

Predictably, respiratory events and inadequate oxygenation and ventilation were more common in these remote location claims than in OR claims.² These findings suggest that patients are at a higher risk of adverse events when undergoing anesthesia for procedures in remote locations. These data underscore the need for conscientious preparation and greater vigilance when caring for patients in these environments. The goal of anesthesia providers must be to mitigate systemic factors that contribute to the excess hazard in these environments.

The purpose of this chapter is twofold: first, to highlight the inherent, common, as well as the unique characteristics of NORA cases that impose unusual challenges for anesthesiologists providing care outside of the OR; and second, to describe the goals, methodologies, and pitfalls of interventions in these environments that might be unfamiliar to some anesthesiologists. This chapter does not reiterate basic principles of anesthesiology practice described elsewhere in the text, nor does it describe the technical details of novel procedures. Instead, it serves as a general guide to the NORA environment and procedures performed outside of the OR and delineates some of the critical issues faced by anesthesiologists. The intention is to promote awareness that encourages preemptive planning, and equips anesthesia providers with a vocabulary with which to establish effective dialogue to cultivate a collaborative practice with colleagues and to maximize the safety of patients.

NOVEL CHARACTERISTICS OF NORA CASES

NORA cases are characterized by three distinctive features: location, operator, and relative novelty. First, the procedure does not take place in a standard operating suite and is typically remote to the main OR section. Second, the operator performing the procedure is generally a medical interventionist rather than a surgeon. Finally, the procedures and technologies used are constantly evolving. Innovative applications of these procedures and technologies pose a challenge for a number of reasons as well. With advances in technology and expertise of the operators performing procedures outside of the OR, the procedures can be performed on patients with complex comorbidities and often on patients who are not candidates for a traditional surgical procedure or for whom surgery is no longer the only therapeutic option. For example, carotid artery stenosis can be treated in the OR, the catheterization laboratory, or the interventional radiology (IR) suite. The ultimate choice of venue may be a function of acuity of presentation but often depends on the referral—who the patient sees first, and who is available. As important, for many patients undergoing a NORA procedure, the scheduling is urgent, emergent, or unknown to the anesthesia provider until immediately before the procedure is to be performed, preventing an adequate periprocedural evaluation. These ever-expanding clinical services requiring anesthesia services outside of the OR provide an opportunity for anesthesiologists to reevaluate and reaffirm the importance of a preoperative assessment, as well as periprocedural and postprocedural needs, for this diverse group of patients. As a result, the perimeter of our landscape has expanded beyond the familiar domain of the OR and requires collaboration with a broad array of medical practitioners including interventional cardiologists,

interventional radiologists, gastroenterologists, radiation oncologists, and electrophysiologists. Given the physical, medical, political, and economic challenges that may arise and that are often unanticipated, the goal must be to adapt to the new environments. We must also strive to evolve our anesthesia practice to meet the demands of a changing patient population.

UNIQUE OBSTACLES: FROM PHYSICAL ENVIRONMENT TO THE MEDICINE-ANESTHESIOLOGY CULTURE GAP

When anesthesiologists are faced with the need to provide services for non-surgeons in non-OR locations, issues such as scheduling inconsistencies, ad hoc requests, and resource limitations can be difficult to resolve, particularly if the usual scheduling process is not available. In addition, the increasing incidence of medically complex cases with patients needing urgent intervention, but lacking periprocedural evaluation, can create challenges. The two most common challenges are poor communication between providers exacerbated by the medicine-anesthesiology culture gap and, for many of the NORA procedures, inadequate physical space to accommodate the needs of a patient requiring anesthesia services.

Procedural suites are often remotely located. This increases the time lag between a request for assistance and the arrival of help, both with technological and medical problems. In addition, the lack of nearby supplies may exacerbate the timely resolution of common electrical and mechanical malfunctions or complicate the resolution of a medical emergency. This situation demands that care be taken before the start of the procedure to ensure that equipment is supplied and working and that backup options (emergency supplies, difficult airway equipment) are functioning and readily available.

In addition, non-OR procedure suites are frequently organized from the perspective of the proceduralist, and unfortunately, the needs of anesthesiologists are often overlooked. For example, procedure suites that use fluoroscopy for guidance are often configured so that the C-arm limits access to the patient's head and obstructs direct communication between the anesthesiologist and the proceduralist. Inadequate access to the patient may be exacerbated if the area around the head of the patient is crowded due to constraints of the room and equipment. Lack of visibility of procedural screens may also make it difficult to follow the progress of the intervention without compromising the attention to the patient. Perhaps most important, hemodynamic monitors may be difficult to visualize by the anesthesiologist or, for some procedures, may not function properly because of interference with mapping systems or other electronic interfaces. Lead protective screens may not be available, and when they are available and positioned to protect the anesthesiologist from radiation, pumps and intravenous lines may become inaccessible. Gas scavenging may be unavailable, and oxygen and suction outlets may be suboptimally placed. For these and other reasons, anesthesiologists should be mindful of how best to orient both the patient and providers spatially within a procedure room, particularly if the setup of the room is unfamiliar. Distraction of focus away from patient care due to an unfamiliar

environment can be potentially disastrous in the face of a novel or complex procedure.

The ASA has formulated a statement regarding NORA locations that articulates minimum standards for all procedures performed in these areas,³ but these standards are quite fundamental. Recognition of the constraints of the environment and anticipatory planning allow for the safe administration of anesthesia within this environment. The challenge is communicating the importance of these issues to the proceduralist and others involved in the care of the patient as well as hospital leadership to ensure that the needs of all parties are met. With newer procedures requiring anesthesia services in nontraditional environments, there may be a need to implement significant environmental changes to optimize the ability of anesthesiologists to deliver safe care.

Communication with the medical proceduralist is key to providing an optimal anesthetic; taking time to discuss the procedure and the patient allows for thoughtful consideration of anesthetic options in the context of both the principles of the procedure and the physiology of the patient. However, mismatches in culture can dominate interactions between medical practitioners and anesthesiologists and undermine communication. These conversations can be challenging since, unlike surgeons, medical providers may be unfamiliar with the skill sets of anesthesiologists and the needs for patient care or unaware of the intricacies associated with administering an anesthetic. For example, while surgeons are accustomed to sharing their procedures with other medical practitioners, proceduralists may be habituated to working alone and ordering sedation to be administered by a nurse. Medical interventionists may also lack experience with relatively rare but serious complications that might arise during the procedure, such as loss of airway. In addition, proceduralists are frequently consultants who are enlisted by primary care providers to perform procedures, but who may not have received all relevant information that may be needed for a patient requiring anesthesia services. Even when all information is provided, specialization predisposes the proceduralists to concentrate on their point of expertise, so many of the concerns of the anesthesiologists are not taken into account.

Similar issues regarding the needs of the patient and the proceduralist may not be taken into account by the anesthesiologist who is unfamiliar with the procedure. In many cases, the anesthesiologist may have only a basic understanding about what is happening during the course of a noninvasive procedure and may not have asked enough questions about the plans, especially when they are new to a particular venue, the procedure is not observable, and fluoroscopy screens are out of the field of view or uninterpretable. Anesthesiologists may be unaware of pitfalls and likely complications of the procedure even though in the OR, they normally would not administer an anesthetic without understanding the idiosyncrasies of the surgery. These issues are important in planning for the anesthesia and procedure but are equally important during the procedure. Extra initiative is often required by the anesthesiologist since the proceduralist may not communicate the course of the procedure during the case. Other aspects of the procedure, such as how coughing on extubation might predispose patients who have had groin sheaths to serious

hematomas, may not have been emphasized by the procedural team or likewise appreciated by anesthesiologists. Bridging the communication gap requires effort, but it is absolutely critical to optimizing outcomes.

When interventionalists undertake novel procedures using new technologies, the situation can become even more challenging. The course of the procedure may be unknown, the timing and sequence of events may be ill-defined, and the focus of the procedure may change mid-stream. At times, the proceduralist may be unsure of what is happening. In these situations, extensive preplanning, a commitment to communication, and the explication of goals for all involved in the care of the patient is crucial to the success of the procedure and, more importantly, the safety of the patient.

As medical procedures, particularly those performed outside of the OR environment, become even more technically demanding and patient clinical conditions more complex, the best possible patient management strategies will arise from collaboration and teamwork between medical proceduralists and anesthesiologists. This requires mutual respect, excellent communication, common vocabulary, shared experience, and overlapping competencies. In pursuit of this goal, we can build on the outstanding record of improved patient safety and outcomes that characterizes the history of anesthesiology.

FINANCIAL AND OPERATIONAL CONSTRAINTS

The impact of performing procedures in new environments has significant financial and operational implications that must be addressed. In the desire and enthusiasm to advance clinical care and extend care to settings outside of the operating room, medical, financial, and operational implications often become blurred. As a result, it is important to understand the difference between what does and what should drive the direction of new program development related to NORA procedures and for all parties to address the specific operational needs while taking into account the financial implications of transitioning care to these alternative settings.

EFFECTS OF PAYMENT SYSTEMS

A variety of payment methodologies are used to compensate providers and facilities for clinical services. While government payment methods remain important, private insurance has become the financial underpinning of the healthcare system in the United States—often allowing hospitals and providers to advance new technologies and innovative care that would otherwise be financially impossible. Private health insurance evolved as hospitals transitioned from repositories for the impoverished and dying into institutions where people actually recovered from illness. Hospitalization plans, initially developed by hospitals in the 1930s, were a way to supplement the economic resources needed for growth and expansion. At that time, hospitals often functioned as extensions of private offices and payment was, and continues to be, a fee-for-service system. As health care has become more expensive and the clinical options have expanded, both the public and private systems have had to adapt, becoming more complex and sophisticated—with

the goal to minimize payment to those practices that have documented, evidence-based outcomes. These changes, and the goal to reduce costs of care, have both encouraged care outside of traditional and expensive environments, such as the OR, but also challenged providers to prove that the care remains safe and of high quality. These conflicting goals make expansion of care to non-OR locations challenging and, in some cases, undermine attempts to innovate.

