher-order brain function testing along with careful perioperative management is important.

55.5.2 Intraoperative

Since there is no evidence that the type of anesthesia influences the risk of POCD, both regional anesthesia and general anesthesia are suitable in older adults, irrespective of depth [3]. Neuromonitoring during anesthesia may improve

recovery. However, bispectral index monitoring did not alter the incidence of postoperative cognitive dysfunction [31]. Interestingly, monitoring the depth of anesthesia in a randomized trial decreased the rate of postoperative delirium, but did not significantly improve the likelihood of postoperative cognitive dysfunction [31]. In one recent study, preconditioning the patient with sevoflurane was found to be potentially protective against the development of POCD, possibly by suppression of inflammatory responses [32]. Furthermore, a shorter and less invasive surgical procedure is associated with a lower rate of POCD. Hypoperfusion or hypoxia of the brain due to blood loss or systemic hypotension has been thought to be a potential cause of POCD in the perioperative period [33]. However, multiple studies did not find an association between low mean arterial blood pressure and POCD in patients who underwent orthopedic surgery [34].

55.5.3 Postoperative

Adequate pain treatment reduces the incidence of POCD, since optimal pain relief contributes to lower systemic stress postoperatively [22]. Oral pain medication is favored above patient-controlled intervention [35]. The well-known detrimental effects of sleep deprivation on mental function need to be evaluated in a postoperative setting in order to clarify the intricate relationship among opioids, sleep disruption, and pain. Furthermore, the subsequent impact of a sleep deficit on cognitive function in elderly patients postoperatively needs to be investigated. The environmental impact of hospitalization may be part of the multifactorial cause of cognitive change and deterioration and may explain why elderly patients are at greater risk of developing POCD. Frequent visits by family and friends while the patient is still in the hospital, as well as early discharge of patients to a familiar home environment, may lead to a reduced incidence of POCD [36].

In summary, perioperative management is important in the prevention of POCD (Table 55.2). Maintaining sufficient homeostasis, intraoperative management of brain circulation and metabolism, and postoperative pain management are also necessary. Patients who receive analgesics postoperatively experience few cognitive functional disorders; thus, in addition to suppressing increases in cortisol levels, which maintain the sleep–wake cycle, preventing persistent inflammatory reactions and cytokinemia is considered to help in preventing POCD. In addition to postoperative analgesic therapy, quick initiation of physical activity after surgery will help prevent brain dysfunction, since reduced postoperative physical activity also effects reduction in cognitive functioning.

Table 55.2 Preventions of POCD

Careful identification of risk factors
Short operation duration
Minimal invasive surgery
Maintain homeostasis
Preventing inflammatory reactions
Adequate pain treatment
Early discharge
Pharmacological sleep improvement

55.6 Conclusion

A rapidly aging society, coupled with advances in medical treatment, has led to a surge in surgeries for the geriatric population. Therefore, prevention and understanding the mechanism of POCD has become an important issue. Clinical studies are required to determine the diagnostic guidelines for POCD and to accumulate useful data. Moreover, further basic research is necessary to look into theories behind inflammatory responses in the brain, particularly in relation to any possible correlation between anesthetic drugs and a higher incidence of brain dysfunction. Clarifying the mechanism behind POCD frequency and determining the risk factors may help in performing surgical procedures and in developing preventive measures.

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Part XII
Complications and Other Considerations

Chapter 56
Electrolyte Disorders

Toru Goyagi

Abstract Electrolyte disorders occur commonly and are associated with a variety of neurological symptoms. Because electrolyte disorders are essentially secondary processes, their management should involve the diagnosis and treatment of the primary disease. The symptoms of electrolyte disorders are mostly reversible. Electrolyte disorders relating to sodium, potassium, calcium, magnesium, and phosphate are reviewed in this section.

Sodium is a cation in the extracellular fluid and a major factor determining osmolality. Common causes of hyponatremia are syndrome of inappropriate antidiuretic hormone secretion and cerebral salt-wasting syndrome. Hypernatremia occurs when fluid replacement cannot keep up with water loss. Diagnosis of diabetes insipidus is very important.

Potassium is the most important and major cation in the intracellular fluid. Hypokalemia is common, with as many as 20 % of patients presenting with hypokalemia. Hyperkalemia may be caused by excessive exogenous potassium administration and medications.

Calcium is important for cellar function. Hypercalcemia is less common than hypocalcemia.

Magnesium ions are important for many biochemical reactions. The most important causes of hypomagnesemia include excessive renal magnesium loss and internal redistribution. Hypermagnesemia is most commonly due to iatrogenic causes.

Phosphate is essential for membrane structure, cellular energy, and cell transport. The most common causes of hypophosphatemia include poor oral intake, the use of phosphate-binding antacids, and the transcellular shift of phosphorus. Severe hyperphosphatemia occurs after tissue damage or cell death.

Keywords Hyponatremia • Hypernatremia • Hypokalemia • Hyperkalemia • Hypocalcemia • Hypercalcemia • Hypomagnesemia • Hypermagnesemia • Hypophosphatemia • Hyperphosphatemia

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56.1 Introduction

Although it is important to maintain the proper electrolyte balance, electrolyte disorders occur commonly and are associated with a variety of neurological symptoms. Because electrolyte disorders are essentially secondary processes, their management should involve the diagnosis and treatment of the primary disease. The symptoms of electrolyte disorders are mostly reversible. Electrolyte disorders relating to sodium, potassium, calcium, magnesium, and phosphate are reviewed as follows.

56.2 Sodium

Sodium is a cation in the extracellular fluid and a major factor determining osmolality. Sodium balance in extracellular fluid is predetermined by the ratio between sodium intake and excretion [1]. Many factors regulate sodium reuptake at the renal tubule, including hemodynamics, physique, hormones, and renal sympathetic nerve activity. The normal range of serum sodium concentration is 135–145 mEq/L.

56.2.1 Hyponatremia

Hyponatremia is defined as a serum sodium concentration below 135 mEq/L and presents in patients as excessive perspiration, vomiting, diarrhea, burn, and diuresis. Hyponatremia frequently occurs in patients with intracranial disease and, following pituitary surgery, occurring in 9–35 % of patients [2]. It is also seen in 30–40 % of patients with subarachnoid hemorrhage (SAH) [3]. Common causes of hyponatremia are syndrome of inappropriate antidiuretic hormone secretion (SIADH) and cerebral salt-wasting syndrome (CSWS). The main risk that hyponatremia and hypoosmolality pose to the brain is cerebral edema, which leads to a life-threatening rise in intracranial pressure (ICP) and occurs when the increase in the intracranial volume to the extracranial volume exceeds 10 % [4].

Antidiuretic hormone (ADH) is secreted linearly when serum osmolarity exceeds 280 mOsm/L or when there is severe blood volume loss. Secretion of ADH acts on the renal collecting tubules to increase the absorption of free water. Great secretion of ADH is associated with the following conditions: SAH, brain tumors, stroke, intracranial hemorrhage (ICH), inflammatory and demyelinating diseases, acute intermittent porphyria, traumatic brain injury (TBI), spinal cord injury, the postoperative state, pain, severe nausea, acute respiratory failure, and the use of particular drugs, including carbamazepine, opioids, and serotonin reuptake

inhibitors [5]. The diagnostic criteria for SIADH include hyponatremia (Na level <135 mEq/L), serum hypoosmolarity (<280 mOsm/L) caused by expansion of the extracellular volume, increased plasma volume, higher urine osmolarity relative to the plasma, sodium excretion >20–25 mEq/L, the absence of clinically evident dehydration, and a urinary sodium concentration less than 25 mEq/L [2]. Patients with SIADH are considered euvolemic; hence, attentiveness to volume status is very important. Several laboratory tests are useful in the evaluation of volume status and salt balance. Elevations in hematocrit, the blood urea nitrogen-to-creatinine ratio, and serum protein levels suggest dehydration and argue against the presence of SIADH. Therapy for SIADH consists of fluid restriction (1–1.5 L/day) and the administration of furosemide, demeclocycline, and hypertonic (3 %) saline (HS) [4]. Rapid corrections of serum sodium levels (>1 mEq/L/h) have been associated with central pontine myelinolysis (CPM) [6].

Cerebral salt-wasting syndrome is defined as the renal loss of sodium during intracranial disease leading to hyponatremia and a decrease in the volume of extracellular fluid and is associated with a variety of intracranial disorders, including tuberculous meningitis, metastatic adenocarcinoma of the lung, TBI, and transsphenoidal surgery. It causes profound natriuresis stimulated by increased levels of atrial natriuretic factor (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) [4]. These peptides suppress aldosterone synthesis, leading to natriuresis, diuresis, and vasodilatation. Cerebral salt-wasting syndrome has been classically described in patients with SAH [7]. Hyponatremia occurs in as many as 30 % of patients with SAH and is associated with cerebral edema. Cerebral salt-wasting syndrome is treated with fluid replacement and the maintenance of a positive salt balance. Hypertonic saline, administered at a rate of >0.5 mEq/L/h, may be used to increase serum sodium levels [5]. It is important to closely monitor serum sodium levels, volume status, and hemodynamic parameters. Again, a rapid rate of sodium correction leads to CPM. The risk of CPM increases with chronic (>48 h) hyponatremia.

It is important to distinguish between SIADH and CSWS, because their respective therapies differ greatly. Table 56.1 shows the differential diagnosis of these two syndromes [2]. However, it is difficult to execute and interpret the diagnosis because many criteria exist. Fluid restriction and diuresis in a patient with CSWS can be fatal because of the possibility of severe hypovolemia and cerebral infarction. Hypovolemia in CSWS and euvolemia or hypervolemia in SIADH may be the most important difference between the two syndromes. Although the urine flow rate is high in CSWS due to the ANP, BNP, and CNP peptides, in SIADH the urine volume decreases due to excess ADH. The furosemide test is useful in the differential diagnosis of these two syndromes [2]. For example, when it is used in the treatment of SIADH, furosemide provokes hypoosmotic diuresis and normalization of serum sodium levels [8].

Table 56.1 Differential diagnosis between syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and cerebral salt-wasting syndrome (CSWS)

	SIADH	CSWS
Extracellular volume	Euvolemia or hypervolemia	Hypovolemia
Body weight	↑	↓
Postural hypotension/tachycardia	−	+
Central venous pressure	↑	↓
Blood urea nitrogen:creatinine ratio	→	↑
Hematocrit	↓	↑
Blood volume by isotope-dilution techniques	↑	↓
Hyponatremia during furosemide test	Normalization	Persistence
Hyponatremia	↓	↓
Natriuresis	Variable	↑
Urine flow rate	Variable	↑
Plasma ADH	↑	↓ or →
Plasma brain natriuretic peptide	→	↑
Plasma aldosterone	↑	↓
Plasma renin activity	↓	↓
Serum uric acid	<4 mg/dL	>4 mg/dL
Fractional excretion of uric acid	>10 %	<10 %

Casulari et al. [2]

56.2.2 Hypernatremia

Hypernatremia occurs when fluid replacement cannot keep up with water loss [9]. It most commonly occurs after SAH, severe TBI, postoperative excision of craniopharyngiomas or pituitary adenomas, or ICH and results from an inadequate intake of water, high-calorie enteral feeding leading to diarrhea, diabetes insipidus (DI), treatment with mannitol and phenytoin, correction of hyperglycemia, or increased total body sodium content due to prolonged volume depletion, which stimulates aldosterone secretion, causing renal retention of sodium. Diagnosis of DI is very important because it is associated with high mortality and impending brain death in patients with SAH or TBI [10]. Although DI is common in the acute phase following neurological intervention, it is usually transient and most patients are able to maintain normal plasma sodium concentrations with oral hydration.

Diabetes insipidus is caused by neurogenic (decreased ADH release from the pituitary gland) or nephrogenic (reduced sensitivity of renal collecting tubules to ADH) mechanisms. Neurogenic DI is more commonly associated with basilar skull fractures and increased ICP than nephrogenic DI. The clinical manifestations of DI include increased urinary output (200–300 mL/h for consecutive hours or >3 L/day), decreased urinary specific gravity (<1.005), reduced urine osmolality to less than that of the serum, hypernatremia (>145 mEq/L), and dehydration. In patients with postoperative DI, there are four distinct patterns of polyuria to consider [5, 11]:

1. Transient postoperative polyuria is the most frequently encountered pattern that begins 1–3 days after surgery and lasts from 1 to 7 days:
2. Triphasic polyuria begins 1–2 days after surgery and lasts from 1 to 7 days, followed by a period of normal urinary output. A recurrence of the polyuria follows from 24 h to several days later and usually persists.
3. Polyuria that may begin within the first 2–3 days postoperatively and is followed by a small decrease in the total urinary volume over the next several days.
4. Permanent polyuria, which presents within the first 2 days postoperatively and persists without any changes.

Treatment comprises correcting the hypovolemia, hypernatremia, and hormonal deficiency. Hypovolemia is corrected using intravenous fluids at a rate that achieves a 1:1 ratio with the urine output [4]. Hypernatremia is corrected by administering enteral water or a parenteral solution. The administration of a saline solution may aggravate the renal loss of water. The goal of free water replacement is to correct serum sodium at a rate that is less than 0.5 mEq/L/h or 12 mEq/L over 24 h [4]. It is important to closely monitor the fluid balance. If the urinary output exceeds 300 mL/h over 2–3 h or the patient is lethargic, aqueous vasopressin should be initiated. Aqueous vasopressin is the first choice of treatment in the early stages of DI because of its short duration of action (4–6 h), enabling errors in fluid balance to be corrected. Initial doses are usually 5–10 U per 1 dose and are preferably administered intramuscularly, thereby preventing a vasopressor response [11].

56.3 Potassium

Potassium is the most important and major cation in the intracellular fluid [1]. The potassium balance between intracellular and extracellular fluids is influenced by insulin, pH, beta-adrenergic agonists, and bicarbonate concentrations. Acute changes in serum potassium levels appear to be less well tolerated than chronic changes. The normal range of serum potassium concentration is 3.7–5.2 mEq/L.

56.3.1 Hypokalemia

Hypokalemia is common with as many as 20 % of patients presenting with hypokalemia during hospitalization, even when those receiving diuretic therapy are excluded [5]. Hypokalemia may occur due to alkalosis resulting from spontaneous or mechanical hyperventilation and in the presence of corticosteroids or diuretics. Lower plasma potassium concentrations on admission have been associated with an increased risk of death, independent of age, stroke severity, hypertension, or smoking history [12]. Hypokalemia has been reported in patients with severe TBIs. This hypokalemia is transitory, resolving within the first day and may

be secondary to the large catecholamine discharge [13]. It is uncommon for patients to report symptoms associated with hypokalemia, but generalized weakness and lassitude may be apparent when serum potassium levels are below 3 mEq/L. Potassium chloride is used at rates of 5–10 mEq/L, depending on the clinical symptoms. Serum potassium concentrations must be closely monitored, especially in elderly patients or those who have received catecholamine infusions. Hypomagnesemia and hypocalcemia may cause refractory hypokalemia. These abnormalities have been linked to cardiac arrhythmias associated with the prolongation of the QT interval. Hypokalemia may be associated with hypophosphatemia.