Medical optimization and financial efficiency are predictably not the end products of fee-for-service payments. With increasing demand for clinical services, the need to reduce costs, hospital length of stay, and readmissions is critical. As the population ages, care is increasingly specialized and complex. The Medicare Payment Advisory Commission (MedPAC) reported that as of 2006, the average Medicare beneficiary saw five doctors per year and Medicare beneficiaries with three or more chronic conditions saw more than 10 physicians a year.⁴ With advances in care, transitions of some procedures from the OR to new settings, and care provided by a “new” group of providers that previously did not perform procedures (cardiologists, neurologists, and others), more providers participate in the care of patients. The implications of these changes are numerous. For example, for patients whose care involved four or more doctors, MedPAC reported that 48% experienced medical errors, medication errors, or laboratory errors. As technology advances and the population ages, risks and benefits change and new genres of service emerge and expand. Imaging services, which have exploded across disciplines in the last decade, are now provided by radiologists, vascular surgeons, cardiologists, internists, anesthesiologists, and surgical subspecialists.⁵ Traditional fee-for-service payment systems are not designed to ensure that the right treatment is performed on the right patient at the right time by the right physician in the right venue. The result is that groups of assorted medical proceduralists provide in-hospital care that is often fragmented, perpetuated by silos of specialized care despite the interdependent nature of specialty services. Coordination of care, particularly for the newer procedures requiring anesthesia services and performed outside of the OR, is needed but often not provided for a variety of reasons. Unfamiliarity with anesthesia services and requirements as well as lack of payment for coordination of care are primary reasons. This uncoordinated or fragmented care creates challenges for the patient and provider, often resulting in duplication of some service, variability of resource use, and inconsistent application of quality standards. Payment silos create misalignment of goals across specialties, creating competition rather than collaboration among disciplines and, in some cases, pitting the needs of one set of providers against another without intending to do so.

Another factor that contributes to the challenges associated with performing procedures requiring anesthesia care in NORA environments is the lag in payment for new technologies by Medicare and other payors. While delaying implementation of new procedures into the clinical environment until peer-reviewed evidence documents the value may be appropriate, particularly when new and/or proprietary, high-cost equipment is required, the lack of payment may actually contribute to higher costs of care or reduced quality.

Anesthesiologists are particularly vulnerable to inadequate or no compensation for some of the procedures performed outside of the OR. In some cases, the lack of payment is related to “historical controls”—healthier patients undergoing procedures outside of the OR with sedation provided by a nurse or proceduralist. The anesthesia service is only compensated when the patient meets criteria for “medical necessity”—and there may be inadequate documentation of the need for anesthesia care by the proceduralist. As important, for some patients there are associated services for which there may be no compensation. Routine preprocedure evaluation and postprocedure care are included in the anesthesia fee; other services often needed to optimize clinical management so the patient is able to undergo the procedure may not be compensated. Discussion of some of these issues related to payment for anesthesia services for the NORA procedures is ongoing at a national level.⁶

Some newer payment methods may help address the challenges of providing anesthesia services for procedures performed outside of the OR. Bundled payment methodologies, accountable care organizations, and the perioperative surgical home are three payment reforms intended to improve coordination and interdisciplinary collaboration. While these models of payment may effectively improve delivery of care in the most appropriate environment with improved outcomes, it remains to be seen how effective these undertakings will be in improving care. In any case, payment models remain a key determinant of behavior. It is incumbent on anesthesiologists to remain at the forefront of new developments as demand for anesthesia services in less traditional arenas broadens in an environment that diminishes control over the revenues we generate.

OPERATIONAL CONSTRAINTS

It is quite clear that despite a multitude of publications documenting significant OR inefficiency, institutional tradition, provider idiosyncrasy, and surgical convenience continue to compromise efficient OR scheduling practices and policies. Outside of the OR, these issues have even greater significance. Medical proceduralists and surgeons performing procedures in unfamiliar environments often do not understand the physical limitations that affect anesthesia care and the need for appropriate preprocedure evaluation and management, and in many cases are not aware of some of the underlying clinical conditions of the referred patient. To make matters worse, the specific procedure(s) to be performed on the patient may not be well-defined until the procedure begins while in other cases the procedure is “novel,” often involving equipment and supplies unfamiliar to the proceduralist or assisting staff. All of these variables make scheduling non-OR cases extremely difficult.

With respect to scheduling and staffing non-OR cases, a number of issues must be considered, including:

1. Non-OR anesthetizing locations are often adapted to the specific procedure being undertaken and the needs of the medical proceduralist. Unlike ORs, they are non-interchangeable. They are often neither designed for nor take the needs of the anesthesia provider into account.
2. Most of the venues for these procedures are smaller and less flexible than traditional OR environments.

3. Block time may not be utilized to facilitate scheduling of NORA cases, making it difficult to utilize anesthesiology staff productively and increasing the likelihood of underutilized personnel and space.
4. Non-OR procedures may take place a long distance from the OR suite. Lack of storage space for anesthesia equipment may also impose longer turnover time and the need for additional anesthesia technical services.
5. Many non-OR procedure suites perform procedures on patients referred from outside providers or services that are booked through a central scheduling office. For most of these patients, the usual preprocedure evaluation process is not used to facilitate assessment and preparation of the patient. Periprocedural evaluations are often very cursory—if performed at all. This imposes an additional bottleneck for the anesthesiologist who may need to perform a preoperative evaluation immediately before the procedure and cancel or delay cases at the last minute.
6. Because many non-OR procedures are novel, it is difficult to estimate the length of time the procedure will take. Booking times may be unrealistic, and scheduling anesthesiology time may be difficult. Additionally, with new technology and noninvasive methods, it is very easy for the proceduralist to modify or extend the procedure after it is started.⁷

As noted, non-OR cases tend to be more variable, less predictable, and, therefore, more difficult to staff cost-effectively. Some of these difficulties are technical, but some are the result of cultural discontinuity and poor communication between anesthesiologists and proceduralists. To ensure effective management for these cases, a number of requirements should be met:

1. Prospectively establish a contract between the anesthesiology and procedural departments that encourages appropriate utilization of available time and minimization of differences between “staffed (contracted) time” and “productive time.” In addition, in those environments where NORA cases cannot or are not scheduled efficiently, the department may need to define a “back-stop” to compensate the anesthesia providers for “availability” time that is not associated with a specific case.
2. All non-OR cases should be scheduled and managed within the electronic database for OR cases, so that resource deployment can be planned and modified as needed.
3. Create a block schedule that takes into account all of the procedural areas and the most effective utilization of the space. The block time should account for the needs of all providers. For example, if cases in some areas tend to run late, anesthesia providers should be scheduled appropriately to reflect the actual times for the cases to be completed.
4. Implement real-time scheduling, including patient arrival times and other issues affecting utilization. Calculate earliest start times, optimal arrival times, and adjusted preoperative fasting (nothing by mouth [NPO]) guidelines for all patients. Avoid having patients sitting in preoperative holding areas for extended periods and account for postprocedure evaluation and monitoring needs wherever recovery of the patient is provided.

5. Improve specialized triage for scheduled outpatients in each procedural area to ensure that patients are appropriately evaluated and prepared for the anticipated procedure. The use of triage forms and staffing intake procedures, either locally within each environment or centrally, will minimize delays and cancellations. Ensure that the proceduralist is invested in the preprocedure process and supports the needs of the patient and anesthesia providers.
6. Oversight of periprocedural triage and postprocedure recovery areas should be provided by the anesthesia department to ensure that the appropriate preprocedure assessment has been completed and, when necessary, that additional preprocedure optimization is required. As part of the oversight process, tracking of unexpected admissions, prolonged recovery times, throughput, efficiency, length of stay, and medical outcomes should be performed and reviewed with all providers.

The scheduling of space, staff, and resources for NORA procedures should be standardized within the institution but can be performed in a number of ways. In general, the principles that apply in the OR should also be used for cases performed outside of the OR. These principles include reducing variability, scheduling to minimize variability as much as possible, and using actual institutional data to guide decision making whenever possible (i.e., real-time scheduling for blocks). In addition, the scheduling should take into account available time and actual productive time. Full schedules and adequate revenue collection should be incentivized; otherwise a subsidy of the anesthesia department is needed because the opportunity cost incurred is often significant. In situations where specific contracts for NORA cases are negotiated, the contracts should take into account full costs and not differentiate costs associated with specific procedures individually. Whenever possible, proceduralists should be involved in scheduling schemes so they are invested in the process. When the institution has specific, predefined areas in which these procedures will be performed, identifying a dedicated anesthesia team, as is done for selected OR service lines, should be considered. Identifying a dedicated team that understands the specific issues in each NORA environment and collaborates with the proceduralists, nurses, and others can greatly improve operational issues, patient and provider satisfaction, and clinical outcomes.

Transitional Priorities for Anesthesiologists Outside of the Operating Room

As more and more procedures are performed outside of the traditional OR environment, we can anticipate that there will be many new opportunities as well as obstacles to overcome. While many have already been articulated, new venues must take the same approach as has been taken so far to best meet patient and provider needs. Unusual procedural venues and practitioners who are unfamiliar with the scope and practice of anesthesiology challenge standard procedure. Adaptation requires that we confront, explain,

reorient, and reinforce our traditional concepts of safe practice and standards of care. Anesthesiology as a specialty has improved OR safety enormously in the past 45 years, and as the scope of anesthesiology broadens, there is even more reason to redefine and remain steadfast in utilizing the same well-established standards of safe practice in new environments.

DEFINING INTERDISCIPLINARY SAFETY IN NON-OPERATING ROOM LOCATIONS: STANDARDIZATION, RELIABILITY, AND COMMUNICATION

The unparalleled record of OR safety established by surgeons and anesthesiologists has been dependent on implementation of standardized, routinized practice. Anesthesiologists depend on the predictable characteristics of ORs and surgical procedures to gauge the process of procedures and optimize anesthetic outcomes. While unplanned challenges arise even in the most standardized environment, a dedicated team with an understanding of the expected (and unexpected) events is best able to tailor care to meet the needs of the patient and providers. For non-OR cases, many of the standards are not predefined and the procedures often are not yet considered routine. In some cases, the technology is novel and, for some patients, preprocedure optimization is not ensured. For many procedures, anesthesia is required because of the inherent challenges and inability to predict clinical responses and needs. In each of these situations, communication at every step in the process is critical to optimizing patient care and outcomes. If communication is poor between proceduralist and anesthesiologist, the potential for error and a less-than-optimal outcome increases.