56.3.2 Hyperkalemia

Hyperkalemia may be caused by excessive exogenous potassium administration and medications, including potassium-sparing diuretics, beta-blocking agents, angiotensin-converting enzyme inhibitors, and nonsteroidal anti-inflammatory drugs [5]. The dangers of abnormal cardiac functions and cardiac electrical disturbances must be considered in patients with hyperkalemia. The management of hyperkalemia depends on changes in the serum potassium concentration and electrocardiographic changes. Hyperkalemia can be managed using calcium gluconate, sodium bicarbonate, glucose/insulin, beta$_2$-adrenergic agonists, and sodium polystyrene sulfate (kayexalate) and by dialysis.

56.4 Calcium

Intracellular and extracellular calcium concentrations are tightly regulated because calcium is important for cellar function [1]. Calcium mediates muscle contraction, cell growth, transportation, and the secretion of fluids and electrolytes. Ionized calcium is physiologically active and can be measured directly. Determining serum protein concentration is important in determining calcium ion concentration. The normal range of ionized calcium concentration is 1.1–1.4 mmol/L (4.5–5.6 mg/dL).

56.4.1 Hypocalcemia

Hypocalcemia frequently occurs in neurosurgical patients [14]. Ionized hypocalcemia commonly presents as cardiovascular or neuromuscular insufficiency. Mild ionized hypocalcemia (0.8–1.16 mmol/L) is usually asymptomatic and often does not require treatment [5]. There is no clear evidence that aggressive calcium supplementation worsens neurological outcomes [15]. Reports of hypocalcemia as a precipitating factor in nonconvulsive status epilepticus have been published

[5]. The commonly available calcium solutions for intravenous use are 10 % calcium chloride and 10 % calcium gluconate. Elemental calcium contained 272 mg in 1 ampule of 10 % calcium chloride and 90 mg in 1 ampule of 10 % calcium gluconate [5]. Total and ionized serum calcium concentrations should be monitored closely.

56.4.2 Hypercalcemia

Hypercalcemia is less common than hypocalcemia [5]. Mild-to-moderate hypercalcemia often has no symptoms and the clinical presentation of hypercalcemia depends on the serum calcium concentration. Symptoms of hypercalcemia are manifested in the central nervous system (e.g., changes in mental status), the gastrointestinal tract (e.g., vomiting), the kidney (e.g., polyuria, renal calculi, and oliguric renal failure), and the heart (e.g., disturbances in cardiac conduction) [1]. The main goal of the treatment of hypercalcemia is to minimize its deleterious effects on the renal, cardiovascular, and central nervous systems [5]. Diuresis and the administration of normal saline are commonly used to dilute plasma calcium. Serum magnesium and phosphorus concentrations should also be measured in all cases of hypercalcemia.

56.5 Magnesium

Magnesium is the fourth most prevalent cation in the body and is essential in regulating calcium access to cells and the actions of calcium within cells. Magnesium ions are important for many biochemical reactions, and a deficiency may have clinically important consequences [1]. The normal range of serum magnesium concentration is 1.5–2.5 mg/dL.

56.5.1 Hypomagnesemia

The most important causes of hypomagnesemia in neurocritically ill patients include excessive renal magnesium loss (e.g., polyuric patients) or internal redistribution (e.g., catecholamine infusion, stress of severe TBI, or extensive neurosurgeries) [5]. The incidence of hypomagnesemia is higher in patients with severe TBI compared with those patients who have trauma without TBI [16]. Symptoms of hypomagnesemia include neuromuscular hyperactivity with tremors, myoclonic jerks, convulsions, nystagmus, dysphagia, Chvostek sign, and Trousseau sign [5]. Hypomagnesemia impairs respiratory muscle power. Magnesium sulfate

should be given at a dose of 1–2 g (8–16 mEq) over 15 min, followed by 1 g/h until serial measurements of serum magnesium levels are corrected [1].

56.5.2 Hypermagnesemia

Hypermagnesemia is most commonly due to iatrogenic causes and excessive use of magnesium-containing antacids or laxatives [1]. Elimination of magnesium involves fluid loading and concomitant diuresis. Calcium can antagonize the effects of magnesium temporarily.

56.6 Phosphate

Phosphate is the most abundant intracellular anion and is essential for membrane structure, cellular energy, and cell transport [1]. The normal range of serum phosphate concentration is 0.8–1.4 mmol/L (2.5–4.5 mg/dL).

56.6.1 Hypophosphatemia

Severe hypophosphatemia has been associated with tissue hypoxia, leukocyte dysfunction, hemolysis, a predisposition to sepsis, and cardiomyopathy [5]. The most common causes of hypophosphatemia include poor oral intake, the use of phosphate-binding antacids, and the transcellular shift of phosphorus from the extracellular compartment to the intracellular compartment [5]. Intravenous phosphate doses of 0.9 mg/kg/h for 4–6 h are commonly used to avoid doses of 0.25 mmol/kg over 4–6 h, which may result in hypocalcemia and tissue damage [1].

56.6.2 Hyperphosphatemia

Severe hyperphosphatemia occurs after tissue damage or cell death. Moderate-to-severe hyperphosphatemia may be caused by an impaired ability to excrete phosphorus because of renal failure [1]. Treatments include the administration of phosphate-binding antacids (e.g., aluminum antacids and sucralfate), calcium citrate, calcium carbonate, and dialysis [1].

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Chapter 57
Crisis Management for Perioperative Complications (Seizure, Hemorrhage, Neurogenic Pulmonary Edema, and Venous Embolism)

Tetsuya Kushikata and Kazuyoshi Hirota

Abstract Seizures, hemorrhage, neurogenic pulmonary edemas, and venous embolisms are all potential perioperative complications. Although they are not usually life-threatening, the anesthesiologist should be familiar with their pathophysiology, diagnosis, and treatment, all of which will be described in this chapter.

Keywords Perioperative complications • Seizures • Hemorrhage • Neurogenic pulmonary edemas • Venous embolisms

57.1 Introduction

This chapter provides approaches in crisis management of perioperative complications. Four topics are described. Seizures, hemorrhage, neurogenic pulmonary edemas, and venous embolisms are all potential perioperative complications. Although they are not usually life-threatening, the anesthesiologist should be familiar with their pathophysiology, diagnosis, and treatment, all of which will be described in this chapter.

57.2 Seizures

57.2.1 Overview

A seizure is an abnormal, unregulated synaptic firing initially developing in the cortical gray matter and which transiently interrupts normal brain function.

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Seizures may typically cause abnormal sensation, loss of consciousness, and focal involuntary movement (convulsion). There are many causes of seizure, including cerebral ischemia, hypoxia, and edema; infections of the central nervous system; head trauma; drug intoxication; hyperpyrexia; expansion of intracranial lesions by cerebral tumor; and congenital abnormalities. Seizures can worsen brain damage and increase intracranial pressure (ICP), so they need to be treated properly and promptly. A seizure lasting more than 5 min is unlikely to stop spontaneously. Seizures or seizure-like phenomena are not uncommon after subarachnoid hemorrhage. Seizures may also reflect symptoms of rebleeding after neurosurgery [1].

57.2.2 Management

The diagnosis of a seizure is based on its clinical symptoms, electroencephalographical findings, and the patient's medical history. Clinical symptoms include tonic-clonic convulsions and loss of consciousness. In some cases, no convulsions may be observed. A bispectral index monitor is helpful in confirming the diagnosis, especially in cases of paralysis. Seizures will increase cerebral blood flow and ICP, so aggressive treatment is required. Whatever the cause, in critical situations, it is often necessary to initiate some kind of emergency treatment aimed at terminating the seizure itself, preventing further seizures, or providing life support [2]. Airway management, in particular, is critical in preventing status epilepticus-induced hypoxia. If necessary, endotracheal intubation should be performed. Rocuronium (0.9–1.2 mg/kg IV) and midazolam (0.1–0.2 mg/kg IV) are helpful in accomplishing endotracheal intubation. Use of antiepileptic drugs is essential in treating seizures. A typical regimen of antiepileptic drugs is described in Table 57.1. Life support must be provided simultaneously. Airway management is crucial as status epilepticus (any seizure lasting more than 5 min) can develop following hypoxia. In such cases, it is necessary to provide endotracheal intubation or use some similar method without delay.

57.2.3 Key Points

1. Treatment strategy should focus on control of seizures and provision of life support.
2. Appearance of seizures or seizure-like phenomena is not uncommon after subarachnoid hemorrhage.
3. Consider seizure as possibly symptomatic of rebleeding.

Table 57.1 Dosage of typical anticonvulsant agents

Agents	Dose (Adult)	Considerations
Diazepam	0.05–0.2 mg/kg IV at every 15 min (max 30 mg)	Thrombophlebitis may occur because of its hydrophobic property
Midazolam	0.2 mg/kg IV	Tachyphylaxis occurs after prolonged use
	0.02–0.06 mg/kg/h	
Propofol	1–2 mg/kg IV	Change whole administration device at every 12 h because of possible bacterial contamination
	0.5–3 mg/kg/h	Rhabdomyolysis, metabolic acidosis, renal failure (propofol-related infusion syndrome)
Thiopental	2–4 mg/kg IV	Severe tissue damage will develop in case of extravascular administration
	2–4 mg/kg/h	
Phenytoin	125–250 mg (50 mg/min) IV as initial dose	Only compatible in saline
	100–150 mg additional dose 30 min later if necessary	

Respiratory and cardiac depressions are common side effect of those agents
Adequate respiratory and cardiovascular management are required

57.3 Hemorrhage

57.3.1 Overview

The brain is a vessel-rich organ that receives about 20 % of the cardiac output. Therefore, once bleeding develops, it can be catastrophic, indicating the need for the anesthesiologist to always be prepared to deal with potentially massive hemorrhage during neurosurgery. Moreover, the risk for this is particularly high during craniotomies, clipping of aneurysms, and resection of arteriovenous malformations. Any increase in mean arterial pressure during the induction of or emergence from general anesthesia may also cause an artery to rupture. Vasodilators may be helpful in preventing such ruptures. Induced hypotension may reduce potential risk of hemorrhage during surgical procedures. However, the anesthesiologist should be aware that excess hypotension could result in cerebral ischemia.

57.3.2 Management

The primary goals of fluid management in anesthesia for neurosurgery are to maintain cerebral perfusion pressure (CPP; CPP = mean arterial pressure – ICP) and prevent swelling of the brain or herniation due to volume overloading. Therefore, it is important to maintain normovolemia and avoid excess reduction in serum osmolality. Any reduction in circulating blood volume can be compensated for with blood products or fluids. Such fluids are classified into two types: crystalloid and

colloid. Initially, any deficit in blood volume should be compensated for at the rate of 2–3 ml of isotonic crystalloid fluid per 1 ml of blood lost, for which lactated Ringer solution is usually used. Physiologic saline may cause hyperchloremic metabolic acidosis if given in large volume. When lost blood volume is large, colloids and blood administration should be considered as crystalloids lack oxygen-carrying capacity and coagulation capability and have a limited intravascular half-life. These disadvantages exacerbate metabolic acidosis and volume overload.

One study of patients with severe head injury and massive hemorrhage revealed an increase in mortality in those receiving crystalloids alone compared with those receiving colloids [3]. Although the lowest acceptable hemoglobin (Hb) level remains to be determined, there is some evidence that a value of as low as 7 g/dL could be harmful in cases of severe brain injury [4]. A practical approach to massive hemorrhage is to consider the rate of bleeding. If the rate is slow, replacement with isotonic crystalloid solution and/or colloids may be the simplest and optimum choice. If the rate is rapid, blood transfusion should be prepared. The first blood product to be given is red blood cells, after which fresh frozen plasma (FFP) and platelets may be administered depending on the degree of hemorrhage. The goal is to maintain CPP and thus normovolemia, but not hyper- or hypovolemia. In addition, the anesthesiologist should be aware of potential blood transfusion-related complications such as hyperkalemia, acidosis, hypothermia, and hypocalcemia. These complications are not only potentially life-threatening, but exacerbate hemorrhage, meaning that further blood transfusion will be required should they occur. Proper treatment of each complication is the only way to terminate this malignant cycle.

57.3.3 Key Points

1. The anesthesiologist should prepare countermeasures to potentially massive hemorrhage during neurosurgery.
2. The policy on fluid therapy in neurosurgery is similar to that in general surgery, except that avoiding hypervolemia, which can potentially result in swelling of the brain or herniation, must also be taken into consideration.
3. The primary goals of fluid therapy are to maintain normovolemia and avoid excess reduction in serum osmolality.
4. The Hb threshold level may be between 8 and 9 g/dL. A lower Hb level (<7 g/dL) over a prolonged period of time can result in inadequate brain perfusion.
5. If massive hemorrhage-induced coagulopathy is suspected, FFP should be administered.
6. Platelet transfusion may be considered if thrombocytopenia occurs (<50,000/mm^3).
7. The anesthesiologist should be aware of blood transfusion-related complications such as hyperkalemia, acidosis, hypothermia, and hypocalcemia, which may induce coagulopathy and exacerbate hemorrhage.

57.4 Neurogenic Pulmonary Edema

57.4.1 Overview

Neurogenic pulmonary edema (NPE) is a life-threatening complication that can occur with insult to the central nervous system, including subarachnoid hemorrhage (SAH), traumatic brain injury, subdural hemorrhage, status epilepticus, meningitis, and spinal cord injury. Neurogenic pulmonary edema will usually develop within minutes to an hour following severe brain injury, although it can sometimes occur between 24 and 48 h [5] and is observed in both adults and children [6]. In the case of SAH, the incidence of NPE ranges between 2 and 42.9 % [5].

Although NPE was first described over 100 years ago, the precise mechanism underlying its occurrence remains to be clarified. A number of possible mechanisms have been reported. A rapid and extreme elevation in ICP is the most causative factor, resulting in dysfunction of vasomotor centers in the hypothalamus and brainstem, which are recognized NPE trigger zones. Damage to these zones results in a massive release of catecholamines and other vasoactive substances, followed by the development of NPE. Inflammation, however, is not implicated in the development of NPE [7].

57.4.2 Management

Patients with NPE complain of respiratory distress. Dyspnea, tachypnea, and hypoxia will develop rapidly. Pink and frothy sputum is commonly observed. Auscultation will reveal bilateral crackles and rales. Hypertension and tachycardia are also observed due to NPE-related high sympathetic tone. Chest radiography reveals bilateral infiltration consistent with acute respiratory distress syndrome. These symptoms usually achieve spontaneous remission within 24–48 h. If elevated ICP persists, however, remission will be delayed.

There are no well-established strategies for the prevention of NPE, and its management is based on one of two strategies. In one approach, the goal is to control the insult to the central nervous system that triggered the NPE, which includes decreasing ICP, removing any hematomas, and controlling seizures. Another, supportive strategy is to treat the pulmonary edema itself, as NPE should show an improvement within 48 h if the trigger is well controlled. Respiratory support is essential to this strategy, so invasive or noninvasive ventilation will be required. In severe NPE, the patient should be intubated and mechanically ventilated. To avoid barotrauma of the lung, relative low tidal volume ventilation is recommended. Although positive end-expiratory pressure (PEEP) is effective in improving oxygenation, if the level is too high, it will impede cerebral perfusion pressure, so less than 15 cm H_2O is recommended. Note that a high level of PEEP and/or peak inspiratory pressure may result in elevation of ICP. Hypercapnia

potentially increases ICP, so should be avoided as much as possible. Cardiovascular control is another important factor as patients with NPE always exhibit a high sympathetic tone. Sympatholytic agents such as α- or β-blockers may be helpful in controlling hypertension and tachycardia, either of which can worsen NPE. The anesthesiologist should check myocardial function and provide proper support while seeking to prevent any harmful effects on the central nervous system.

57.4.3 Key Points

1. Symptoms of NPE may develop within minutes to an hour following severe central nervous injury.
2. Elevated ICP increases sympathetic tone, which then triggers NPE.
3. Neurogenic pulmonary edema is a life-threatening complication. Treatment of hypoxia is essential, and mechanical ventilation is usually required. High levels of PEEP and/or peak inspiratory pressure may result in elevation of ICP. Normocapnia should be maintained.
4. Sympatholytic agents such as α- or β-blockers may be helpful in controlling hypertension and tachycardia, which in turn helps control NPE.

57.5 Venous Embolism

57.5.1 Overview

Embolism during neurosurgery is classified into two major categories: deep vein thrombosis (DVT) and venous air embolism (VAE).

Deep vein thrombosis tends to develop in patients who are immobile due to a neurologic deficit such as paralysis owing to a brain tumor or cerebral hemorrhage. Another risk factor for DVT is prolonged surgery, especially in cases of malignancies, where the incidence of DVT has been noted to range between 3 and 26 % [8]. Age and discontinuation of anticoagulants because of a tendency to bleed are other risk factors for DVT. Patients with any neurologic event tend to exhibit relative hyper-coagulation, probably due to their sympathomimetic status.

Venous air embolism is a pathological condition caused by entrainment of air or other exogenous gases from surgical or other sites communicating with the venous or arterial vasculature. The rate of VAE depends on the surgical procedure, intraoperative position, and detection methods involved [9]. Although many cases of VAE are subclinical, if the embolism obstructs the circulation or decreases cardiac output, it may cause hemodynamic collapse and subsequent death. Unfortunately, it is difficult to accurately determine what constitutes a lethal volume of entrained air. Based on experimental data from dogs and rabbits, the value for an

adult appears to be 200–300 ml or 3–5 ml/kg [9]. The common sources of severe VAE are the major venous sinus, including the transversus, the sigmoid, and the posterior half of the sagittal sinus. These are all non-collapsible because of their dural adhesion. Therefore, VAEs developing during surgery performed on the posterior fossa with the patient in the seated position are usually fatal.

57.5.2 Management

57.5.2.1 DVT

Prevention is crucial to the management of DVT, as once an embolism occurs, it can be lethal. Methods of prophylaxis include elastic stockings, intermittent pneumatic compression, and continuous intravenous administration of heparin. Heparin is effective, but carries the potential risk of inducing bleeding, so its use should be avoided perioperatively.

Tachycardia, tachypnea, and hypoxemia, increased gap between $PaCO_2$ and $EtCO_2$, and hemodynamic instability are all indicative of a possible DVT. Therefore, if any of these conditions develops, differential diagnosis is required. Transesophageal echocardiography is helpful in pinpointing thromboses located in the pulmonary artery. Chest Xp (usually normal in the case of a DVT) and computed tomography may be useful.

During the critical period, DVTs should be treated with oxygen supply, mechanical ventilation, and/or hemodynamic support (if necessary). The placement of an inferior vena cava (IVC) filter can prevent further accumulation of thromboses. Radical treatment is also available and involves the surgical removal of the thrombosis. This is often difficult to perform during neurosurgery, however, due to the need for whole body heparinization for cardiopulmonary bypass and would therefore increase the risk of hemorrhage.

57.5.2.2 VAE

Prophylaxis is also crucial in the case of VAEs. The main cause of VAEs is entrainment of air in the venous system, so it is necessary to block any potential such flow if this problem is to be prevented. The first step is to avoid having the patient placed in a seated position in order to reduce the pressure gradient between the right atrium and the surgical site. Hydration and ventilation also need to be controlled to manage the pressure gradient. Hydration should be performed carefully so as not to increase ICP. It is recommended that administration of nitrous oxide be avoided in patients at high risk of VAE as this can serve to further enlarge the air embolism. If a VAE develops in a patient receiving nitrous oxide, administration should be terminated immediately.

Hypoxemia and acute right heart failure are both signs indicative of a large VAE. In this situation, some form of cardiovascular collapse may occur such as tachycardia, elevation in pulmonary artery pressure (PAP) and central venous pressure (CVP), hypotension, or myocardial ischemia. If the patient is awake, an altered mental state can be observed. Transesophageal echocardiography is helpful in revealing the location of air in the right atrium, ventricle, and pulmonary artery.

The treatment of VAE during the acute phase is divided into two steps. The first is to prevent further entry of air. For this purpose, the anesthesiologist should ask the surgeon to flood or pack the surgical site and close the open vein. The anesthesiologist should discontinue nitrous oxide administration and start controlling ventilation if the patient is spontaneously breathing. Ventilation with 100 % oxygen is recommended. Try to aspirate the air through central venous pressure or a pulmonary artery catheter if available. Hemodynamic support is also necessary. In the case of severe VAE, cardiopulmonary resuscitation will be needed.

57.5.3 Key Points

1. Once an embolism develops, it may be a life-threatening complication, so prevention is essential.
2. Capnography ($EtCO_2$) is a practical method of detecting emboli.
3. For this purpose, application of elastic stockings or intermittent pneumatic compression is considered valuable.
4. Placement of an IVC filter should be considered in patients with a history of or confirmed DVT.
5. Avoid having the patient assume a seated position as much as possible.
6. Preserve adequate intravascular volume.
7. Employ positive pressure ventilation.
8. Avoid administration of nitrous oxide.

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Chapter 58
Pain Management in Neuroanesthesia

Hidekimi Fukui

Abstract Neurosurgeons typically aim for patients to quickly regain consciousness after brain surgery. Moreover, in pain management after craniotomy, it is common to underestimate pain or provide insufficient analgesia because of the low level of postoperative consciousness. Thus, acute postoperative pain can on occasion progress to chronic pain along with the occurrence of central nervous system sensitization. During neurosurgical procedures, anesthesiologists must manage anesthesia while keeping in mind that patients should be restored to a lucid state immediately after the operation and receive adequate and appropriate postoperative analgesia. In craniotomy, perioperative pain management is basically performed with opioids, such as remifentanil and fentanyl. If postoperative analgesia is provided by administering opioids alone at sufficient doses, intracranial pressure may be increased by nausea and vomiting, opioid-induced respiratory depression may occur, or neurological findings may not be adequately assessed due to oversedation. For these reasons, scalp nerve block or cranial local infiltration analgesia is used before or after surgery, or opioids are administered via the patient-controlled analgesia system. Moreover, regular administration of acetaminophen is added to reduce the dose of opioids. Furthermore, anticonvulsants, α-2 adrenergic agonists, and N-methyl-D-aspartate receptor agonists are administered in the perioperative period to prevent the prolongation of pain. It is important to provide pain management after craniotomy through multimodal approaches that take pain progressing from the acute to the chronic phase into account.

Keywords Multimodal postoperative pain management • Preventive analgesia

58.1 Introduction

Pain is sometimes called the fifth vital sign. To perform adequate analgesic interventions for pain after neurosurgical procedures, accurate assessment of pain and maximization of analgesic effects are important. In the past, treatment was

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provided based on anecdotal evidence, such as case reports. At present, there is still no consensus on standard treatment protocols for pain after neurosurgical procedures. Reports presenting a small amount of evidence or contradictory outcomes may have resulted from inconsistent treatment protocols or lack of critical examination of the care provided.

In the past 10 years, various techniques designed to achieve adequate postoperative analgesia have become available due to improved quality of wakefulness and advances in postoperative pain management. Pain after neurosurgical procedures is reportedly more severe than expected even when treated by a perioperative pain management team. A recent study revealed that, in 50 % of cases, moderate to severe postcraniotomy pain is attributable to inadequate pain management [1]. Neurosurgeons typically aim for patients to quickly regain consciousness after brain surgery. Thus, in anesthetic management for neurosurgical procedures, anesthesiologists must keep in mind that patients should be restored to a lucid state immediately after surgery and receive postoperative analgesia.

In patients who have undergone brain surgery, frequent neurological examinations are required, and the use of opioids is often determined to be inappropriate. Aggressive analgesia involves risks of unexpected oversedation and the induction of related complications. After neurosurgical procedures, the mental state of patients may vary from hour to hour, or they may develop neurological disorders. Thus, it is difficult for some patients to provide caregivers with sufficient information about the pain they might be experiencing.

Adequate analgesia achieved by pain service providers who manage acute postoperative pain may reduce agitation, hypertension, tremor, vomiting, and so forth and also prevent complications, such as intracranial hemorrhage and increased intracranial pressure, postoperatively [2]. However, a recent report also revealed that postcraniotomy pain is often not sufficiently managed and that 80 % of patients experience serious acute postoperative pain [3].

Moreover, insufficient pain management may lead to chronic pain. Typical postoperative pain management with opioids poses the dilemma for providers of acute pain services of achieving a balance between analgesia and prevention of complications. Pain after spinal surgery is a major contributor to postoperative suffering. Because patients undergoing spinal surgery have chronic pain, high-dose antipsychotics are often prescribed for pain relief. In these patients, postoperative pain management employing monomodal approaches is difficult. For example, in postoperative pain management cases given opioids alone, the administration of high-dose opioids to obtain analgesic effects is associated with a risk of inducing respiratory depression. Thus, pain management with anesthesia requires various approaches, tailored to individual patients. This chapter reviews pain management with a focus on pain after neurosurgical procedures.

58.2 Physiology of Pain

Pain is detected by nociceptors, and free nerve terminals are located in the skin, muscles, joints, mucosa, and internal organs. The mechanical nociceptors transmit sharp pain or stabbing pain through myelinated A-fibers. The A-fibers are characterized by a low ignition threshold and fast conduction velocity. The polymodal nociceptors respond to intense mechanical, chemical, and thermal stimuli through unmyelinated C-fibers. Due to surgical invasion, substance P and calcitonin gene-related peptide (CGRP), which are inflammatory mediators, are released, causing vasodilation, plasma extravasation, and activation of nociceptors. Pain stimuli reach the primary afferent neurons in the posterior horn of the spinal cord and are modified by heightened noxious stimuli and the descending inputs. The primary afferent neurons form synapses with the secondary neurons, called wide dynamic range neurons, in the posterior horn. The primary afferent neurons communicate with sympathetic neurons and motor nuclei. The secondary neurons transmit pain, temperature, and mild tactile sensations to the central nervous system. These neurons form synapses with the tertiary neurons in the thalamus to transmit information to the cerebral somatosensory area. Before reaching the thalamus, the neurons send collaterals to the reticular formation, locus coeruleus, mesencephalic gray matter, and brain stem. Noxious stimuli are modified by a variety of peripherally and centrally expressed mediators, such as substance P, CGRP, γ-aminobutyric acid (GABA), glycine, dopamine, serotonin, somatostatin, bradykinin, histamine, norepinephrine, enkephalins, prostaglandins, L-glutamate, aspartate, corticotropin-inhibiting peptide, neuropeptide-Y, and adenosine triphosphate (ATP). These pain-mediating molecules are treatment targets. Pain associated with craniotomy is somatic pain and originates from the scalp, muscles, and soft tissues of the skull, dura mater, and so forth. Postcraniotomy pain frequently occurs due to surgical wounds in the subtemporal or suboccipital region. The scalp is innervated by the cervical spinal and trigeminal nerves. The frontal scalp is innervated by the supraorbital or epitrochlear nerves and branches from the frontal nerve. The temporal scalp is innervated by the zygomaticotemporal nerve and the auriculotemporal nerve (which are both branches of the trigeminal nerve). The occipital scalp is innervated by the cervical plexus, great auricular nerves, and greater and lesser occipital nerves. The innervation of the dura mater transmits pain through the nerves running along the meningeal arteries. Although the mechanism of postcraniotomy pain remains unknown, strong associations between postoperative pain and surgical procedures have been recognized. Gottschalk et al. reported that severe pain frequently occurs in the early postoperative period and that 70 % and 48 % of patients complain of severe pain on the first and second hospital days, respectively. Moreover, chronic postcraniotomy pain typified by headache characteristically persists for 2 months or more [1]. The incidence of chronic pain after acoustic neuroma resection is reportedly as high as 44 % [4]. On the other hand, the incidence of chronic pain after craniotomy for supratentorial lesions was reported to be 29.3 % [5], while that of chronic headache and neuropathic pain at 2 months after

craniotomy was as high as 56 % [6]. However, because no studies have compared chronic postcraniotomy pain according to surgical procedures, further investigation may be needed in the future. Although the mechanism underlying chronic pain remains unknown, chronic pain may also be caused by traction of muscles and remaining in a body posture imposing a burden on the head or neck for a long period of time during surgery, adhesion between the dura mater and muscles after surgery, and so forth. Regarding the patient-related risk factors, there is also a report that female patients, people with anxiety, and patients in a depressive state are likely to develop chronic headache after craniotomy for supratentorial lesions [7]. If pain stimuli persist beyond the acute phase, posterior horn cells will become hypersensitive, causing central sensitization, in which even weak stimuli elicit excessive responses. Furthermore, glial cells proliferate or are activated in the posterior horn. This is associated with neuropathic pain and further complicates the experience and management of pain.