Frankel⁸ and others have emphasized that environments that facilitate safety and reliability are characterized by the following:

1. Encouragement of continuous learning among all participants
2. A just and fair culture of accountability and responsibility
3. Support for teamwork
4. Data-based drive for safety and reliability
5. Effective communication and flow of information

Depending on the specific venue, routines can be defined for many NORA procedures—though for many NORA procedures, the routines may differ from those developed for specific OR procedures. Specialty-specific procedure units can accommodate each of the above with varying degrees of difficulty, depending on the medical, financial, and operational constraints and priorities in place. All of these elements are critical characteristics of a safe environment.

OTHER GENERAL CONSIDERATIONS FOR NORA CARE

A number of other processes are relevant to the practice of anesthesiology in general with some specific examples of their importance for anesthesia provided in settings outside of the OR environment. They include continuous learning,

accountability, teamwork, and communication, all of which are critical to improving systems to optimize care.

Continuous Learning

The concept of continuous learning as an element of process improvement was initiated for other industries⁹ but also applies to anesthesia practice and patient care. The principles associated with continuous learning have relevance to the delivery of anesthesia in environments outside of the OR suite, in large part because NORA services continue to expand and evolve. Lessons learned from current practices can be applied to new models of care delivery, while also implementing and evaluating the use of new technologies to expand anesthesia services to new patient populations and new locations. As clinical opportunities evolve and modifications are made to the delivery of anesthesia care, the use of objective data (where available) will be an essential element of the continuous learning process. Inherent to the concept of continuous learning is the need to evaluate clinical practices with input from all participants, including the patient, and to consider needs from a multidimensional perspective.

Culture of Accountability and Responsibility

As is true for all clinical environments of care, the anesthesiologist and all other providers must assume responsibility and accountability for patient safety and quality of care. An ongoing evaluation as to what is working and what is not—and an understanding of the reasons for adverse outcomes—is critical to process improvement. In some cases, individual actions may be responsible for an unanticipated event, though for many (if not most) adverse events, both individual and systems issues contribute. To successfully analyze adverse events and the contributing factors, formal root cause analyses (RCAs) with participation of all parties is most effective in defining how to avoid similar events in the future. This type of analysis can be very helpful in assessing the quality of care for patients undergoing anesthesia outside of the relatively controlled OR environment. The RCA process should be collaborative and non-punitive. If the actions of an individual need to be addressed, this process should be done using human resources or medical staff processes outside of the RCA process. We can learn how to initiate these reviews from other industries. For example, the launching and recovery of US Navy aircraft is a well-known process in which this type of outcome-focused, non-punitive review takes place.¹⁰

Support for Teamwork Structure

Support for a teamwork structure is a crucial foundation of successful interdisciplinary work. It requires that jobs are clearly defined, that debriefing occurs constructively and within a reasonable time frame, and that outcomes are reviewed to continually refine and improve care and reduce the likelihood of repeating errors. Fundamental to this is an attitude of mutual respect for other team members; this is often the most difficult for physicians to generate, because they are educated and trained to be self-sufficient, independent, and non-delegating. “Virtuoso teams”¹¹ are characterized by smart people who are opinionated, strident, and challenged by an acute need to perform. They get the job done by confronting each other and arriving at a mutually

acceptable solution. Leadership is clearly important in this endeavor; conflict resolution and negotiation are significant parts of the process.

Effective Communication and Flow of Information

As is true in any clinical environment, communication among providers is critical to the delivery of care. Effective communication is particularly relevant in the care of patients outside of the OR for a number of reasons, many of which have already been outlined. Novel interventions and technologies used by proceduralists create potential for misunderstanding or unintended consequences due to unfamiliarity with the supplies, equipment, or maintenance. As is true for procedures performed in the OR, time-outs that include identification of the patient, description of underlying medical conditions that might impact care, and other relevant issues are perhaps even more important for NORA cases. In some cases, the primary proceduralist may be unaware of underlying medical conditions or comorbidities that impact anesthesia care, selection of sedatives and analgesics, and monitoring needs. The issues of concern to the anesthesia provider must be discussed with the proceduralist and those that might impact how a procedure will be performed must be discussed with the anesthesia provider, nurses, and others. Even medically correct actions on the part of the anesthesiologist or proceduralist, if not communicated to the other party, could drastically alter outcome. If, for example, the anesthesiologist supports decreasing blood pressure but fails to tell the proceduralist about the hemodynamic instability, s/he might continue under the assumption that the patient is tolerating the procedure when in fact a search for a cause for the blood pressure fall, such as evaluation for possible retroperitoneal bleed, is more appropriate. To create the same degree of safety and reliability outside of the OR as exists in the OR, compromise and adjustment of cultural and medical assumptions is required by all parties. Without good communication this cannot occur.

NON-OPERATING ROOM ANESTHESIA LOCATIONS: SOME LOGISTICAL ISSUES

Sites of Care

Potential sites for procedures performed outside of the OR continue to expand. As new sites are proposed, they must be carefully and thoroughly evaluated to ensure that care can be provided safely with appropriate monitoring and all supplies, equipment, and support are available. The needs must take into account the patient population(s) that will be served, including consideration of the complexity of the intervention and common comorbidities.

For anesthesia care provided outside of the OR, appropriate emergency supplies and procedures should be clearly identified, including posting of phone numbers or other contact information for accessing emergency help. In addition to considering the specific space needs to facilitate completion of a procedure, appropriate space must be identified to provide pre- and postprocedure care. In addition, any patient receiving anesthesia for a procedure must be monitored in an appropriate location equipped for that purpose with skilled nursing staff and the availability of an anesthesia provider during the recovery period.¹² The same safety

standards implemented for procedures performed in the OR must be assured for all NORA cases regardless of where they are provided.

Supplies and Equipment

No matter what type or level of anesthetic care is anticipated to be required to facilitate completion of a procedure, for the majority of locations and clinical situations an anesthesia machine should either be present or readily available in anticipation of the need to convert to general anesthesia and/or require mechanical ventilatory support. If the proposed location for a procedure cannot accommodate anesthesia equipment (for size, electrical, or other spatial reasons), an alternative location should be identified.

All anesthetizing locations should have appropriate monitoring equipment. While the monitoring needs may vary for each procedure, the usual monitoring equipment should be available, preferably the same equipment that is available in the ORs to ensure that all providers know how to use and troubleshoot the equipment. The ASA Standards for Basic Anesthesia Monitoring¹³ may serve as a fundamental guide, but often specific procedures require more than basic monitoring. As sicker patients are increasingly cared for in NORA locations, monitoring needs must be considered to ensure that the patient receives appropriate care to address both procedural needs and any clinical issues that may arise as a result of underlying medical conditions. The appropriate monitors increase the likelihood of early detection and amelioration of problems and undesirable outcomes. The success in establishing and maintaining unparalleled safety records in the OR results largely from the consistent use of appropriate monitoring equipment. The same standards should apply in NORA settings.

MONITORING IN NON-OPERATING ROOM ANESTHESIA LOCATIONS

Physiologic monitoring is a critical feature of safe anesthesiology practice wherever the anesthetic is delivered (see also [Chapters 36 and 41](#)). Just as monitoring standards of care exist throughout the OR, they must be consistently in place in NORA locations as well. Some studies suggest that adverse events occurring outside of the OR may in fact be associated with more deleterious outcomes and serious injury than those in the OR because minimal monitoring standards are lacking.^{14,15} Monitoring in NORA locations is often suboptimal because the need is not identified by anesthesiologists and, in some cases, the proceduralist is not well-educated about what may be required. Until recently, pulse oximetry was the primary monitoring used to assess adequacy of oxygenation and ventilation, despite the fact that pulse oximetry has significant limitations. Several publications indicate significant misunderstanding among non-anesthesiologists using pulse oximetry to monitor patients outside of the OR.¹⁶ Anesthesiologists providing services outside of the OR should clarify the need for both pulse oximetry and monitors of ventilation. Several excellent articles and websites are available as resources.¹⁷ Over the last 20 years, capnography has become the standard of care for monitoring not only for ventilation, but also for circulation and metabolism¹⁸⁻²⁰ by directly measuring expired carbon dioxide levels and indirectly measuring production

of CO₂ at the tissue level and delivery of CO₂ to the lungs. Despite broad utility and clear clinical superiority, capnography is not always available in non-OR locations. The mandate for capnography may not be understood by either proceduralists or hospital administrative staff without significant education about its utility. Capnography equipment is bundled with other monitoring equipment on the anesthesia machine. Similar monitoring should be routinely available in NORA locations independent of the anesthesia machine which may not be required for every case.

PREPROCEDURAL EVALUATION FOR NON-OPERATING ROOM ANESTHESIA CASES

Preprocedural evaluation is an essential component of anesthesia practice, regardless of where the procedure is performed or who is performing it (see also [Chapter 31](#)). Increasingly, patients with serious comorbidities and/or significant compromise are scheduled to undergo procedures outside the OR. For many of these patients, preprocedure assessment identifies clinical issues that may be difficult to optimize prior to proceeding with the procedure. In some cases the procedure is an emergency or of such urgency that a delay to address underlying clinical issues is not possible. For all NORA cases, the ASA Guidelines for Preanesthesia Evaluation²¹ of 2012, should guide management. They specifically define a preanesthesia evaluation which should, at a minimum, include the following:

1. A patient interview that includes a physical examination and a review of medical, surgical, anesthetic, and medication history
2. Diagnostic laboratory tests and other relevant diagnostic information
3. Assessment of ASA status
4. Formulation of potential anesthetic plans and presentation of these to the patient

Because several studies have dispelled the notion that there is a body of routine testing that reduces anesthetic risk,^{22,23} anesthesiologists should obtain testing based on the patient's history, the procedure they are to undergo, and anesthesia requirements. Since many NORA cases are performed as urgent referrals to a proceduralist, patients may not have been evaluated by any provider prior to the procedure. As a result, accumulating the appropriate clinical information in a timely manner may be challenging, if possible at all. For patients known to have significant underlying medical conditions, the proceduralist should require that, if possible, the patient be evaluated in a preoperative evaluation clinic (if one is available). If not, the patient may require an extensive preprocedure assessment that could delay the procedure or necessitate rescheduling at a later time. Occasionally, periprocedural admission or consultation with a specialty service is required. Guidelines regarding preanesthetic evaluation can be found in [Chapter 31](#) and many other texts²⁴; in general, the same guidelines apply to procedures performed in the OR or non-OR locations.