58.3 Pain Assessment

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." Moreover, pain can be divided into two very different basic types: acute and chronic. Acute pain is largely caused by disease, damage to tissues, or inflammation. Moreover, acute pain occurs suddenly after injury or surgery in general and is often accompanied by anxiety or emotional distress. Usually, the causes of acute pain can be diagnosed and treated. Acute pain is self-limited in terms of duration and severity. In rare cases, acute pain becomes chronic pain.

Chronic pain persists for a longer time than acute pain (at least 3 months beyond the onset) and is resistant to most drug therapies. This is a serious problem for patients and often causes physical disability. Moreover, chronic pain is also compounded by distress due to environmental and psychological factors and elicits stronger complaints. It is important to assess this pain to understand what causes it. First, detailed information on each of the different types of pain (nociceptive, neuropathic, and psychosocial pain) should be collected to start the assessment. The first step in assessing pain is to know how severe the pain is at the time of assessment, based on each of the available assessment scales. There are measures that allow information exchange on the severity of pain and are helpful for determining the severity.

In adults, pain is commonly assessed with a 0- to 10-point scale or visual analog scale (VAS). On this scale, 0 means no pain and 10 means the worst pain imaginable.

This scale is used for obtaining approximate assessments of pain from patients.

Moreover, the Wong–Baker FACES Pain Rating Scale is a measure that many medical professionals use for determining the severity of pain in children or adults

with verbal communication difficulties. This measure is recommended for use especially in patients 3 years of age or older. With this scale, patients can determine the severity of their pain by pointing at an appropriate image of a face corresponding to the levels of their pain.

As an alternative to quantitative scales, verbal assessment scales using words describing pain are qualitative assessment measures. One example is the McGill Pain Questionnaire, which is often used for patients who cannot effectively describe the levels of their pain. This scale, based on observation, provides information on pain derived from objective measurements. These include facial expression, muscle tone, blood pressure, and heart rate.

Scales for monitoring pain include the FLACC (face, legs, activity, cry, consolability), CRIES (cry, requires oxygen, increased vital signs, expression, sleeplessness), and COMFORT scales.

In recent years, a device designed to analyze perception and pain, called Pain Vision, has been used in attempts to objectively assess pain. This device allows estimation of the severity of pain with numerical values calculated from responses to artificially induced current stimuli too weak to cause pain.

Psychological tests include the Cornell Medical Index, Self-Rating Depression Scale, and Anxiety Inventory. These tests are used to examine depressive states associated with chronic pain.

Moreover, drug challenge tests (in which drugs effective for pain, such as phentolamine, lidocaine, ketamine, and morphine, are administered intravenously) are often performed to identify effective drug therapy based on the underlying pain mechanism after due consideration of the pain etiology. How pain levels change during these tests is assessed.

58.4 Multimodal Pain Management

In awake craniotomy, scalp block (Fig. 58.1) before surgery and local infiltration anesthesia into the sutured wound at the end of surgery are often used for anesthetic management and may alleviate postcraniotomy pain especially in the early phase [8, 9]. Scalp block is a practical and effective technique for temporary analgesia that was reported to be as effective as morphine administered for analgesia in the postoperative-transition phase after anesthesia with remifentanil [10]. During scalp block, it is essential to avoid injection into the temporal artery. In practice, by injecting local anesthetics through the entire thickness of the scalp up to the border with the skull, an area from the back to the front of the auricle and the temporal area are both anesthetized. Then, an area from the glabella to the front and the back of the opposite auricle is anesthetized. In order to avoid facial nerve palsy, local anesthesia is applied to the area above the level of the zygomatic bones. Local anesthetics are selected at the discretion of individual physicians. In general, 0.25–0.5 % bupivacaine or 0.375–0.75 % ropivacaine, added to 1:200,000 adrenaline, is used with an expectation of long-term effects. It is important to calculate the drug

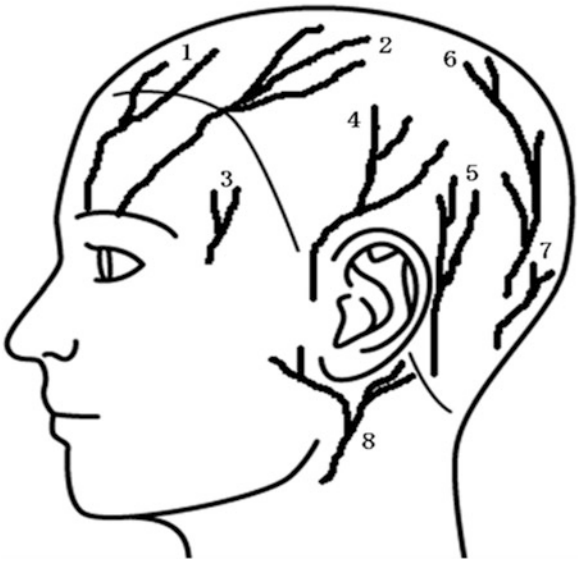

Fig. 58.1 Scalp block with local anesthetic is administered for each nerve innervating the scalp, in an attempt to achieve pain relief. (*1*) Supratrochlear nerve. (*2*) Supraorbital nerve. (*3*) Zygomaticotemporal nerve. (*4*) Auriculotemporal nerve. (*5*) Lesser occipital nerve. (*6*) Greater occipital nerve. (*7*) Third occipital nerve. (*8*) Great auricular nerve

dose per body weight and to ensure administering a dose that does not exceed the maximum allowed. Because the scalp is rich in blood vessels, absorbed adrenaline may affect the cardiovascular system. On the other hand, the merits of scalp block are that it allows appropriate perception and motor neuron tests to be performed after surgery. Furthermore, scalp block not only reduces doses of analgesics needed during surgery but also reduces the doses of narcotics for postoperative analgesia and contributes to achieving lower pain scores. Moreover, scalp block and infiltration anesthesia may act as preemptive analgesia, preventing central nervous system sensitization to pain and the transition to neuropathic pain [6]. Although the frequently performed preoperative local infiltration anesthesia into the wound is effective for minimizing intraoperative bleeding, sufficient evidence of postoperative analgesic effects has not been obtained. On the other hand, local infiltration anesthesia and scalp block can be applied to the surgical wound after closure and can be regarded as effective postoperative analgesic techniques associated with few complications after craniotomy for supratentorial lesions.

58.4.1 Postoperative Analgesia with Parenteral Administration of Opioids

Parenteral administration of narcotics plays a central role in postoperative management of moderate to severe pain.

Opioids exert analgesic effects through the following process: they activate μ- and κ-opioid receptors in the central and peripheral nervous systems to inhibit

voltage-gated calcium channels; consequently, the inflow of potassium ions increases, and excitation of cells is reduced. The primary afferent neurons pre- and postsynaptically inhibit transmission of pain stimuli to the secondary neurons. Intermittent administration of opioids associated with insufficient analgesia often causes oversedation and induces complications, such as respiratory depression. Patient-controlled analgesia (PCA) with morphine, oxycodone, fentanyl, and so forth is widely used as an analgesic technique after craniotomy [11–13]. For postoperative analgesia, administration of opioids alone at adequate doses is commonly performed. If postoperative analgesia after craniotomy relies on opioids alone, intracranial pressure may be increased due to nausea or vomiting and respiratory depression, both of which are adverse reactions to opioids, or neurological findings may not be adequately assessed due to oversedation. Thus, nalbuphine, a peripheral opioid agonist–antagonist, inhibits the onset of vomiting and pruritus and appears to be useful for postcraniotomy analgesia. Moreover, a combination of nalbuphine 0.15 mg/kg and the nonsteroidal anti-inflammatory drug (NSAID) paracetamol was also reported to be effective [2].

By employing PCA with the opioid antagonist nalmefene and morphine, excellent analgesic effects can be achieved without adverse reactions, such as nausea and pruritus, for postcraniotomy analgesia [12]. With the use of opioids, it is important to determine doses giving consideration to the balance between sufficient analgesic effects and the incidence of adverse reactions.

58.4.2 Tramadol

Tramadol is a weak μ-opioid receptor agonist that inhibits reuptake of serotonin and noradrenaline. This drug was reported to have postoperative analgesic effects superior to those of a combination of opioids and acetaminophen for craniotomy patients. However, there is also a report describing the incidence of postoperative nausea and vomiting as being higher in patients receiving tramadol [2].

58.4.3 NSAIDs

The use of NSAIDs allows the consumption of opioids for postoperative analgesia to be reduced. However, nonselective COX-2 inhibitors, which exert a platelet aggregation inhibitory action, are difficult to administer to patients with a risk of postoperative bleeding.

Although selective COX-2 inhibitors (e.g., rofecoxib, celecoxib, meloxicam, and nimesulide) are associated with a lower risk of bleeding and are safer than conventional nonselective COX inhibitors, caution is necessary because the former drugs increase the risk of cardiovascular events. Moreover, the use of NSAIDs requires caution because they can induce myocardial ischemia and also lead to renal

dysfunction due to retention of sodium ions and a reduced glomerular filtration rate. Thus, the use of NSAIDs after craniotomy should be restrained in "high-risk" cases, such as those with tumors, vascular disorders, and trauma, whereas in other cases, NSAIDs should be carefully administered after a postoperative interval of 24 h [14].

58.4.4 Paracetamol

Administration of paracetamol alone is insufficient for postcraniotomy pain, as is the case with NSAIDs. However, doses of opioids can be reduced by regular administration of paracetamol after surgery [2].

58.4.5 Antiepileptic Drugs

Gabapentin is known as an anticonvulsant with analgesic effects on acute postoperative pain. Administration of gabapentin before surgery was also reported to reduce morphine use and postoperative pain after craniotomy [15]. Moreover, pregabalin is recognized as being similarly effective for acute pain. Furthermore, because there is also a report that these drugs have inhibitory effects on chronic pain [16], preoperative prophylactic administration may prevent the transition to chronic pain. However, there is also a possibility of causing oversedation depending on doses [17]. Further studies may be needed.

58.4.6 Alpha-2 Adrenergic Receptor Agonists

Alpha-2 adrenergic receptor agonists are associated with the descending pain inhibitory system in the posterior horn. Dexmedetomidine, which provides sedation and analgesia without causing respiratory depression, is used for anesthetic management of awake craniotomy and other procedures. Although the use of dexmedetomidine alone is insufficient due to its weaker analgesic effects than those of opioids, a combination of these drugs may allow the use of opioids to be reduced. Moreover, it appears that dexmedetomidine does not aggravate respiratory depression, an adverse reaction to opioids [18]. However, there is also a report that dexmedetomidine resulted in a longer time for recovery from anesthesia than propofol, preventing any detailed tests of cognitive function from being performed [19]. Thus, caution is needed.

In a rat model of chronic pain, dexmedetomidine reportedly exerts antinociceptive effects on chronic pain [20]. Thus, this drug may be useful for prevention of the transition to chronic pain.

Furthermore, because cerebroprotective effects have also been reported, this drug type may increasingly be used in the perioperative period in patients undergoing craniotomy.

58.4.7 NMDA (N-Methyl-D-Aspartate) Receptor Antagonists

Ketamine is effective for chronic pain such as neuropathic pain and, as an adjuvant for postoperative analgesia, can also reduce the use of morphine in the perioperative period [21, 22]. Dextromethorphan was also reported to reduce the postoperative need for analgesics when it is administered before surgery in the same manner [23]. These NMDA receptor antagonists are considered to have preemptive analgesic effects [24]. Ketamine may be difficult to use for pain management after craniotomy because intracranial or blood pressure is increased due to the pharmacological action of the drug. However, it may be possible to use dextromethorphan as an adjuvant analgesic after craniotomy.

58.4.8 Chronic Pain Management

Although the mechanism of chronic postcraniotomy pain has not yet been elucidated, the possibilities include contraction of pericranial muscles. To prevent the transition to chronic pain, inhibition of inflammation and pain in the acute postoperative period is important. It is also important to prevent the development of central nervous system sensitization.

Regarding perioperative management to prevent the transition to chronic pain, gabapentin or pregabalin is administered for preemptive analgesia before surgery, and scalp block or wound infiltration anesthesia is performed immediately before surgery, at the time of wound closure, and after surgery. In some cases, dextromethorphan or dexmedetomidine is administered. After surgery, paracetamol is regularly administered in aggressive efforts to achieve analgesia. Opioids are always used throughout the perioperative period. However, when the doses are large, it becomes difficult to obtain accurate neurological findings. Thus, opioids should be administered at the minimum required dose whenever possible. It appears that the incidence of the transition to chronic pain can be reduced by performing seamless management based on the procedures described above. We described here only the management of pain in terms of postoperative pain, but mental factors should be considered in cases with chronic pain [25]. If the procedures described above are considered to be insufficient, an antidepressant, such as a selective serotonin reuptake inhibitor (SSRI), may also be needed.

Table 58.1 Perioperative pain treatment with multimodal approaches

Timing of administration	Drug	Administration method	Dosage	Presence in Japan
Intraoperative postoperative	Bupivacaine	Infiltration	0.25–0.5 % bupivacaine with 1:200,000 epinephrine	○
Intraoperative postoperative	Ropivacaine	Infiltration	0.75 % ropivacaine	○
Postoperative	Paracetamol	i.v.	1 g regularly 6-hourly	○
Postoperative	Codeine	i.m.	30–60 mg 4-hourly as required	×
Postoperative	Morphine	PCA	1 mg bolus with a 10-min lockout	○
Postoperative	Fentanyl	PCA	0.5 μg/kg every 15 min (maximum 4 times/h)	○
Postoperative	Tramadol	PCA	10 mg boluses with a 5-min lockout and an 4-h limit of 200 mg	○
Postoperative	Oxycodone	PCA	0.03 mg/kg bolus with a 10-min lockout (maximum 3 times/h)	○
Preoperative	Gabapentin	p.o.	300–600 mg	○
Preoperative	Dexmedetomidine	i.v.	1 μg/kg	○
Preoperative	Dextromethorphan	p.o.	30–150 mg	○

58.5 Conclusions

We have discussed the management of acute and chronic pain following anesthesia for neurosurgical procedures. In the past, postoperative pain management was often insufficient due to a marked tendency to emphasize the state of consciousness of patients after surgery and the appropriate execution of neurological examinations to check their conditions. Thus, acute and chronic pain can become serious. However, the provision of analgesia starting in the preoperative period with various approaches may allow adequate management of acute pain and prevention of the transition to chronic pain. Table 58.1 shows examples of prescriptions for the drugs explained above. The doses given for each of these drugs are only examples. Further studies on appropriate doses are still needed.

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Chapter 59
Hypothermia for Brain Protection

Yoshimasa Takeda

Abstract During ischemia, neuronal cells remain intact until the onset of anoxic depolarization. Most damage to the cells occurs during anoxic depolarization, although some damage is still sustained after membrane potential has been regained. Hypothermia decreases neuronal damage by delaying the onset of anoxic depolarization during the pre-depolarization period, by suppressing the accumulation of intracellular calcium and/or subsequent processes during the anoxic depolarization period, and by suppressing inflammatory response and the apoptotic process during repolarization. As the majority of neuronal damage is initiated during anoxic depolarization, hypothermia is most effective during this period.