OTHER CONSIDERATIONS

Additional issues must be considered for patients undergoing NORA procedures, particularly related to the management

of underlying clinical conditions or periprocedure needs that might not be anticipated by other providers. These include the following limitations that should be considered before proceeding:

1. Many procedure suites have beds with lower weight limits and less mobility than OR beds.
2. Procedure suites for fluoroscopy have beds that cannot be placed in Trendelenburg or reverse Trendelenburg position.
3. Anticoagulation status is often an issue and guidelines may be extended for some procedures.
4. Renal status may impact the use of contrast.
5. During percutaneous procedures, bleeding may be occult, and the potential need for transfusion should be addressed preprocedurally.
6. Percutaneous procedures often require that the patient remain still. Patients with extreme anxiety, chronic pain, claustrophobia, mental disability, movement disorders, obesity, or obstructive sleep apnea (OSA) or those who are at the extremes of age may not tolerate lying on a table for long, even if the proposed procedure is not very stimulating. For these patients, deeper sedation or general anesthesia may be needed.

Current NPO guidelines for procedures are 6 hours for a light meal, 8 hours for a full meal, and 2 hours for clear liquids applied to patients without increased risk for aspiration (gastroesophageal reflux disease, gastric dysmotility, hiatal hernia, diabetes mellitus, bowel obstruction, or intraabdominal pathologic conditions).²⁵ This is often a source of disagreement between anesthesiologists and proceduralists, who may not realize the ramifications of a full stomach or may insist that contrast or barium be administered before the procedure. Timely preprocedure evaluation and enforcement of clear standards for NPO status can help prevent scheduling mishaps and unnecessary delays and cancellations. This may require education of the proceduralists and their staff.

Specific Procedure-Related Issues

GASTROINTESTINAL PROCEDURES IN THE ENDOSCOPY SUITE

Over the past 10 years, enormous growth in the number of gastrointestinal (GI) endoscopic procedures related to an aging patient population, increased awareness of cancer screening benefits, broad-based reimbursement for screening colonoscopies, and better technology is quite evident.²⁶ Increasingly complex procedures, higher-acuity patients, and increased case volume broaden the scope of challenges anesthesiologists face in caring for these patients. The choice of anesthetic approach requires a thorough understanding of both the procedure and the comorbidities of the patient. Similarly, preprocedure evaluation and postprocedure care, which carry financial and operational constraints, assume greater importance. Historically, most endoscopists managed healthy patients undergoing minor procedures with moderate sedation administered by nurses. However, moderate sedation is often inadequate in the context of sicker

patients for simple procedures or healthy patients for complex procedures. Therefore, this chapter discusses the focus and methods of common GI procedures, reimbursement issues that may affect practice, the frequent comorbidities associated with patients undergoing those procedures, and anesthetic approaches suggested by anesthesiologists with expertise in the area.

A broad spectrum of GI procedures takes place in the endoscopy suite, ranging from routine screening colonoscopies to complex endoscopic pancreatic necrosectomies. Each of these requires specific levels of anesthesia depending on the invasiveness and stimulation imposed by the procedure as well as patient factors relating to their comorbidities. The most common procedures are esophagogastroduodenoscopy (EGD), sigmoidoscopy and colonoscopy, and endoscopic retrograde cholangiopancreatography (ERCP).

Reimbursement Constraints

Rapid increases in charges to Medicare and private insurance companies for anesthesiology support of colonoscopies provoked the attention of both Medicare and commercial payers. As a result, in 2008, a major insurance company amended its reimbursement policies²⁷ stating that they would no longer pay for anesthesiologists to administer propofol for screening colonoscopies in routine cases and that costs would be reimbursed only if the patients had documented comorbidities that would likely contraindicate moderate sedation. The carrier's actions were prompted by an acute rise in billing, significant regional differences in the use of propofol for routine colonoscopies, and the growth of independent colonoscopy centers that treated many patients per day facilitated by the use of propofol, which permitted very rapid turnover of cases. Despite the fact that the list of acceptable comorbidities included more than 200 diagnoses, nationwide protests from patients and physicians prompted the carrier to delay and then cancel implementation of this policy change. The finances of this situation continue to drive practice, and the debate continues. Anesthesiologists must continue to consider patient need and procedural requirements as the criteria by which anesthetic plans are formulated because the political and economic aspects of the debate will undoubtedly continue.

Esophagogastroduodenoscopy

EGD involves examination of the upper GI tract (esophagus, pylorus, and stomach) using a fiberoptic endoscope. The most difficult parts of the procedure for the patient include passing the scope into the esophagus (past the cricopharyngeus muscle) and through the pylorus. Any interventions that occur during the procedure (biopsy, resection, dilation) should be discussed with the endoscopist before the procedure because they constitute additional procedure time. Important and potentially stimulating therapeutic undertakings during endoscopy include hemostasis, biopsy, stenting, dilation, and mucosal or submucosal dissection.²⁸

Most patients tolerate this procedure well with opioid or benzodiazepine sedation, but for those who are hemodynamically unstable, at risk for obstruction or aspiration, very anxious patients, or for children, general anesthesia may be the best alternative. Unfortunately, many patients presenting for EGD are in this high-risk category, including patients with severe GI reflux disease, morbid obesity,

asthma, or OSA. In some cases, thorough topicalization is all that is needed, but in some patients, this is inadequate for the procedure or is difficult to achieve. ProSeal laryngeal mask airways (LMA), which have a built-in gastric drainage port, permit the passage of a pediatric endoscope, and this approach may be the best option for children and other patients²⁹ who require general anesthesia and are appropriate for LMA use. As with all procedures above the nipple line that use cautery, precautions must be taken to reduce the potential for airway fires.³⁰ This subject is discussed in Chapter 44. Rare, but serious complications include aspiration and gastroesophageal injury including perforation.

Sigmoidoscopy and Colonoscopy

Sigmoidoscopy and colonoscopy can be diagnostic and/or therapeutic and involve the examination of the lower GI tract, including either the sigmoid colon only or up to the distal ileum. This examination can be difficult for some, although most patients tolerate it with a combination of benzodiazepines and opioids. Interventions such as biopsies or polyp removal may require increased analgesia. Most anesthesiologists provide sedation with propofol; however, even in situations in which GI endoscopists are permitted to direct nurses to administer propofol, one study found that the mean bispectral index (BIS) score of patients was 59, indicating they were under general anesthesia.³¹ Some gastroenterologists maintain that this depth of sedation or anesthesia allows for more thorough examination, but no data have indicated that a better examination is performed. Remifentanil has been compared with propofol in the context of sedation for colonoscopy. Although patients given remifentanil recovered earlier, they also had more nausea and respiratory depression than the propofol groups. When inhaled anesthetics such as sevoflurane and nitrous oxide were compared with total intravenous anesthesia (TIVA) using drugs such as propofol, fentanyl, and midazolam in patients undergoing colonoscopy, the TIVA group emerged faster but had longer-lasting psychomotor impairment than the inhalational group.³²⁻³⁴

As with upper endoscopy, specific interventions during sigmoidoscopy and colonoscopy constitute additional stimulation including introduction of the endoscope, colonic insufflation, advancement of the endoscope, and additional endoscopic intervention such as biopsy, polypectomy, stenting dilation, and mucosal resection.

The ability and need to titrate a drug quickly and appropriately drive the choice of anesthetic, and new studies looking at patient-controlled sedation pumps are under way. Studies of patient satisfaction and indicators of procedural success are ongoing, as are several trials of patient-administered sedation and other types of computerized pumps.

One potential complication is bowel perforation, which is heralded by ongoing abdominal pain; emergent surgical intervention is indicated in this situation. Bleeding is another complication that can occur during therapeutic lower GI procedures. A current blood bank sample is imperative as well as adequate intravenous access.

Endoscopic Retrograde Cholangiopancreatography

ERCP is a fluoroscopic examination of the biliary or pancreatic ducts accomplished through an endoscopically

guided injection of contrast through the duodenal papilla. This type of procedure constitutes the up-and-coming interventional gastroenterology field. Patients are usually in the prone position. Many patients who require ERCP are compromised. Their diagnoses include cholangitis (with or without sepsis), pancreatitis, bile duct obstruction secondary to stones, or pancreatic or hepatocellular tumor masses. Potentially stimulating interventional maneuvers during ERCP include sphincterotomy, hemostasis, stent placement, stone extraction, pancreaticobiliary visualization, and laser lithotripsy.

These procedures can range from straightforward to highly complex interventions. Furthermore, gastric insufflation is required and most proceduralists prefer CO₂ instead of air. Consequently, prolonged procedures can lead to very high arterial CO₂ levels. Procedural failure rates are twice as high for sedation patients as they are for general anesthesia patients, and the complication rate for general anesthesia cases may be lower.^{35,36} In addition, the patient's airway is effectively inaccessible to the anesthesiologist and ventilation can be challenging. For this reason, many anesthesiologists prefer general anesthesia for ERCP.

NATURAL ORIFICE TRANSLUMINAL ENDOSCOPIC SURGERY: THE NEXT FRONTIER?

Natural orifice transluminal endoscopic surgery (NOTES) represents an approach to abdominal and peritoneal procedures that integrates the perspectives of endoscopic medicine and minimally invasive surgery. The use of NOTES in humans is in the early phases, and several cases have been reported of transvaginal and transgastric cholecystectomy.^{37,38} Thus far these cases have required a pneumoperitoneum and general anesthesia; however, as technology improves, these parameters may change and NOTES procedures may take their place among the numerous other interventions performed outside the OR.

An example of a NOTES used by GI endoscopists to treat esophageal achalasia is peroral endoscopic myotomy (POEM). Esophageal achalasia is characterized by poor peristalsis of the esophagus in combination with increased muscle tone and incomplete relaxation of the lower esophageal sphincter (LES). Symptoms arising from impaired entry to the stomach include nausea and vomiting, dysphagia, and/or pain. The POEM procedure has been developed as a minimally invasive procedure to correct achalasia by endoscopically insufflating the esophagus with CO₂ and then making an incision into the mucosa from the mid-esophagus (through the gastroesophageal [GE] junction) to 2 to 3 cm into the proximal stomach. During insufflation, patients may have an increase in ETCO₂ that can be controlled using mechanical ventilation. Potential risks of insufflation range from subcutaneous emphysema to pneumothorax, pneumomediastinum, and pneumoperitoneum. This procedure commonly requires several hours and is best accomplished using general anesthesia with an endotracheal tube, which protects the patient from aspiration of gastric contents and allows the anesthesiologist to minimize the perils of CO₂ insufflation. As with all NORA procedures, vigilance, teamwork, and communication are vital to ensure not only the success of the procedure but the safety of the patient as well.

Interventional Pulmonary Procedures

Innovations in interventional pulmonology have expanded the pulmonary field tremendously. Bronchoscopic interventions have grown to encompass many traditional surgical procedures performed in the OR. Anesthesiology services are required for high-risk patients and given the nature of the procedures involving the airway, the potential for complications is high. Fluoroscopy plays a major role for these procedures. Discussion, communication, planning, and radiation safety are particularly critical in this environment.

COMMON BRONCHOSCOPIC PROCEDURES

Common bronchoscopic procedures include the following (see also Chapter 53):

1. Endobronchial stenting: placement of self-expanding metallic stents to treat stenosis
2. Endobronchial biopsy, laser treatment, and cauterization
3. Balloon dilation and cryotherapy

Technological advances in this field have given rise to new innovative procedures used in treating a broader patient population. Several interventions that represent amalgamations of preexisting technologies in the bronchoscopy suite are as follows:

1. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). This procedure is used to image the bronchial wall and adjacent structures. It allows ultrasonic visualization of mediastinal lymph nodes and other peribronchial lesions and therefore is a useful staging tool.
2. Electromagnetic navigation bronchoscopy (ENB). This technique permits biopsy of endobronchial tissue that is not visible using computer software that creates a virtual multiplanar lung reconstruction from computed tomography (CT) data. A sensor probe and electromagnetic location board guides the operator to the appropriate location during the bronchoscopy.
3. Fiducial marker implant. Markers are placed before stereotactic radiosurgery via bronchoscopy or ENB.³⁹

Novel Anesthetic Concerns

The site of intervention creates several special anesthetic considerations. Preoperatively it is important to review common comorbidities, which in these patients include obstructive and restrictive lung disease, cardiac disease, malnutrition, chronic aspiration, and tobacco and alcohol use. Although simpler procedures may be completed with sedation, complex procedures may require general anesthesia. Because a rigid bronchoscope is used during some aspects of these interventions, intravenous anesthetics are preferred. Instrumentation of the airway and insertion of biopsy or therapeutic equipment will compromise delivery of inhaled anesthetics to the patient and potentially pollute

the procedure room. Propofol and remifentanil infusions are well tolerated and can be titrated to effect. Dexmedetomidine may be used as well. Processed EEG monitoring may be helpful, though no data document the specific value of this type of monitoring for these procedures. Use of muscle relaxants is also preferred to prevent coughing and eliminate any chest wall rigidity. Muscle relaxation also facilitates introduction of bronchoscope. The use of steroids during and after treatment has not been demonstrated to be effective in reducing edema. For patients whose airway is not controlled during the procedure, aspiration is a potential risk. For this group of patients, administration of antiemetics and dexamethasone may be helpful.⁴⁰ High-frequency jet ventilation (HFJV) has been increasingly used to provide ventilation and as a strategy to provide a static field during therapeutic pulmonary interventions. Complications commonly encountered include airway obstruction, bronchospasm, bleeding, hypoxia, and airway fire (see also [Chapter 70](#)). Because potential complications are significant, patients should be observed in an appropriate unit postprocedure and, if needed, admitted to the hospital for overnight observation.

Anesthesiology for Image-Guided Interventions: Evolution of a New Interface

In the 1950s the field of radiology was redefined by Charles Dotter, the father of IR.⁴¹ Through his pioneer work with the treatment of peripheral atherosclerotic lesions and angioplasty, the specialty grew from being diagnostic to one that now encompasses an ever-expanding menu of interventional undertakings, in keeping with technology development and patient needs. The scope of procedures performed in IR settings is as broad as the number of diagnoses known to the medical profession and is expanding. In fact, not all interventional radiation procedures are performed by radiologists. Some take place in specialty areas with other names, such as catheterization laboratories, neuroradiology suites, CT scanners, magnetic resonance imaging (MRI), and even in ORs. Some are performed by interventional cardiologists or surgeons. For that reason the discussion will address the purpose for which they are performed rather than categorizing them by the location in which they are performed or the specialty of the person performing the procedure. The common characteristics shared by most of these interventions are that there are no surgical incisions, there is some type of imaging involved (fluoroscopy, ultrasound, CT, positron emission tomography [PET], MRI), and access to the organ, tumor, or vascular structure in question is through a small hole by wires or catheters. Beyond that, the array of available technologies and possible interventions (both diagnostic and therapeutic) is astonishingly broad. The scope and intensity of procedures undertaken in interventional suites rivals that of surgeries performed in any OR, and often, patients undergoing non-OR procedures are sicker than those undergoing conventional surgeries. Unfortunately, they often lack preoperative evaluation and are not medically optimized. Frequently non-OR patients become candidates for noninvasive procedures

precipitously because they are felt to be too sick or too high risk for the OR or because the need for intervention develops urgently or emergently.

It is important that anesthesiologists make the effort to understand the planned course of the procedure and the nature and acuity of the patient's comorbidities, which may not be apparent to the proceduralist. As in the OR, the challenge is to think preemptively about how the prospective procedure will affect the patient's physiologic status and design a successful anesthetic plan for the case. However, the additional caveat, as with all non-OR anesthetics, is that this may require learning about a procedure, technology, or modality that may be novel, unfamiliar, or in clinical trial. Also, it may fall to the anesthesiologist to introduce the potential ramifications of the patient's comorbidities and anesthetic risks to the proceduralist in a constructive manner. Many interventional specialists are consultants and are not involved in the primary care of the patients they are treating. They may be unaware of seemingly peripheral aspects of their patient's physical status that are in fact quite central to positive outcome. Creating a clear, collegial, and workable path of communication between medical proceduralist and anesthesia provider is paramount. The need for anesthesia support may reflect the needs of the patient and not the complexity of the procedure. The interventionalist may be highly focused and technically oriented and may not understand the concerns of an anesthesiologist. Our mutual tasks are to understand what needs to be accomplished and to bring our skills to bear in a manner that bridges the knowledge gap, creating an atmosphere of safe and reliable interdisciplinary collaboration that optimizes outcome.

Diagnostic and Therapeutic Interventions: New Challenges

The need for anesthesia during minimally invasive procedures continues to grow as the scope of image-guided interventions broadens. In addition, as the population ages and technologic advancement marches forward, image-guided procedures will continue to supplement and perhaps replace conventional surgeries, especially for patients whose comorbidities make traditional surgical approaches risky. Image-guided procedures, although noninvasive, can cause anxiety and postprocedural pain and carry the risk for potentially life-threatening complications. Anesthesiologists are called on to keep patients safe and comfortable and to facilitate optimal outcomes. Image-guided interventions may be diagnostic, therapeutic, or both. Many diagnostic procedures are short and tolerated well with nothing more than conscious sedation; however, for a compromised patient, even the most minor procedure can be problematic. Interventional procedure suites impose constraints not normally encountered in the OR. Additional considerations that emerge in these environments include unfavorable equipment layout, radiation exposure, occult bleeding risk, and contrast allergies.

These procedures have some special issues that need to be addressed by the anesthesia providers to optimize patient care and protect themselves.

EQUIPMENT LAYOUT

The layout in any radiology suite can be problematic for anesthesiologists because x-ray tubes and moving C-arms create a zone of inaccessibility around the patient's head and limit placement of the anesthesia machine. This necessitates the use of extensions on ventilator circuits and intravenous lines, increasing the potential for mishap. Infusion pumps, blood warmers, and other monitors must be placed far away from moving imaging equipment to prevent them from being knocked down or tangled during C-arm rotation and movement. In addition, imaging screens are often at right angles to the anesthesiologist, making it impossible to see what the interventionalist is doing or assess the progress of the case. Anticipating events is therefore difficult unless good communication occurs between the anesthesiology and radiology teams.

Radiation Exposure

Radiation exposure is a serious consideration for anesthesiologists, and steps must be taken to minimize it. Most exposure results from scatter of the x-ray beam. The specifics are not discussed in this chapter; however, excellent discussions and guidelines for optimization of radiation safety are readily available (see also [Chapter 89](#)).

Many anesthesiologists do not undergo consistent or repetitive training in radiation safety. All radiation exposure should follow the ALARA ("As Low As Reasonably Achievable") principle. The radiation beam attenuates based on the inverse square of the distance from the radiation source ($1/d^2$).⁴² Shortened exposure time, increased distance from the source of radiation, and barriers to radiation (lead shielding and screens) are three ways in which to reduce exposure. It is important that anesthesia providers wear properly fitting lead shielding; ill-fitting lead shielding is suboptimal as lead shielding is maximally protective only if it fits properly. Protective equipment should include the use of thyroid shields and leaded glasses. Anesthesiologists should routinely use portable lead screens and wear radiation badges that are monitored on a monthly basis. Even so, several recent studies indicate that exposure of anesthesia personnel to radiation is quite high and that the exposure of the head and face of anesthesiologists can exceed three times the exposure of radiologists⁴³ because of their position in the room.

Related to the exposure problem is the need for the anesthesiologist to leave the room during specific imaging runs such as a digital subtraction angiography (DSA), a novel aspect of NORA. This can be planned and executed so that it does not interfere with the anesthetic or compromise safety.