Hypothermia is indicated when interruption of cerebral blood flow is planned during neurosurgical procedure and can be initiated before the onset of ischemia. It is also recommended in patients experiencing cardiac arrest to improve neurological outcome. In patients with traumatic injury, hypothermia is induced to control intracranial pressure and should be terminated very slowly.

Keywords Hypothermia • Depolarization • Membrane potential • Pharyngeal cooling • Nasal cooling • Selective cooling

59.1 Introduction

During ischemia, neuronal cells are damaged mostly during anoxic depolarization with some damage also occurring after they regain their membrane potential. Hypothermia decreases neuronal damage by prolonging the onset of anoxic depolarization during the pre-depolarization period, by suppressing the accumulation of intracellular calcium and/or the subsequent processes during anoxic depolarization period, and by suppressing inflammatory response and the apoptotic process during the repolarization period. Since neurons are damaged mostly during anoxic depolarization, hypothermia is most effective during anoxic depolarization.

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59.2 Mechanism of Neuronal Damage

The mechanism of neuronal damage is shown in Fig. 59.1. Although oxygen consumption in the brain accounts for 25 % of that in the whole body, the brain does not have myoglobin, which stocks oxygen to be used when there is increased oxygen demand. Therefore, brain tissue easily falls into an energy crisis with interruption of blood supply. It has been reported that oxygen pressure in brain tissue decreases within several seconds after the onset of ischemia [1]. In the same situation, cardiac muscle and skeletal muscle can generate ATP by producing lactate during anaerobic glycolysis. However, brain tissue does not have sufficient lactate dehydrogenase to generate ATP. Therefore, ATP content in brain tissue decreases within 10–20 s [2]. This decrease in ATP content activates ATP-dependent potassium channels that release potassium ions from neuronal cells, leading to hyperpolarization of membrane potential. Since hyperpolarization inhibits the electrical activities of the cell membrane, EEG activities are suppressed. It has been reported that humans lose consciousness within 10 s [3] and that dogs show a flat EEG within 20 s after the onset of ischemia. Since neuronal cells consume 60 % of total energy to maintain electrical activities, inhibition of electrical activities saves energy consumption.

If blood flow is not restored, the cell membrane gradually loses its potential due to energy failure. At 2 min after the onset of ischemia in rats (1.3 min in gerbils [4]), voltage-dependent sodium channels on neuronal cell membranes are activated for a few milliseconds and anoxic depolarization is initiated. Due to the loss of membrane potential, voltage-dependent calcium channels are activated, increasing intracellular calcium levels, which further initiates release of glutamate into the synaptic spaces. Glutamate binds to ionotropic and metabotropic receptors, resulting in an increase in intracellular calcium levels from the extracellular space and endoplasmic reticulum, respectively.

Since calcium ions work as a second messenger in the intracellular space, the intracellular calcium level is controlled to a ten-thousandth of the extracellular calcium level under normal conditions. During anoxic depolarization, however, intracellular calcium level increases to 300 times the normal level within 8 min [5]. Accumulation of intracellular calcium inhibits mitochondrial ADP phosphorylation [6] and protein synthesis due to the disaggregation of ribosomes [7] and activates many enzymes, including phospholipase and protease, leading to accumulation of arachidonic acid [8] and collapse of cytoskeletal elements [9]. Multiple failures of cellular functions are triggered during anoxic depolarization.

During the reperfusion period, neuronal cells regain their membrane potential within several minutes of blood supply, even after 3 h of continuous anoxic depolarization [10]. However, multiple failures triggered during anoxic depolarization may not be canceled by blood supply. In rats, 50 % of cortical neurons are damaged by 18 min of anoxic depolarization [10] (8 min in gerbils [4]). Moreover, inflammatory response (e.g., generation of reactive oxygen species) and the apoptotic process occur during the reperfusion period [11]. As a consequence of these

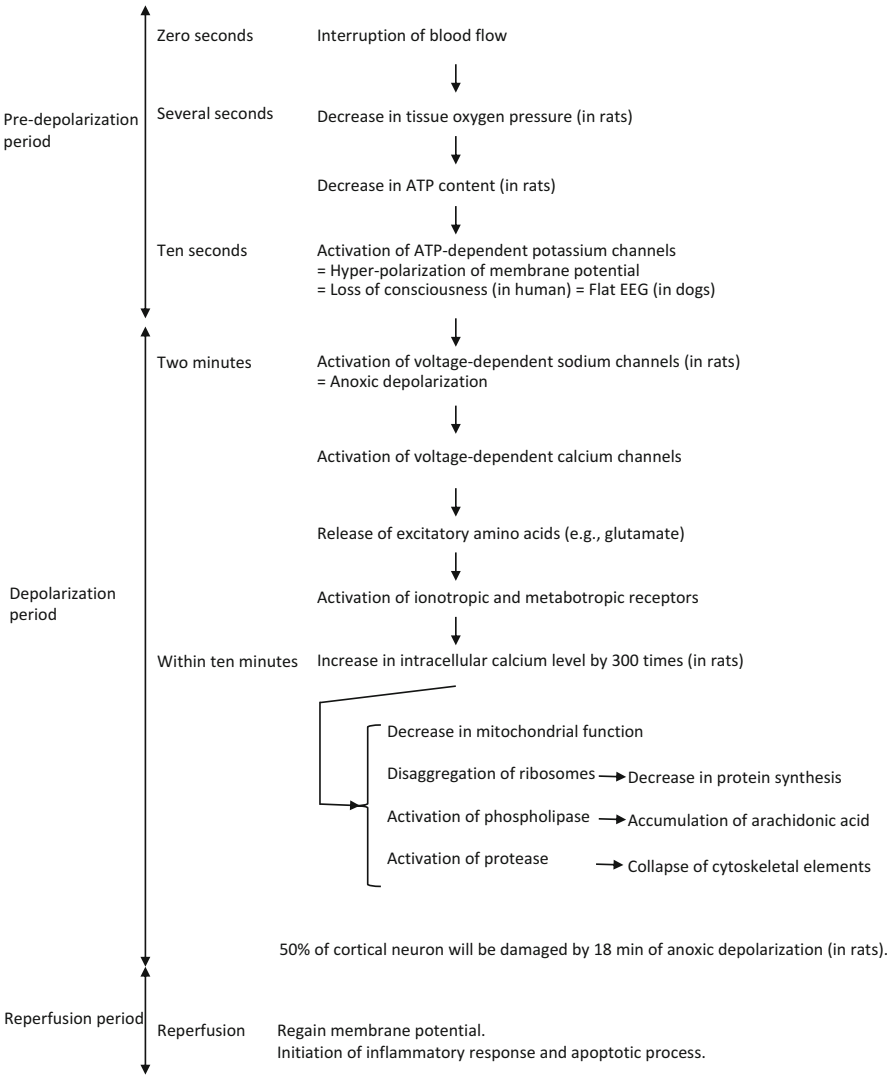

Fig. 59.1 During ischemia, neuronal cells are still intact until the onset of anoxic depolarization (pre-depolarization period). Most neuronal damage occurs during anoxic depolarization (depolarization period), with some damage also being sustained after membrane potential is regained (reperfusion period). Hypothermia decreases neuronal damage by delaying the onset of anoxic depolarization during the pre-depolarization period by suppressing the accumulation of intracellular calcium and/or subsequent processes during the depolarization period and by suppressing inflammatory response and the apoptotic process during the reperfusion period

complicating factors, neuronal cells will be histologically damaged within 1–3 days, depending on the severity of ischemic stress.

59.3 Use of Hypothermia in a Clinical Setting

Delaying the onset of anoxic depolarization during the pre-depolarization period is a rational approach to treatment. Since hypothermia decreases energy consumption in neuronal cells, how long onset is delayed depends on the decrease in brain temperature. As shown in Table 59.1, onset time was delayed by 1.1 min by lowering brain temperature to 31 °C in gerbils [4]. Propofol and thiopental are also useful in delaying the onset of anoxic depolarization [12].

Suppressing the accumulation of intracellular calcium and/or subsequent processes activated by calcium (e.g., degradation of mitochondrial function and uncontrolled activation of endogenous enzymes) is a rational approach to treatment during the depolarization period. It has been reported that hypothermia suppresses increase in intracellular calcium levels and subsequent activation of enzymes during anoxic depolarization. As shown in Table 59.2, the maximal neuroprotective effect of hypothermia seems to be exerted in this phase [4]. Thirty-four degrees of hypothermia extends the depolarization time required for neuronal damage to occur by 78 % (6.2 min) of the control level, while 31° extends it by 225 % (18.0 min) [4].

Suppression of enzyme activities, inflammatory response, and the apoptotic process is a rational approach to treatment during the reperfusion period. As shown in Table 59.3, only 20 min of hypothermia has a neuroprotective effect if it is initiated immediately after the onset of reperfusion. The neuroprotective effect of hypothermia is diminished by initiating it at a later time [13]. If hypothermia is initiated several hours after the onset of reperfusion, the duration of hypothermia should be sufficiently long (e.g., 12–24 h) to suppress the long-lasting inflammatory response and apoptotic process.

59.3.1 Anesthesia Management in Neurosurgery

Interruption of cerebral blood flow is sometimes planned during neurosurgical procedures to allow clipping, superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis, or carotid endarterectomy. Since interruption of cerebral

Table 59.1 Effect of treatments on onset time of anoxic depolarization in gerbils [4, 12]

	Normothermia (37 °C)			34 °C	31 °C
	Halothane	Thiopental	Propofol	Halothane	Halothane
Onset time of anoxic depolarization (min)	1.3	1.6	2.4	2.2	2.4

Table 59.2 Effect of treatments on anoxic depolarization causing 50 % of neuronal damage in gerbils [4, 12]

	Normothermia (37 °C)			34 °C	31 °C
	Halothane	Thiopental	Propofol	Halothane	Halothane
Duration of anoxic depolarization causing 50 % of neuronal damage (min)	8.0	11.3	9.4	14.2	26.0

Table 59.3 Neuroprotective effect of hypothermia (20 min, 31 °C) initiated in variable timing in rats subjected to 5 min of cardiac arrest [13]

	Onset of ischemia	Onset of resuscitation	Onset of repolarization	10 min after onset of repolarization	No treatment
Percentage of neuronal damage	5 ± 3 %	29 ± 22 %	58 ± 18 %	70 ± 15 %	82 ± 10 %

blood flow is planned before the operation, the patient can be treated from the pre-depolarization period. If the planned duration of ischemia is short enough (within 2–3 min in clipping), if occlusion of the artery is planned in the distal portion of the middle cerebral artery in STA-MCA anastomosis, or if the patient has sufficient co-lateral flow in carotid endarterectomy, any anesthetic agent can be used. Thiopental or propofol may be preferred, since they can extend the onset time of anoxic depolarization and the duration of anoxic depolarization, which causes neuronal damage within 18 min in rats. However, if planned ischemia is critical, hypothermia should be performed before initiation of ischemia.

59.3.2 Cardiac Arrest

Table 59.4 shows two randomized clinical trials of hypothermia, one performed in Europe ($n = 234$) [14] and the other in Australia ($n = 77$) [15]. In both studies, hypothermia had significantly improved the neurological outcome 6 months later or at the time of discharge without causing major complications. Based on those results, the International Liaison Committee on Resuscitation recommended hypothermia (32–34 °C for 12–24 h) for patients achieving return of spontaneous circulation following out-of-hospital VF cardiac arrest [16]. To minimize the onset time of hypothermia after return of spontaneous circulation, rapid infusion of ice-cold fluid (intravenous infusion, 30 mL/kg) may be performed [17]. However, since rapid infusion of a fluid may increase central venous pressure and decrease coronary perfusion pressure [18], it needs to be initiated after return of spontaneous circulation. Pharyngeal cooling [19] or nasal cooling [20, 21] can decrease brain temperature in a short period of time without increasing central venous pressure and can be used before return of spontaneous circulation.

Table 59.4 Randomized controlled trial of hypothermia in survivors of ventricular fibrillation [14, 15]

						Percentage of patients showing good neurological outcome		
Author	Number of patients	Target temperature	Time to initiate hypothermia after ROSC	Time to reach target temperature after ROSC	Duration of hypothermia	Control	Hypothermia	*P*
		°C	min	min	hour	%	%	
HACA study	234	33 ± 1	105	480	24	39	55	$P = 0.009$
Bernard	77	33	Immediately after ROSC	120	12	26	49	$P = 0.046$

59.3.3 Traumatic Head Injury

Trauma is not an ischemic injury in which energy depletion plays an important role in the development of neuronal damage, but rather a mechanical injury that generates severe brain edema with increase in intracranial pressure. Hypothermia is useful for controlling intracranial pressure if it is initiated early after the onset of injury. Hypothermia needs to be continued for more than 48 h to prevent an increase in intracranial pressure during rewarming. Also, patients should be rewarmed very slowly (1 °C per day). Since patients are usually dehydrated to suppress brain edema, vasodilation during rewarming tends to cause severe hypotension.

59.3.4 Stroke

Tissue plasminogen activator (tPA) should be used within 4.5 h after the onset of stroke to restore cerebral blood flow [22]. Otherwise, brain tissue suffers from permanent ischemia with anoxic depolarization persisting until necrosis occurs. In laboratory and clinic settings, the therapeutic effect of hypothermia is limited if cerebral perfusion is not restored. One possible application of hypothermia in stroke patients is to extend the therapeutic time window for tPA application. Since few patients can be treated with tPA within 4.5 h after the onset of stroke, extension of the therapeutic time window by hypothermia may be a rational approach, although clinical evidence of this has yet to be reported.

59.3.5 Subarachnoid Hemorrhage

It has been reported that hypothermia induced during clipping surgery does not ameliorate life prognosis or neurological outcome [23]. However, the therapeutic effect of hypothermia on the acute phase (e.g., for the first 24 h) of subarachnoid hemorrhage has not been examined clinically and needs to be evaluated.

59.4 Methods of Decreasing Brain Temperature

59.4.1 Cold Blanket That Circulates Air or Water

A cold blanket is used in many facilities to decrease systemic temperature, and medical staff are usually familiar with these devices. Since the exchange rate of heat between the skin and the blanket is slow, it takes a long time to decrease body temperature, and it is difficult to control body temperature to within a narrow range.

59.4.2 Gel-Coated Pad That Circulates Water

Since the exchange rate of heat between the skin and the gel pad is high, this is one of the best noninvasive methods of controlling body temperature.