Contrast Material

Contrast material is commonly administered during interventions guided by imaging. Standard ionic, high-osmolality contrast agents are associated with dose- and concentration-dependent adverse reactions in 5% to 8% of patients. Idiosyncratic reactions are unrelated to dose or concentrations administered.⁴⁴ Reactions can be severe and include laryngeal edema, bronchospasm, pulmonary edema, hypotension, and respiratory arrest or seizures. Oxygen, epinephrine, and bronchodilators are the recommended rescue regimen. For pretreatment of patients with a history of contrast reaction,

steroids and diphenhydramine are recommended. Numerous prophylactic protocols exist, but none have shown superiority.⁴⁵ The use of low-osmolality contrast reduces the risk for adverse reactions but does not eliminate the risk. Patients with renal insufficiency are at risk for contrast-induced nephropathy (CIN). Risk is further increased for patients with diabetes mellitus. Despite mixed evidence, these patients should undergo prophylactic protection strategies including a combination of periprocedural hydration.⁴⁶⁻⁴⁸ Carbon dioxide can be used as an alternative if contrast is absolutely contraindicated. Contraindications to carbon dioxide include patients with patent foramen ovales (PFOs) or any right-to-left shunting.⁴⁹

Bleeding

During most percutaneous interventions bleeding may be occult while in some it is the reason for the procedure (i.e., splenic embolization). This is a serious concern, especially for patients receiving anticoagulation (see also [Chapter 50](#)). Guidelines for optimizing coagulation parameters change frequently and are procedure dependent. For patients who do not undergo anticoagulation for other reasons, the international normalized ratio (INR) should be less than 1.5 and the platelet count more than 50,000. If possible, warfarin should be held for 5 to 7 days before the procedure, clopidogrel and aspirin for 5 days, and fractionated heparin for 12 to 24 hours. Heparin infusion should be stopped 4 to 6 hours before the procedure. Nonsteroidal antiinflammatory drugs (NSAIDs) should be held for 1 to 2 days, if possible.⁵⁰ As mentioned earlier, certain percutaneous procedures may proceed with anticoagulation on board (i.e., cerebral angiogram). It is not unreasonable to send a sample to the blood bank for any patient undergoing high-risk interventional procedures (e.g., transjugular intrahepatic portosystemic shunts [TIPS]). Of course, it is critical to communicate clearly with the interventionalist prior to the planned intervention or when hemodynamic parameters change or the initiation of blood pressure support becomes necessary. Often the therapeutic modality can be used for diagnostic purposes.

VASCULAR INTERVENTIONAL PROCEDURES

Angiography, the general term for imaging of blood vessels, includes arteriography and venography (see also [Chapter 56](#)). This involves the acquisition of images during injection of contrast material. In many institutions, this technique has been replaced by CT angiography (CTA). DSA, a technique that imposes a contrast-injected image on top of a previously acquired non-contrast image, improves accuracy. Arteriography can be used to evaluate atherosclerotic and ischemic disease, define the arterial supply of tumors and vascular anomalies, and define traumatic injury. After diagnostic imaging, interventions using balloons, stents, balloon-mounted stents, or delivery catheters take place. Follow-up arteriography is used to evaluate the result. In some cases, arteriography serves as a precursor to later surgery.

Thrombolytic therapy can be delivered to veins, arteries, or conduits that are thrombosed. The earlier the intervention the more successful it is likely to be. Various agents are used, including recombinant tissue plasminogen activator

(r-TPA), urokinase, and others.⁵⁰⁻⁵² Thrombolytic therapy is generally contraindicated in patients with ongoing bleeding, recent bleeding, pregnancy, known allergy to thrombolytic agents, suspected aortic dissection, or the presence of a nonviable extremity.

Embolization therapy is used in a wide range of conditions, including trauma, hemorrhage, vascular anomalies, fibroids, aneurysms, and tumors. The goal is to occlude arteries or veins either temporarily or permanently. This can be done mechanically with coils, balloons, or glue or with chemical agents that are temporary (Gelfoam) or permanent (alcohol). In these cases, arteriography first defines and localizes the lesion and the embolic agent is then delivered to the appropriate place with imaging guidance.

For all of these vascular interventions, the nature of the case, the comorbidities of the patient, and the intricacies of the procedure will determine the need for and extent of an anesthesiologist's involvement. Complications to anticipate include bleeding during thrombolysis, undesired embolization of nearby structures during embolization, and vessel disruption. Depending on where the target vessels are, potential complications should be appropriately anticipated in terms of planning for physiologic sequelae and the need for blood products.

Venography or imaging of the venous system is used in the context of stent placements, inferior vena cava (IVC) filter placement or removal, pulmonary arteriography, embolization of pulmonary arteriovenous malformations (AVMs), thrombolysis, and selective venous sampling. Central venous angioplasty is most frequently undertaken in patients who have indwelling devices. IVC filters are placed to minimize the risk for pulmonary embolus arising from the migration of deep vein thromboses from the lower extremities or pelvic veins. Indications for IVC placement include high risk for pulmonary embolism, failure of anticoagulation or contraindications for anticoagulation, and allergy to anticoagulants. Both removable and permanent filters are available and can be placed via transfemoral or transjugular approach. For the most part, these procedures require little or no sedation; however, patients who cannot lie flat or with extreme anxiety will need anesthesia support. Pulmonary arteriography is used less frequently than in the past because of the speed and reliability of pulmonary CTA; however, the procedure is useful to evaluate pulmonary hypertension.⁵² This modality is also useful for diagnosis and treatment of pulmonary and bronchial AVMS and pseudoaneurysms.

Fistulograms, graftograms, and tunneled hemodialysis (HD) lines, grouped collectively as hemodialysis vascular access procedures, represent a unique type of vascular interventional case and a large percentage of IR caseload. Their uniqueness derives from the fact that the patient population is entirely comprised of those with end-stage renal disease (ESRD). These patients often require multiple interventions in the maintenance of their dialysis access lines. Vascular access dysfunction may be due to failure of maturation of an arteriovenous (AV) fistula, excessive bleeding or increased pressures during dialysis, or clotted vascular access. As a result, these patients require both diagnostic procedures such as fistulograms and therapeutic interventions such as balloon angioplasty and thrombectomy.⁵³ Anesthesia care is needed as ESRD is rarely an isolated medical condition

and this patient population tends to have multiple complex medical comorbidities that are often not optimized. Patient evaluation is like any procedure requiring anesthesia care with special consideration placed on volume status, serum potassium level, and electrocardiograph (ECG) changes. Patients with dysfunctional access require special attention to these parameters, as dialysis runs are often suboptimal. Care must be taken to weigh the risks and benefits of proceeding with borderline high potassium levels versus postponing the case and asking for a temporary dialysis line to get potassium to reasonable levels. Sedation is adequate in most cases. However, angioplasty can cause extreme discomfort for some patients, especially in cases where access is distally located (radiocephalic fistulas). Regional anesthesia techniques can be tailored for these cases but care must be taken as these patients are often on chronic anticoagulation. For patients unable to lie flat, ramping can be useful. Most patients have a history of prior anesthetics and this can guide future anesthetic plans. Procedure duration can range from very short (<30 minutes) to very long (several hours or more) depending on whether there are multiple stenotic areas or whether thrombectomy needs to be performed. Thrombectomies present a special consideration as declotting procedures use r-tPA. Thrombus can be dislodged from the fistula/graft and travel into the circulation. Patients with severe pulmonary hypertension or right ventricle failure should be considered for open surgical thrombectomy.⁵⁴

BILIARY AND HEPATIC INTERVENTIONS

Procedures to treat biliary or hepatic pathology are particularly challenging in that they are painful, intricate, and technically demanding. Patients are often extremely compromised. Hepatic and biliary procedures include transhepatic cholangiography, percutaneous transhepatic biliary drainage, hepatic venography with hemodynamic measurement, liver biopsy and the creation of TIPS, and portal vein embolization (PVE). Patients scheduled for biliary procedures may present with jaundice, cholangitis, shock, bile duct leak, or other related abnormalities. Clearly, significant comorbidities accompany these disorders. Contraindications for these procedures include bleeding diathesis, inability to tolerate contrast, and the presence of large hepatic AVMs, significant ascites, and hydatid disease.

Biliary drainage is accomplished by placing the patient supine on the table and inserting a long needle obliquely into the hepatic parenchyma (the ninth intercostal space). Contrast is delivered with the goal of imaging the necessary structures. Cholecystostomy tube placement is performed to improve symptoms in patients with acute cholecystitis but who are not candidates for surgery. Here, the gallbladder is imaged with ultrasound, CT, or fluoroscopy; the gallbladder is accessed through a needle that traverses the liver; and a drainage catheter is placed. For these procedures, the choice of anesthetic depends entirely on the patient's body habitus, comorbidities, and pain tolerance. Obese patients are difficult to image, and optimization of needle position also can be difficult. Patients may present with a history of tolerance to opioids and with compromised metabolism, which requires careful choice of drugs. Regional anesthesia may be useful for procedural or postprocedural pain

management.⁵⁵ Lying flat may be difficult for patients with pulmonary compromise or ascites.

Hepatic venography and hemodynamic assessment are performed to assess suspected venous anomalies (Budd-Chiari) and quantitation of portal hypertension. Liver biopsies can be performed during these procedures. Access for these procedures is usually transjugular and involves needle insertion followed by wire access and insertion of a long vascular sheath. Many patients find this extremely difficult to tolerate. Hepatic venography and pressure monitoring is done through an angled catheter before it is advanced to wedge in the hepatic vein. A calculation of corrected sinus pressure, the difference between free pressure and wedge pressure, defines the degree of portal hypertension.⁵⁶ The creation of a portosystemic shunt requires positioning of a needle advanced through the hepatic parenchyma and into the portal vein. The parenchymal tract is dilated with an angioplasty balloon and a stent is inserted. This is a painful and difficult procedure, vastly oversimplified for clarity. It may be quite lengthy and general anesthesia is advisable. Indications for the creation of TIPS include repeated esophageal variceal bleeding refractory to medical treatment and intractable ascites. It is often used as a bridge to liver transplant. Relative contraindications to this procedure include preexisting hepatic encephalopathy and ongoing alcohol abuse, which preclude liver transplantation. In elective situations, significant pulmonary hypertension, valvular heart disease, and congestive heart failure are contraindications to this procedure.⁵⁷ TIPS can be performed emergently in patients with end-stage liver disease as a way to treat ongoing bleeding. The risk for bleeding from TIPS is high and a blood bank sample should always be obtained. Adequate access and blood products, including fresh frozen plasma (FFP) should be secured. PVE is a relatively new technique designed to reduce blood flow in hepatic segments containing tumor while encouraging hypertrophy of remaining hepatic tissue. The goal is to improve survival among patients undergoing resection of hepatic neoplasms by increasing postsurgical hepatic tissue mass. Embolization is accomplished with portal vein angiography and coils. Postprocedure pain can be significant. Acute complications include bleeding, bile leak, pleural insults, and contrast reactions.