59.4.3 Application of Ice Packs to Body Surface

This method decreases body temperature in a short period of time and can be used outside the hospital after return of spontaneous circulation.

59.4.4 Rapid Infusion of Ice-Cold Fluids (30 mL/kg)

This method decreases body temperature in a short period of time and can be used outside of the hospital after return of spontaneous circulation.

59.4.5 Intravascular Cooling Catheter

A cooling catheter directly controls blood temperature and offers the best method of controlling body temperature to within a narrow range. The rate of decrease in body temperature depends on the length and surface area of the catheter. Insertion of the catheter is invasive and may generate a thrombus in major vessels.

59.4.6 Cooling Helmet

A cooling helmet is a device that selectively decreases brain surface temperature. However, it may not decrease core brain temperature.

59.4.7 Nasal Cooling [20, 21]

Nasal cooling selectively decreases brain temperature in a short period of time by delivering cold oxygen or spray of a coolant into the nasal cavities. This method can be initiated before return of spontaneous circulation.

Fig. 59.2 A pharyngeal cooling cuff and a circulator
The cuff is made of vinyl chloride and is equipped with pressure and temperature sensors

59.4.8 Pharyngeal Cooling (Fig. 59.2)

Pharyngeal cooling decreases brain temperature in a short period of time by circulating cold saline into a cuff placed in the pharynx [19]. Since the carotid artery runs along with the pharynx, cooling the pharyngeal region decreases brain temperature by lowering blood temperature. This method can be initiated before return of spontaneous circulation.

59.5 Future of Hypothermia

Ischemic neuronal damage is initiated after the onset of anoxic depolarization. Although mild hypothermia can extend the onset of anoxic depolarization, the duration of the extension is limited. The therapeutic effect of hypothermia is mostly achieved during ischemic depolarization and immediately after the onset of reperfusion. Therefore, it is important to decrease brain temperature during anoxic depolarization (i.e., before the return of spontaneous circulation in cardiac arrest patients). Although it is difficult to decrease brain temperature by cooling the whole body (50–70 kg) in a short period of time, it is possible to decrease brain temperature by selectively cooling the brain (1.4 kg). Nasal cooling and pharyngeal cooling, which enable selective cooling during cardiac arrest, may increase the therapeutic potential of hypothermia in the future.

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Chapter 60
PCPS for Brain Extracorporeal Cardiopulmonary Resuscitation (ECPR)

Ken Nagao

Abstract There is insufficient evidence to recommend the routine use of extracorporeal cardiopulmonary resuscitation (ECPR) for adult patients in cardiac arrest; in conjunction with normothermia, however, it has been shown to be superior to standard cardiopulmonary resuscitation (CPR) in terms of return of spontaneous circulation. Early implementation of ECPR with intra-arrest cooling and percutaneous coronary intervention is likely to protect cells from ischemic/hypoxemic/reperfusion injury and enhance neurological benefits for adult patients in cardiac arrest refractory to standard CPR.

Keywords Cardiac arrest • Cardiopulmonary resuscitation • Reperfusion injury • Cardiopulmonary bypass • Therapeutic hypothermia • Percutaneous coronary intervention

60.1 Introduction

First, I would like to define the term "extracorporeal cardiopulmonary resuscitation" (ECPR) (an alternative term might be "extracorporeal life support," ECLS). Extracorporeal cardiopulmonary resuscitation refers to invasive cardiopulmonary resuscitation (CPR) using artificial circulation and lung devices for patients in cardiac arrest refractory to attempts at standard CPR. One of the procedures involved in ECPR is percutaneous cardiopulmonary support (PCPS), in which cannulation is performed blindly, while others include cardiopulmonary bypass (CPB) and extracorporeal membrane oxygenation (ECMO). The 2010 Guidelines for CPR [1–3] indicate that there is insufficient evidence to recommend the routine use of ECPR for adults in cardiac arrest (Class IIb, benefit $\geq$ risk; LOE C, studies using retrospective controls) or for children in cardiac arrest with potentially reversible cause (Class IIa, benefit $>>$ risk; LOE C, studies using retrospective controls).

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In this section, I will give an outline of ECPR inclusive of therapeutic hypothermia and/or coronary reperfusion therapy for adult patients in cardiac arrest refractory to attempts at standard CPR.

60.2 Criteria of ECPR for Adults in Cardiac Arrest

The 2010 Guidelines for CPR state that ECPR may be considered when the time without blood flow is brief and the condition leading to the cardiac arrest is reversible or amenable to heart transplantation or revascularization [1–3]. Moreover, it is hard for emergency medical service (EMS) responders and/or attending doctors to determine whether a patient has the required inclusion criteria for ECPR when performing initial CPR.

60.2.1 Factors Related to Neurologically Intact Survival for ECPR

Figure 60.1 shows the change of cerebral tissue oxygen saturation during CPR period [4].

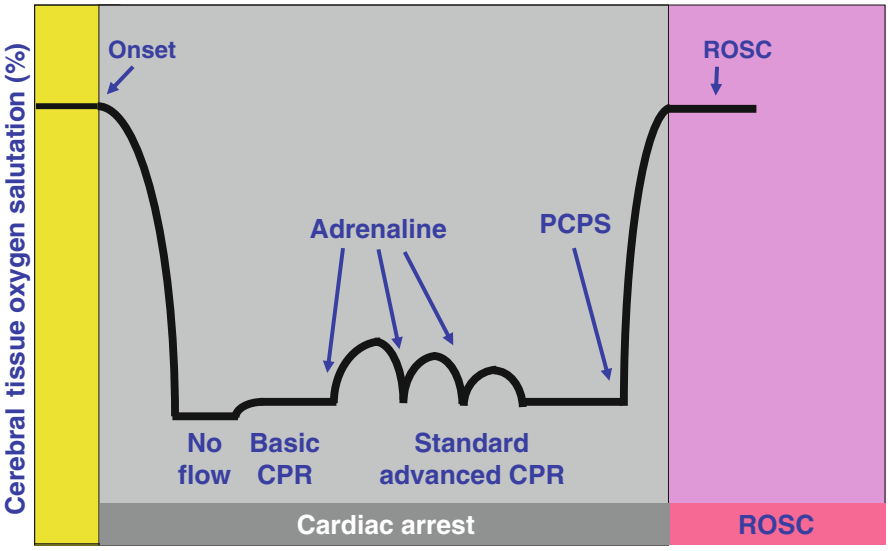

Fig. 60.1 Change of cerebral tissue oxygen saturation from cardiac arrest to implementation of ECPR

A healthy brain and a functional patient are the primary goals of CPR. There are various factors related to neurologically intact survival for ECPR. These factors are roughly divided into three groups.

The first factors are causes of cardiac arrest (cardiac etiology vs. noncardiac etiology) and initial cardiac arrest rhythm (shockable arrest vs. non-shockable arrest).

The second factors are coronary and cerebral perfusion flow during cardiac arrest, inclusive of no-flow duration (time interval from arrest to initiation of basic CPR), the quality of basic CPR and the time interval from initiation of basic CPR to administration of adrenalin or vasopressin, and the quality of standard advanced CPR and the time interval from initiation of standard advanced CPR to implementation of ECPR.

The third factors are the quality of post-cardiac arrest care, inclusive of the degree of reperfusion injury, the quality of ECPR and the time interval from implementation of ECPR to return of spontaneous circulation (ROSC), and the quality of post-ROSC care.

We measured cerebral tissue oxygen saturation levels during ECPR [4]. The cerebral tissue oxygen saturation increases slightly after standard CPR (basic and advanced life support), especially during chest compressions with administration of adrenaline or vasopressin, and normalizes immediately after implementation of ECPR. These findings suggest that ECPR produces the sufficient coronary and cerebral perfusion flow. Although ROSC can be achieved in about 90 % of the patients treated with ECPR, frequency of favorable neurological outcome varies from the conditions of ischemic/hypoxemic/reperfusion injury during resuscitation, inclusive of the time interval from cardiac arrest to ROSC.

60.2.2 Time Window

After 2000, some studies showed that early implementation of ECPR was associated with improved neurological outcome after cardiac arrest [5–15]. Chen et al. reported that the probability of survival rate was 50 %, 30 %, and 10 % when the time interval from initiation of basic CPR to implementation of ECPR was 30, 60, and 90 min in 135 adult patients with in-hospital cardiac arrest [7]. In our study of ECPR with therapeutic hypothermia, the cutoff value for the identification of favorable neurological outcome was 55.5 min in the time interval from cardiac arrest to implementation of ECPR in 171 adult patients with out-of-hospital cardiac arrest [12]. These findings suggest that it is necessary to initiate ECPR within 60 min of cardiac arrest.

60.2.3 Candidates

Some studies reported inclusion and exclusion criteria. Concerning in-hospital cardiac arrest, Chen et al. reported that inclusion criteria were adults ($\geq$18 years

Table 60.1 Criteria of ECPR for out-of-hospital cardiac arrest

Our team	SAVE-J study
Inclusion criteria	*Inclusion criteria*
1. Age of 18–74 years	1. VF/pulseless VT as an initial rhythm
2. Bystander-witnessed arrest	2. Cardiac arrest on ER arrival
3. Presumed cardiac etiology	3. Call-to-ER interval < 45 min
4. Interval within 15 min from collapse to patient's side	4. Conventional ALS for 15 min after ER arrival
5. Defibrillations by bystander and/or EMS personnel	
6. Persistent cardiac arrest on ER arrival	
Exclusion criteria	*Exclusion criteria*
1. Temperature < 30°C	1. Age of < 20 years or >= 75 years
2. ROSC within 10 min of ER arrival with conventional ALS	2. Noncardiac etiology
3. Noncardiac etiology	3. Accidental hypothermia < 30°C
4. Pregnancy	4. Families refused to give informed consent
5. Families refused to give informed consent	

and ≤75 years or ≥18 years and ≤80 years) and standard CPR duration >10 min. Exclusion criteria were trauma, previous severe brain damage, and terminal status of malignancy [6, 7], and Shin TG et al. reported that inclusion criteria were adults (≥18 years and ≤ 80 years), standard CPR duration >10 min, and witnessed arrest due to cardiac etiology [8]. Table 60.1 shows the criteria for our team [12] and the SAVE-J study [16] concerning out-of-hospital cardiac arrest.

The common criteria of these studies are as follows:

- In-hospital cardiac arrest
  1. Witnessed cardiac arrest due to presumed cardiac etiology
  2. Adults under the age of 80
  3. Refractory standard CPR for >10 min
- Out-of-hospital cardiac arrest
  1. Shockable (ventricular fibrillation [VF] or pulseless ventricular tachycardia [VT]) cardiac arrest
  2. Cardiac arrest due to presumed cardiac etiology
  3. Adults under the age of 75
  4. Refractory standard CPR for >10 min after ER arrival
  5. No accidental hypothermia <30 °C

60.3 Neurological Outcome

60.3.1 Standard CPR Alone

Neurologically intact survival was 8 % [8] to 9 % [6] in adults who were treated with standard CPR alone after in-hospital cardiac arrest. In adult patients who arrived at the emergency room in cardiac arrest and were treated with standard CPR alone after out-of-hospital shockable cardiac arrest due to cardiac etiology, frequencies of admission to hospital, 30-day survival, and 30-day favorable neurological outcome were extremely low at 24 %, 3 %, and 1 %, respectively [17] (Fig. 60.2). These findings suggest that an alternative CPR strategy is needed for adult patients with cardiac arrest refractory to standard CPR attempts.

60.3.2 ECPR Without Therapeutic Hypothermia for Adult Patients with In-Hospital Cardiac Arrest

Figures 60.2 [6] and 60.3 [8] show frequencies of neurologically intact survival for adult patients who were treated with ECPR without hypothermia. Chen et al. showed that ECPR with normothermia produced a high achievement of ROSC over standard CPR, but they did not identify 1-year neurological benefits

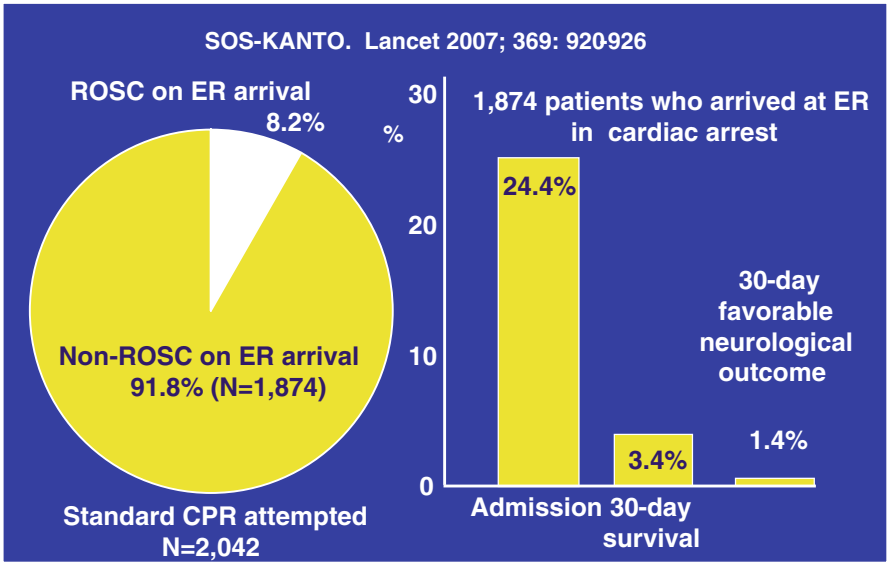

Fig. 60.2 Outcomes for adult patients who arrived at ER in cardiac arrest and were treated with standard CPR after out-of-hospital shockable cardiac arrest due to cardiac etiology

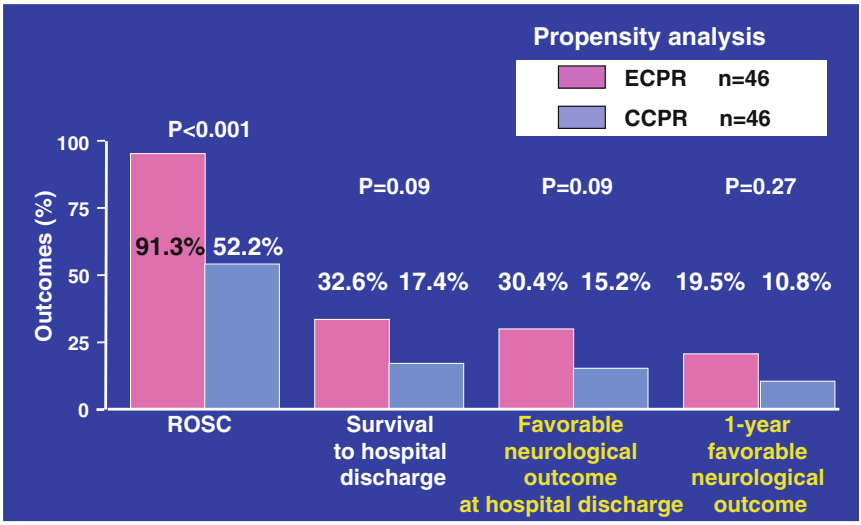

Fig. 60.3 ECPR vs. conventional CPR in adults with in-hospital cardiac arrest: an observational study and propensity analysis (Chen et al. [6])