GASTROINTESTINAL AND GENITOURINARY INTERVENTIONS

Interventional radiologists perform direct-access GI procedures, the most common of which is the percutaneous gastrostomy tube (G-tube). Other variants include cecostomy and jejunostomy tubes. For G-tube placement, the stomach is distended with air via a nasogastric (NG) tube or a small French catheter and glucagon administered to decrease gastric emptying. Subsequent gastropexy is performed by some practitioners as a means of stabilizing the stomach; the stomach is entered with a needle and a wire and an appropriate tube is inserted and placed in the proper location. Acute complications include bleeding, violation of adjacent structures, and peritonitis. In many cases, these procedures can be tolerated with sedation except in situations where patients are at high risk for gastric aspiration (e.g., esophagectomy).

Genitourinary (GU) procedures in the radiology suite focus on obtaining direct access to the renal collecting system. Dilation and stenting can be performed, and suprapubic cystostomy is also a procedure commonly performed in radiology suites. Nephrostomy tube placement is performed to divert urine in the face of obstruction from stones, tumor, or other obstructive pathology. In general, the technique involves injecting contrast medium, identifying the renal pelvis, accessing it, and inserting a tube.⁵⁸ Prone positioning of the patient is preferred, which generates an attendant list of potential anesthesia concerns including airway issues, pain management, access, and more. In formulating the anesthesia plan, one must carefully weigh the risks and benefits of prone sedation versus general anesthesia. Factors to take into consideration include patient body habitus and hemodynamic condition, proceduralist skill, and duration of procedure (e.g., accessing a dilated renal pelvis in a thin patient may be quicker than in a morbidly obese patient).

PERCUTANEOUS INTERVENTIONS FOR ONCOLOGY

Interventional oncology is a rapidly expanding area and is revolutionizing oncologic care. These treatment modalities are gaining momentum over surgical interventions. Imaging guidance is achieved via CT, ultrasound, or fluoroscopy. Transarterial chemoembolization and percutaneous ablations (with microwave or to a lesser extent radiofrequency, laser, cryoablation, or alcohol) can be directed at tumors and image-guided insertion of radioactive materials can be performed. Commonly, hepatic, kidney, lung, and adrenal lesions are targeted. Complications are similar to those of other percutaneous interventions. Positioning depends on the site to be accessed. Anesthesia services are frequently used as these patients are truly high risk for surgical intervention. General anesthesia works best as the interventions may be intermittently painful, control of breathing may be optimal, and patient cooperation may not be compatible with the level of sedation required.⁵⁹ Postprocedure patients can experience pain, malaise, and nausea and vomiting, as part of a postembolization syndrome or post-ablation syndrome. High-dose steroids can be beneficial in prophylaxis and non-opioid analgesics can be beneficial in treating symptoms.^{60,61}

Procedures Guided by Computed Tomography, Positron Emission Tomography, and Magnetic Resonance Imaging

COMPUTED TOMOGRAPHY

CT is now a commonly used guidance modality for a broad array of percutaneous interventions, and CT fluoroscopy, which combines the improved imaging capacity of CT with the real-time imaging of fluoroscopy, is also widely used. CT is used to guide both diagnostic and therapeutic procedures. Diagnostic undertakings include biopsies and drainage of fluid collections; therapeutic interventions include tumor

ablation and injections for pain management. Procedures occurring in the CT suite encompass the usual constraints of radiation exposure on operators and anesthesiologists; patients are at risk for bleeding and contrast reaction. In addition, some special preprocedural considerations are important. Obese patients may not fit inside the scanner, and longer needles and drains may be needed. Positioning in the scanner may be difficult, and the usual airway considerations apply, especially because it is nearly impossible for the anesthesiologist to have continuous access to the head. For the most part, biopsies performed under CT guidance can be accomplished with sedation, but when the stimulation is intense, repeated breath-holds are required, or when the procedure is complex, general anesthesia may be needed. For patients with significant comorbidities (obesity, pulmonary or cardiac compromise, chronic pain, or history of difficult intubation), securing the airway before the procedure is prudent.

Computed Tomography–Guided Biopsies

CT guidance is useful for obtaining biopsy tissue for cytologic or histologic examination. Needles range from 25 to 18 gauge, and the patient is positioned to minimize the distance from skin to lesion and to maximize the safety of the approach. Liver biopsies are usually performed with the patient supine or slightly oblique, and retroperitoneal masses may require lateral decubitus or prone positioning. For the most part, it is helpful to the interventionalist if the level of sedation remains consistent throughout the procedure, so that large shifts in target location resulting from alterations in ventilation do not occur. However, levels of stimulation during these procedures can vary tremendously, presenting considerable challenge to the anesthesiologist if general anesthesia is not planned. Post-procedure bleeding can occur for these patients, especially those with bleeding diathesis (e.g., cirrhosis); thus, obtaining a blood bank sample is reasonable. Biopsies of carcinoid or adrenal tumors can be equally problematic, whether in the radiology suite percutaneously or in the OR. In both cases, stimulation of hormone release can precipitate severe hypotension or hypertension, which can be difficult to manage. If pheochromocytoma or carcinoid are suspected, pretreatment should be considered.

Computed Tomography–Guided Therapeutic Interventions

CT-guided therapeutic interventions include catheter drainage, ablation of tumors, and injections for pain management. Anesthetic planning for these procedures requires understanding of patient comorbidities and the techniques of the interventionalists. Excellent communication between anesthesiologist and interventionalist is needed for coordination of procedure and anesthetic because unanticipated patient movement or interventional shortfall can have drastic consequences for procedural outcome.

Catheter Drainage

CT-guided abscess drainage has become common. Options include the modified Seldinger and trocar techniques. Although local anesthesia may suffice for superficial collections, the insertion or dilation phase of the needle or trocar and the subsequent anticipated trajectory required

for deeper fluid collections may be quite painful. Before the procedure, the proceduralist and anesthesiologist should discuss the intended approach, potential anesthetic choices, and backup planning for transitioning to a deeper plane of sedation or anesthesia. Preemptive planning can make the difference between a smooth procedure with a good outcome and a prolonged, difficult intervention. Anesthesiologists should be prepared to treat potential complications, which can occur as a result of injury of surrounding structures.

Computed Tomography–Guided Ablation

A variety of ablation techniques are now used to target malignant neoplasms. Percutaneous injection of alcohol (95%) or phenol (6%) is used to target tumors. Alcohol can be instilled using needles or catheters, but the injection is usually quite painful. Large volumes of alcohol or inadvertent injection into a vascular structure can cause tachycardia and respiratory depression. These techniques are older and not as frequently used. More popular ablation techniques involve the use of radiofrequency ablation, cryoablation, and microwaves. These procedures may be lengthy because they involve precise placement of applicators for the delivery of the ablation tool, whatever that may be. Reproducible breath-holds may be needed to facilitate placement. Radiofrequency ablation induces coagulative necrosis at temperatures above 50°C; the heating process can produce pain, whereas cryoablation is a less painful procedure.^{62,63} As stated previously, postablation syndrome can occur and is characterized by fever, malaise, nausea, vomiting, and right upper quadrant pain. Dexamethasone may be helpful in prophylaxis. Regional techniques can be used for primary anesthetic and for postprocedural pain.⁶⁴

Computed Tomography–Guided Injections for Pain Management

Procedures for pain management include phenol and alcohol injections into a plexus, ganglion, or nerve. Neurolysis is the intended outcome. Injection of steroids into joints for local pain management and mitigation of inflammatory processes is also performed. Many patients requiring these procedures are tolerant to pain medication. Body habitus may be an important factor in these patients as well, and depending on the source of pain, patients with cancer may be especially challenging in terms of attendant comorbidities. Most often these are palliative procedures. Discussion frequently revolves around addressing advanced directives prior to start of anesthesia.

POSITRON EMISSION TOMOGRAPHY AND POSITRON EMISSION TOMOGRAPHY COMPUTED TOMOGRAPHY

PET is an imaging technique used for diagnosis, staging, and follow-up of malignancies. Scanning is undertaken after injection of a radiolabeled glucose analogue fluorodeoxyglucose (18F-FDG), which is taken up by malignant cells preferentially and is not metabolized, thereby serving as a tumor marker. FDG-PET is used to distinguish benign from malignant lesions, identify metabolically active portions of necrotic tumors, and monitor

responses to treatment. The combination of PET/CT provides both the metabolic information of PET and the anatomic precision of CT. PET/CT-guided intervention is an emerging modality.⁶⁵ For these procedures, patients are imaged beginning 60 minutes after injection. Imaging may require serial positioning, during which PET and CT images are acquired sequentially, so care must be taken to maintain consistent patient positioning throughout the image acquisition so that misregistration of image overlap does not occur. PET scanners include a long, mobile gantry that both limits access to the patient and requires that monitoring equipment be long enough to accommodate motion of the table.

Hence, PET/CT suites represent another potentially challenging anesthetizing location. Whenever possible, anesthesiologists should be involved in the planning of these suites because wall-mounted gases, suction, and installed monitoring equipment must be strategically placed. It is likely in the future that PET will be used to augment CT-guided interventions; therefore, planning a space that will allow inclusion of anesthesiology equipment will ensure uneventful interventions and optimal outcomes.

MAGNETIC RESONANCE-GUIDED INTERVENTIONS

MRI is an ionizing radiation-free technique that uses magnetic fields and radio waves to create images. The quality of soft tissue images generated by MRI surpasses that of ultrasound or CT. MRI is still largely a diagnostic tool but is emerging as an interventional modality as well. Because MRI can acquire multiplanar, temperature-sensitive, and contrast-enhanced images, complete visualization of interventional implements such as wires or needles is possible.⁵⁸ Image quality is proportional to magnet strength. Field strength, measured in Tesla units, ranges from low (0.1-0.5 T), medium (0.5-1.0 T), high (1.5-3.0 T), and ultrahigh (>3.0 T). Imaging sequences can be manipulated to highlight tissue characteristics based on water content, vascularity, and presence of hemosiderin. The superiority of MRI-generated soft tissue images facilitates biopsy and ablation of structures that evade CT or ultrasound.⁵⁹

Physical Constraints of Magnetic Resonance Imaging Suites

All equipment used in the MRI suite must be MRI compatible meaning that the equipment will not cause harm to the patient, affect image quality, or be affected by the MRI scanner. Objects containing iron or stainless steel become mobile projectiles in an MRI suite because of the magnetic field regardless of their size. Therefore, special care must be taken to ensure that all equipment used in an MRI suite is unaffected by magnetic attractive forces, heating, or current induction. Similarly, patients themselves must be screened. Any implanted devices must be assessed for MRI compatibility. Patients with pacemakers, implantable cardioverter-defibrillators (ICDs) (see also [Chapter 38](#)), cochlear implants, pumps, nerve stimulators, or other metal objects such as aneurysm clips, metal fragments, or bullets, should not be scanned. These objects are subject to heating and movement. Increasingly, vascular clips,

staples, orthopedic implants, heart valves, pacemakers, and other prostheses are non-ferromagnetic and scanning of patients with these implants is possible. Monitoring devices are increasingly available in MRI-compatible format, as are interventional equipment, surgical equipment, and anesthesia equipment.⁶⁶ Detailed information regarding MRI safety is available in [Chapter 89](#) and elsewhere.