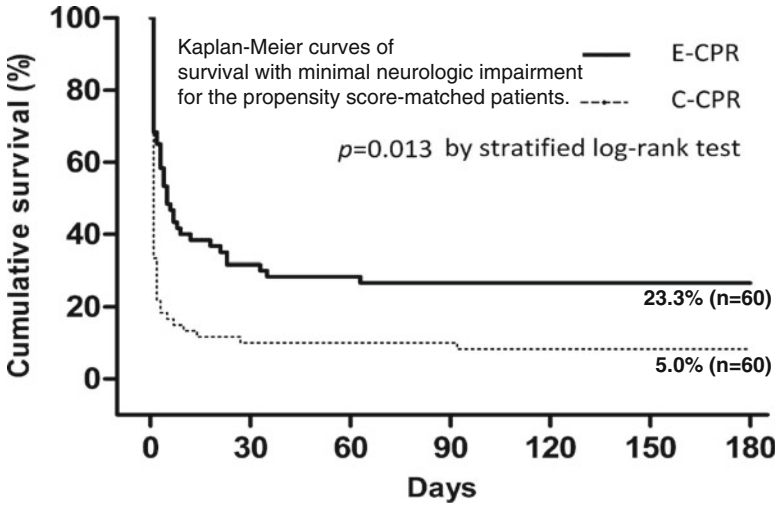

Fig. 60.4 ECPR in patients with in-hospital cardiac arrest: a comparison with conventional CPR (Shin et al. [8])

when the CPR duration was shorter than 95 min [6]. Shin et al. showed that ECPR with normothermia produced a high achievement of 3-month neurologically intact survival over standard CPR when the CPR duration was shorter than 60 min (Fig. 60.4) [8]. These findings suggest that it is necessary to initiate ECPR with normothermia within 60 min of in-hospital cardiac arrest.

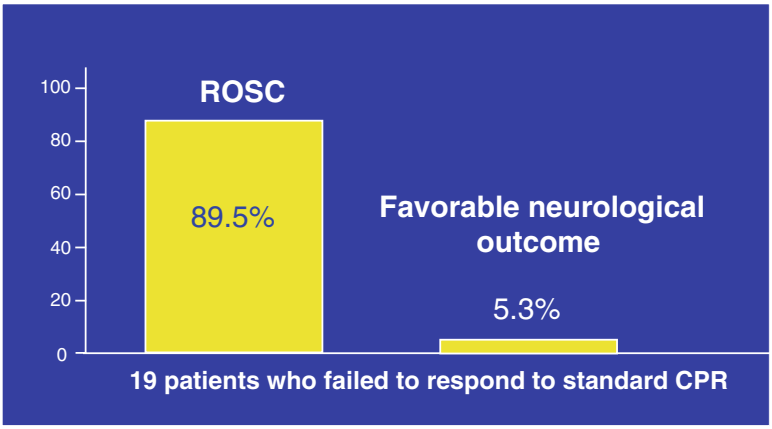

Fig. 60.5 Favorable neurological outcome for adults who arrived at ER in cardiac arrest and were treated with ECPR with normothermia after out-of-hospital shockable cardiac arrest due to cardiac etiology (Nagao et al. [18])

60.3.3 ECPR Without Therapeutic Hypothermia for Adult Patients with Out-of-Hospital Cardiac Arrest

Figure 60.5 shows our first ECPR study with normothermia, including percutaneous coronary intervention (PCI), for adult patients who arrived at the emergency room in cardiac arrest and failed to respond to standard CPR after out-of-hospital shockable cardiac arrest due to acute myocardial infarction [18]. ECPR with normothermia increased the frequency of favorable neurological outcome when compared to standard CPR alone (Fig. 60.2), but neurological benefit was still insufficient.

60.3.4 ECPR with Therapeutic Hypothermia for Adult Patients with Out-of-Hospital Cardiac Arrest

Since 1996, we have performed ECPR with therapeutic hypothermia. Our second study showed that ECPR with therapeutic hypothermia after achievement of ROSC (post-ROSC cooling) may improve the chance of favorable neurological outcome, with a low risk of complications [19]. Animal studies have shown that the induction of hypothermia during cardiac arrest (intra-arrest cooling) provided neurological benefits [20–22]. Therefore, we changed the timing of the initiation of cooling from post-ROSC cooling to intra-arrest cooling. Figure 60.6 showed our strategies of ECPR with therapeutic hypothermia including post-ROSC cooling and intra-arrest cooling [12].

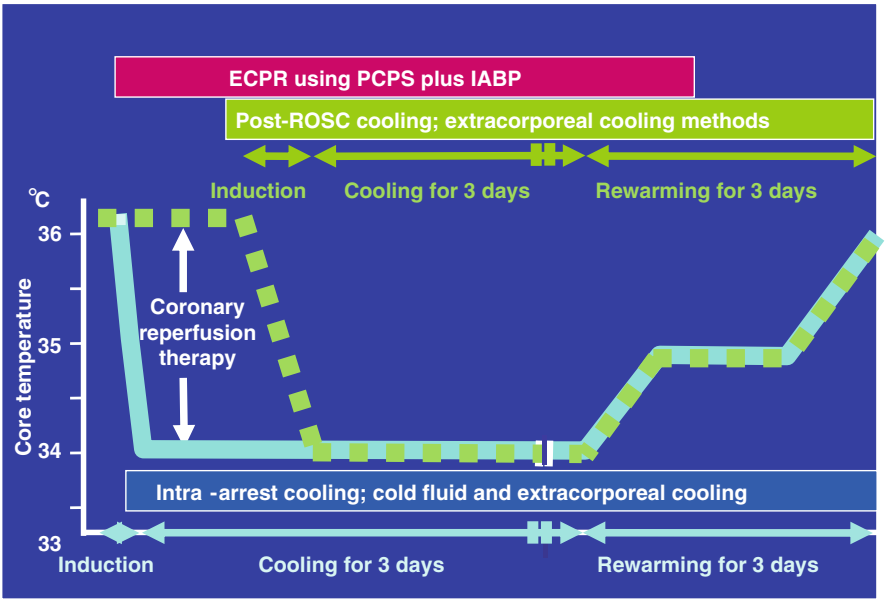

Fig. 60.6 Strategies of ECPR with hypothermia (Nagao et al. [12])

As reported previously [12], PCPS was primed with 600 ml lactated Ringer's solution with 2,000 U heparin. Flow of 100 % oxygen through the oxygenator was adjusted to keep $PaCO_2$ between 35 and 45 mmHg. The PCPS flow rate was kept at $\geq$70 ml · kg–1 · min–1 until ROSC or 3 h after the commencement of PCPS. After implementation of PCPS plus IABP, emergency coronary angiography was performed during cardiac arrest in cases of suspected acute coronary syndrome (ACS). Subsequently, coronary reperfusion therapy using PCI during ECPR was performed immediately if needed. When ROSC was achieved within 3 h of the commencement of PCPS, the PCPS flow rate was adjusted to maintain the mean arterial pressure between 90 and 120 mmHg and the pulmonary artery occlusive pressure between 15 and 20 mmHg. Regarding the intra-arrest cooling, cardiac arrest patients were cooled to the target temperature of 34 °C using an internal cooling method with rapid intravenous infusion of 2 L of lactated Ringer's solution at 4 °C and PCPS primed with 600 ml of 4 °C lactated Ringer's solution. Until PCPS implementation, 2 L of cold lactated Ringer's solution was infused using high-pressure intravenous infusion bags. The goal of intra-arrest cooling was to reach the target temperature of 34 °C within 30 min of the implementation of PCPS. In comatose survivors who achieved ROSC within 3 h of the implementation of PCPS, the target temperature was maintained for 3 days using the extracorporeal cooling method.

Figures 60.7 and 60.8 show the outcomes of 171 adults treated with ECPR and therapeutic hypothermia plus PCI. The median time intervals between collapse and hospital arrival and between collapse and implementation of PCPS were 33 min and 65 min, respectively. The collapse-to-34 °C interval ranged from 67 to 329 min,

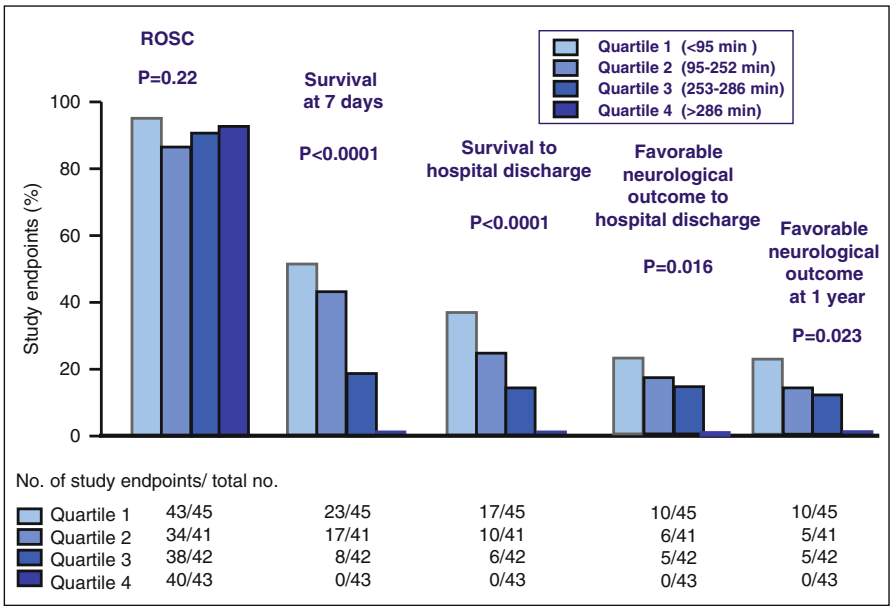

Fig. 60.7 Association between the quartiles of the collapse-to-34°C interval and the frequencies of study endpoints (Nagao et al. [12])

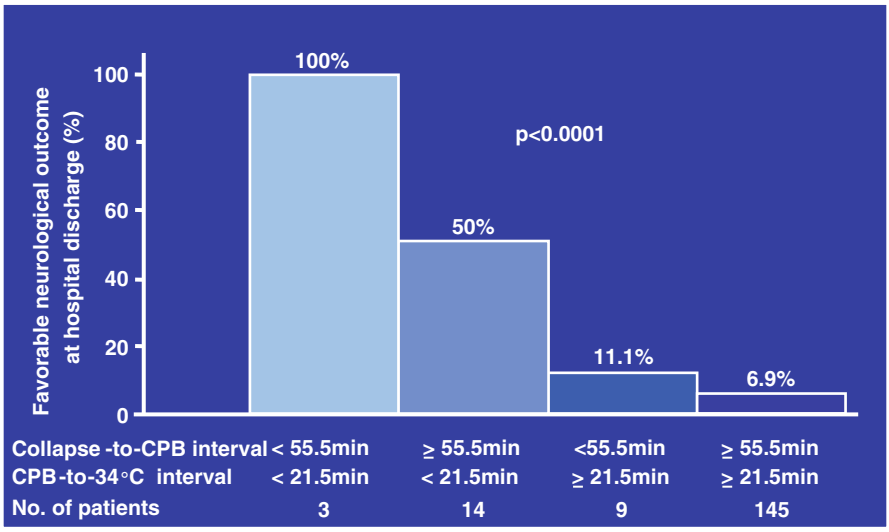

Fig. 60.8 Favorable neurological outcome among four subsets of patients who were classified by the two cutoff values (Nagao et al. [12])

with a median of 252 min, with 25th and 75th percentile values of 94 min and 286 min, respectively. Among the four groups divided by the quartiles of the collapse-to-34 °C interval, no significant difference was observed in the proportion of cardiac arrest caused by ACS (about 75 %), in the successful coronary reperfusion rate by PCI (about 90 %), in the ROSC rate (about 90 %), or in the CPB-to-ROSC interval (about 30 min). Frequencies of 7-day survival, survival to hospital discharge, favorable neurological outcome to hospital discharge, and favorable neurological outcome at 1 year decreased in a stepwise fashion with the increasing quartiles of the collapse-to-34 °C interval (Fig. 60.7). A significant difference was seen in favorable neurological outcome among the four subsets of patients who were classified by two cutoff values (collapse-to-PCPS interval and PCPS-to-34 °C interval). Very early attainment of a core temperature of 34 °C before ROSC and PCI during ECPR was likely to improve survival outcomes even if the patients received prolonged standard CPR (longer than 60 min) (Fig. 60.8).

However, the majority of patients who achieved ROSC by PCPS died of myocardial dysfunction during the cooling stage, which suggests that cardiac function during the cooling stage after ROSC was worse in our clinical study than in animal studies. Several reasons might account for the low neurologically intact survival rate. There was a significant difference in the cause of the cardiac arrest between our study and animal studies. In our study, ACS accounted for approximately 80 % of cases of cardiac arrest, although coronary reperfusion therapy using PCI during cardiac arrest successfully restored antegrade coronary flow (TIMI flow grade 3) in 88 % of the patients and the unadjusted rate of favorable neurological outcome at hospital discharge decreased in a stepwise fashion with the increasing quartiles of the collapse-to-34 °C interval in the subgroup of patients who achieved TIMI flow grade 3 after PCI. Knafelj et al. reported that early PCI with post-ROSC cooling was superior to early PCI without hypothermia in comatose survivors after cardiac arrest due to ST-elevation myocardial infarction (STEMI), in terms of survival benefit (55 % in the cooling group vs. 16 % in the non-cooling group, $p = 0.001$) [23]. Kagawa et al. reported that rapid-response PCPS plus intra-arrest PCI is feasible and associated with improved outcomes in patients who are unresponsive to standard CPR after out-of-hospital cardiac arrest due to acute coronary syndrome [11]. Yellon et al. reported a review article on the myocardial reperfusion injury [24]. After onset of STEMI, early and successful myocardial reperfusion using thrombolytic therapy or primary PCI is the most effective strategy for reducing myocardial infarct size and improving the clinical outcome. However, the process of restoring blood flow to the ischemic myocardium can induce injury. The myocardial reperfusion injury can paradoxically reduce the beneficial effects of myocardial reperfusion. The injury to the heart during myocardial reperfusion causes four types of cardiac dysfunction: (1) myocardial stunning, (2) no-reflow phenomenon or microvascular dysfunction, (3) reperfusion arrhythmia, and (4) lethal reperfusion injury. Lethal reperfusion injury is defined as cardiomyocyte death mediated by reperfusion after ischemic myocardium. The prevention of lethal reperfusion injury with a cardioprotective intervention at the beginning of myocardial reperfusion can reduce infarct size by a further 25 %, realizing the full benefits of reperfusion. The targets for cardioprotection include the treatment of

oxygen paradox, calcium paradox, pH paradox, inflammation, metabolic modulation, mitochondrial permeability transition pore and apoptosis, magnesium therapy, and therapeutic hypothermia. These findings suggest that early induction of hypothermia and PCI protects the myocardium for patients with post-cardiac arrest syndrome complicating ACS. Therefore, the strategy of ECPR with intra-arrest cooling plus PCI produces neurological benefits while protecting the myocardium.

60.4 Ethical Issue of ECPR

An ethical issue surrounding ECPR is the cessation of PCPS, which is an emotionally complex decision for family and staff. I consider the following four factors to be associated with an irreparable state: asystole, apnea, absence of papillary response to light, and papillary dilatation. When these factors continued for 3 h after commencement of PCPS or appeared as a result of aggravation after admission to hospital, we asked the family for informed consent to cease PCPS. Most of the families agreed, but in most cases it took almost 3 days after commencement of PCPS [12].

60.5 Conclusion

Figure 60.9 shows my view of ECPR with intra-arrest cooling plus PCI [25].

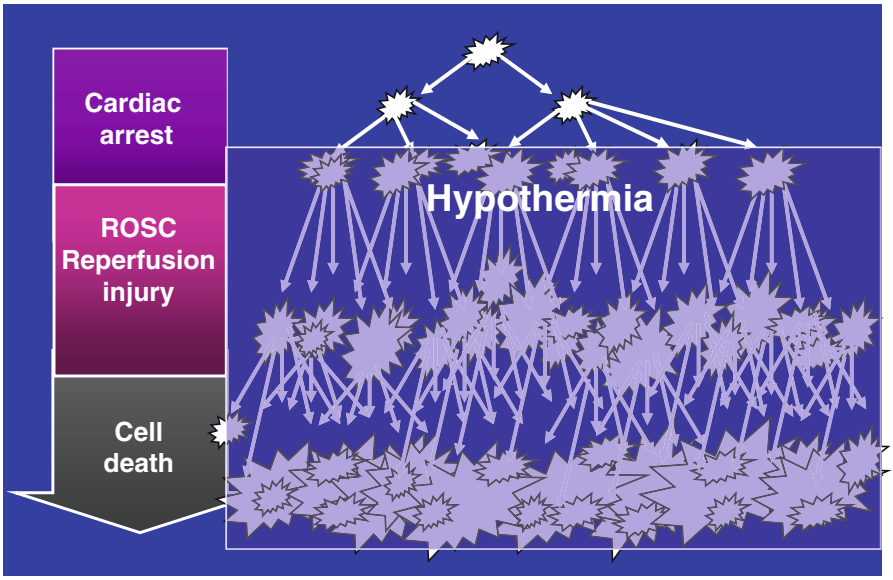

Fig. 60.9 The effect of intra-arrest cooling (Nagao [25])

Early implementation of PCPS with intra-arrest cooling plus intra-arrest PCI is likely to protect any cells from ischemic/hypoxemic/reperfusion injury and enhance neurological benefits for adults in cardiac arrest refractory to standard CPR attempts.

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Chapter 61
Brain Death and Organ Donation

Kuniyoshi Kumaido, Satoru Sugiyama, and Haruhiko Tsutsumi

Abstract Human death is used to be defined as the cessation of heart function. However, since the renal transplantation animal experiments of Ullmann in 1902, the development of new technologies and therapeutic procedures for organ dysfunction and failure has led to improvements in organ transplant treatment. The widespread use of internal organ transplantation requires a lot of donors. Accordingly, brain death was introduced as a novel definition of death. There are two commonly used definitions of brain death: whole-brain death and brain stem death. In Japan, brain death is only used as a definition of death when the subject is a potential organ transplant donor. In such cases, whole-brain death is employed as the criterion for death. There has been no increase in the number of organ transplant donors in Japan since the Organ Transplant Act was revised. The development of alternative sources of transplant organs should be examined in future studies.

Keyword Brain death • Brain stem death • Organ transplant • The Istanbul Declaration • The revised Organ Transplant Act

61.1 Introduction

Since the second half of the twentieth century, medical technology has progressed rapidly, resulting in improvements in both diagnosis and treatment. As a result, it has become possible to cure people of conditions from which they previously would have died, including conditions in which the patient would have technically been considered dead according to traditional definitions. Accordingly, changes in the accepted definition of death have become necessary.

Even if some of a patient's internal organs have stopped functioning, their life can be maintained by substitute apparatus. Moreover, it has also become possible to transplant internal organs from healthy people, and the development of immunosuppressive agents has facilitated progress in this field. In such a situation, brain death is a more appropriate definition of death than heart stoppage. This section

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describes brain death and organ transplantation and focuses on the present state of these issues in Japan.

61.2 Brain Death vs. a Vegetative State

There is the clear difference between a vegetative state and brain death.

Brain death refers to a condition in which the functions of the entire brain, including the brain stem, are irreversibly lost due to primary brain damage, whereas a vegetative state is a condition in which all or some cerebral functions are lost and the patient is unconscious, but the function of the brain stem is maintained. Therefore, spontaneous respiration is maintained in many patients who are in a vegetative state. In addition, some patients who fall into a vegetative state subsequently recover; thus, a vegetative state is fundamentally different from brain death.

Brain death will only be declared if an organic injury with an attributable cause is observed in the brain and the following criteria are met:

1. Deep coma.
2. Dilated and fixed pupils.
3. Loss of brain stem reflexes.
4. Flat brain waves.
5. Loss of spontaneous respiration.
6. Two or more doctors with the requisite expertise and experience confirm that no changes were observed during a second examination conducted six or more hours after the initial examination
   (24 h or more for children between the ages of 12 weeks and 6 years).

Brain death cannot be declared in persons suffering from drug intoxication, low body temperature, or endocrine/metabolic diseases.

61.3 Views on Brain Death

Brain death means that a person is considered dead when his or her brain is dead, and this is recognized as a definition of death throughout the world. The recognition of brain death as a definition of death is particularly important for organ transplantation. Therefore, the recent promotion of organ transplantation in Japan has made it necessary for brain death to become nationally accepted as the definition of death.

Artificial respiration can be maintained with mechanical ventilators after respiratory function has arrested, and the use of such ventilators is widespread in medical practice. In other words, vital functions can be maintained artificially after brain function has failed.

61.4 History of the Establishment of the Concept of Brain Death

In 1959, Mollaret and Goulon introduced the term "coma depasse," which refers to an irreversible coma [1]. They described 23 cases of coma depasse, in which the patients lost consciousness, brain stem reflexes, and respiratory function and exhibited flat electroencephalograms (EEGs).

In 1967, when Christiaan Barnard carried out the first human heart transplants in Cape Town, there were no guidelines for the diagnosis of death in beating heart donors [2].

In 1968, the Ad Hoc Committee of Harvard Medical School produced the first definition of brain death, which suggested that irreversible coma should be used as a criterion for death [3]. According to the latter report, the presence of 3 of the following criteria is sufficient for diagnosing irreversible comas, and isoelectric EEGs (obtained at 5 μV/mm) are of great confirmatory value and should be used where possible:

1. Unreceptivity and unresponsitivity
2. No movement (observe for 1 h)
3. Apnea (3 min off respirator)
4. Absence of elicitable reflexes

In addition, it was stated that the above tests should be repeated at least 24 h after the initial tests and that no changes should be observed during the second set of tests.

In the USA, improved guidelines for the determination of death were subsequently reported [4, 5].

On the other hand, EEG is not necessary for diagnosing brain death in the UK, where the presence/absence of brain stem function is considered to be the most important issue.

In 1971, Mohandas and Chou claimed that damage to the brain stem is necessary for severe brain damage to lead to a profound irreversible coma [6]. In 1976, the UK Conference of Royal Colleges and their faculties accepted this and defined brain death as the complete and irreversible loss of brain stem function [7]. In 1983, Christopher Pallis examined brain stem death in detail [8, 9].

61.5 Brain Death in Japan

Japanese people commonly view human death as the cessation of heart function, which requires the confirmation of three signs: (1) cessation of the individual's heartbeat, (2) cessation of spontaneous respiration, and (3) loss of the light reflex/dilated pupils. In addition, because of the unique views of the Japanese people

toward life, death, ethics, and religion, they often find it difficult to equate brain death with death. However, this is gradually changing.

In Japan, the 1997 Act on Organ Transplantation legalized the use of brain death as a determinant of death in cases in which organs are to be procured from a brain dead patient. It had previously been considered that organ transplantation would never become as common in Japan as it is in other developed countries due to the views of the Japanese people about death. The abovementioned law was the first in Japan to have accepted that brain death could be used as a criterion for determining death in addition to the cessation of cardiac function. However, as mentioned above, it only allowed brain death to be used as a definition of death in cases involving organ transplantation.

61.6 Criteria Used to Define Brain Death Around the World [10–12]

However, brain death is accepted as a definition of death in most countries. According to the World Health Organization (WHO), only a few countries such as Pakistan and Romania do not recognize brain death as human death. On the other hand, the criteria for diagnosing brain death differ in each country. For example, in the USA, brain death is considered to be the absence of brain function, whereas in the UK, brain death is judged to be a brain dysfunction involving the cessation of brain stem function. On the other hand, Japan has decided that brain death can only be used as a definition of death when all brain function has been lost and an organ transplant is to be performed.

61.7 Act on Organ Transplantation and the Revised Organ Transplant Act

Organ transplants from brain dead patients seem to be most common in the USA and Canada. As for European countries, according to reports in the Japanese media, organ transplants are most common in Germany.

In Japan, the Organ Transplant Act did not permit children to be organ donors. The act states the following:

A: The donation of organs by a brain dead donor is permitted only if ". . .the donor expressed in writing prior to death his/her intent to agree to donate his/her organs and agrees to be subject to an authorized brain death declaration, and his/her family members (spouse, parents, children, grandparents, grandchildren, and live-in family members) do not object to the donation."

B: "Only persons aged 15 years and above can express the intent to donate."

This stipulation has greatly reduced the possibility of small children receiving organ transplants, and heart transplants to small children have become impossible.

Therefore, Japanese pediatric organ donor recipients had to travel abroad for transplants. The frequency of such cases increased after the implementation of the act, which became a social issue.

The Transplantation Society (TTS) released the Istanbul Declaration in 2008. This declaration announced that each country should strive to provide organs to meet the transplant needs of its residents from donors within its own population or through regional cooperation. In 2010, the WHO adopted new organ transplant guidelines based on the above declaration [13].

Under this international situation, a revision to the act that allowed pediatric organ transplants became inevitable. In addition, there was no marked increase in the number of organ transplantations from brain dead patients after the act was enforced, which further increased the need for a revision of the act.

In 2009, the issue was discussed in the Diet (the Japanese parliament), and a bill to revise the Organ Transplant Act was passed and promulgated on July 17. On July 17 of the following year, the revised act came into force [14]. The rule change meant that even if an individual's intention was unclear, it was possible to obtain his/her organs for transplant with the consent of their family. In addition, it allowed the donation of organs after brain death by children under the age of 15.

The following amendments were made to the act:

1. The revised act made it possible to designate family members as priority organ recipients subject to certain requirements.
2. In addition, organ donations became possible regardless of whether the donor's intention had been clearly stated, provided their family gave their consent. This change allowed children under the age of 15 to be eligible donors following brain death.

After the revised law was enacted, reports of organ transplants after brain death appeared in the mass media almost every week.

In addition, a rapid increase in the number of transplantations performed in Japan was expected. In fact, the total number of organ transplants has not changed much since the revision.

One reason for this is the fact that some brain dead donors would also have been eligible for organ donation as heart dead donors (Fig. 61.1) [15].

In Japan, the use of brain death criteria as determinants of death is still exclusively limited to organ donors, and the default definition of death continues to be based on cardiopulmonary criteria.

Thus, it seems that only limited increases in the frequency of organ transplants can be achieved under the present circumstances.

In order to promote organ transplantation in Japan, it is necessary to change not only the clinical environment surrounding organ transplants but also the views of the Japanese people regarding organ transplantation.

In addition, the current lack of organs for transplant from organ donors necessitates the use of other approaches to solve this problem. Regenerative medicine

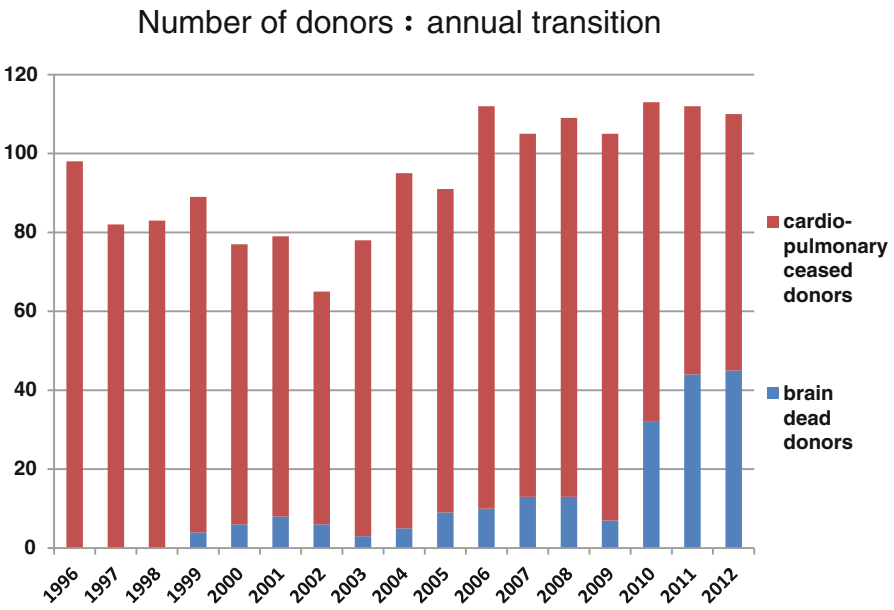

Fig. 61.1 Number of donors: annual transition

techniques have developed rapidly, and it is expected that induced pluripotent stem cells will soon be put to clinical use. In the future, it might be possible to produce all organs via regenerative medicine, which would solve the current organ shortage.

In Japan, there is a need to create an environment that facilitates the rapid advancement of medical techniques, including regenerative medicine techniques, which are expected to be more socially acceptable than organ harvesting.

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