Claustrophobic or large patients may be unable to tolerate being inside of an MRI machine, making even diagnostic procedures difficult for them. Newer MRIs combine a wider bore with high-field systems, improving accessibility and making it easier for patients to tolerate procedures. Because interventional MRI requires constant movement in and out of the scanner, typical interventions take much longer than the same procedures done elsewhere. Emergencies must be planned for because the MRI interventional suite may be isolated, and conventional emergency equipment may not be MRI compatible. Even a standard laryngoscope can become a deadly missile in an MRI suite.

Magnetic Resonance Imaging-Guided Interventions

In cases in which CT is inadequate, MRI may be useful because of its multiplanar capability. MRI has been used to guide breast and prostate biopsies and biopsies of other tumors not well visualized by other means. For the most part, local anesthesia and sedation suffice for these procedures. Tumor ablation using cryoablative technology can be performed in the MRI suite. This procedure can be done with ultrasound or CT as well, and the choice of MRI as an imaging modality indicates the need for precise soft tissue imaging. MRI also provides better visualization of tissue during freezing and thawing than CT or ultrasound, and MRI-guided cryoablation is safe and effective for liver, kidney, breast, and prostate tumors and in the treatment of uterine fibroids.⁶⁷ For these cases, repeated breath-holds may be needed, and the procedures may be lengthy. Pain is not uncommon during freezing and heating of tissues; therefore, general anesthesia may be required.

Bleeding is the most common complication after some of these procedures (also see [Chapter 50](#)). Thrombocytopenia is a rare but serious complication of extensive liver ablation. Extensive ablations can also induce myoglobinemia or myoglobinuria. Cryoablation of adrenal lesions can induce hypertensive crises as normal adrenal tissue responds to thawing.⁶⁸ MRI can facilitate the use of focused high-intensity ultrasound therapy by providing more precise imaging. Clinical trials of this technique are in progress. Temperature-sensitive MRI images can assess dosage of ultrasound and gadolinium-enhanced MRI images can assess tissue response. MRI offers many potential advantages that may broaden the scope of current interventional procedures because of its capacity to provide improved imaging over that available with CT or ultrasound. The need to develop MRI-safe environments, equipment, and monitoring and to understand the limitations of sedation and need for anesthesia during long and uncomfortable procedures are the next steps in extending the usage of this modality.

Image-Guided Procedures for Specialty Areas: Neuroradiology and Interventional Cardiology

Neuroradiology and interventional cardiology are considered here as specialties because they each mirror areas that anesthesiologists have also chosen to designate as areas of specialization or fellowship training (neuroanesthesia and cardiac anesthesiology) (see also [Chapter 57](#)). The language of neurology, neuroradiology, cardiology, and interventional cardiology is part of the language of neuroanesthesia and cardiac anesthesia. Thus, a platform for clear communication exists and should be used to optimize procedural outcome. Of course, as mentioned earlier in this chapter, common vocabulary is necessary but not sufficient; mutual respect, a culture of safety and learning, and a functional teamwork structure are important elements of a successful unit.

Advances in neuroradiology and interventional cardiology have been incredibly rapid—technology has developed and target patient populations have broadened. In both these areas, percutaneous approaches to formerly surgical problems have multiplied, as has the potential for the involvement of anesthesiologists. In many ways, the development of new techniques represents a “disruptive technology”⁶⁹ within the field of medicine that promises to further blur distinctions between medical and surgical treatments. The unpredictable and demanding new landscape of novel interventional cases is the future of the practice and the success of these new, cutting-edge interventions relies on our adaptability.

Procedures in the Neuroradiology Suite

The field of interventional neuroradiology has grown broadly and rapidly as a result of technological advances in devices (catheters, coils, and stents), improved imaging techniques, and safer contrast media (see also [Chapter 57](#)). Cerebral angiography remains the gold standard for imaging the cerebral vasculature. Diagnostic cerebral angiography usually can be performed with conscious sedation while interventional procedures require a broad range of anesthesiology care due to the complexity of the techniques, need for a still patient, and long procedure duration. Certain procedures generate hemodynamic perturbations that require management by the anesthesiologist. On the other hand, some procedures (i.e., carotid stenting) can be done with the patient awake, to facilitate neurologic assessment. Anesthesia for each of these procedures must be considered in concert with patient comorbidities and status on a case-by-case basis. Although the technical details of neuroradiology procedures are beyond the scope of this chapter (see [Chapter 57](#)), the basic focus and required steps in commonly performed interventions are outlined here.

GENERAL CONSIDERATIONS FOR ANESTHESIOLOGISTS IN THE INTERVENTIONAL SUITE

As with other areas outside of the OR, physical characteristics of the interventional suite affect the practice of

anesthesia (see also [Chapter 39](#)). Equipment makes access to the patient’s head difficult and radiation exposure must be considered as these procedures emit large amounts of radiation due to bi-plane imaging techniques. In addition, contrast reactions must be anticipated. Because of the intricacy of the procedures, uncooperative patients and those with impaired consciousness or movement disorders should be considered candidates for general anesthesia. If time permits, arterial lines are advisable; if not, the neurointerventionalist can upsize a femoral sheath to permit arterial monitoring. Other neuromonitoring technologies can be helpful as indirect measures of cerebral perfusion; electroencephalography and somatosensory, motor, and brainstem evoked potentials have all been studied in this regard. Many neuroanesthesiologists use opioids, avoiding inhalational agents because of their confounding effects on electroencephalography and evoked potentials. As in the OR and other non-OR sites, the anesthesiologist and proceduralist need to be aware of each other’s plan, progress, and complications.

ENDOVASCULAR TREATMENT OF CEREBRAL ANEURYSMS

Endovascular treatment of cerebral aneurysms achieves percutaneous isolation of aneurysms from the circulation by placement of a soft platinum coil within the aneurysm (see also [Chapter 57](#)). Intraaneurysmal embolization may require the placement of several coils. Coiling procedures are least complex in aneurysms with a small, narrow neck. Coiling of wide-necked aneurysms requires the introduction of a stent with the coil subsequently introduced through the stent.⁵¹ Stent implantation, which requires preprocedure and postprocedure anticoagulation, increases bleeding risk; therefore, stent-assisted coil embolization is limited to unruptured aneurysms. Endovascular treatment with coils demonstrated better outcomes than surgical clipping in patients who sustained a subarachnoid hemorrhage related to an aneurysm, but clipping improved resolution of cranial neuropathies.⁷⁰

Complications include aneurysm rupture or thromboembolism. If rupture occurs, heparin should be reversed with protamine (1 mg/100 IU heparin) and the arterial blood pressure decreased by the anesthesiologist. The usual course of action is to continue the coiling as quickly as possible. Thromboembolic events, usually platelet related, occur in 3% of cases and cause permanent neurologic deficit in 1.7% to 5% of cases⁷¹ (see also [Chapter 50](#)). If a thromboembolic event occurs, the proceduralist will make an attempt to dissolve or remove the clot with either a mechanical device or the intraarterial administration of a thrombolytic or antiplatelet agent.

Some aneurysms have no neck or are inaccessible. This is the case most commonly with cavernous, petrous, extracranial vertebral, internal carotid, or giant aneurysms of the subarachnoid space. Treatment of these aneurysms requires parent artery occlusion, which is possible only if good collateral flow exists. This requires a preliminary procedure known as a parent artery balloon test occlusion.⁷² It involves first advancing a wire to the site of the proposed artery sacrifice. A neurologic examination is then performed, heparin is administered to prolong the activated

clotting time, and a balloon is inflated to occlude the artery. Neurologic examination follows. In some institutions radioisotope enhanced cerebral vascular studies are undertaken. If the patient tolerates occlusion, coiling may proceed. If not, a surgical intracranial bypass may be required.

ENDOVASCULAR TREATMENT OF ARTERIOVENOUS MALFORMATIONS

AVMs in the brain are an area of direct connection between small arteries and the venous system without normally intervening capillaries. The usual presentation of this lesion is intracranial hemorrhage. Patients with AVM must be angiographically evaluated for the presence of associated aneurysms. This evaluation involves catheterization of selective feeder arteries to determine the precise source of the hemorrhage. Current therapy for cerebral AVM includes embolization, microsurgical resection, stereotactic radiosurgery, or combination treatment. Embolization preceding surgery can minimize bleeding and reduce AVM size. Small AVMs may be appropriate for endovascular treatment. Techniques for embolization of AVMs in the neuroradiology suite include the use of flow-directed microcatheters, solid occlusive devices, particulates, and liquid embolic agents. Complications include embolization of post-AVM vessels precipitating rupture, passage of embolic material into the pulmonary circulation, and microcatheter entrapment.⁷³

Interventional Neuroradiology: Acute Stroke Treatments

Acute embolic stroke treatment has evolved significantly over the last 10 years. Intravenous r-tPA treatment has been supplemented with intraarterial thrombolysis as it allows extension of the treatment time window from 3 to 6 hours, delivers a higher concentration of lytic drug to the target vessel, yields higher recanalization rates, and can be combined with other interventional techniques.

Initially, a detailed cerebral angiogram is obtained and the level of occlusion is identified. A microcatheter is inserted over a microguidewire, contrast is injected, and the clot is localized. At this point, r-tPA is injected beyond the clot and the catheter is pulled back through the thrombus. If the occlusion persists, mechanical means of clot disruption or extraction are considered. This must be undertaken within 8 hours of the event. Several devices are available for retrieval or aspiration. Stent placement or angioplasty is also possible. A recent study of thrombectomy in patients treated within 8 hours demonstrated a recanalization rate of 57.3% of treatable vessels and 69.5% after adjunctive therapy. Thirty-nine percent of patients had favorable outcomes.⁷⁴ The therapeutic window available for interventions is 6 hours after the patient was last seen as normal for intraarterial thrombolysis and 8 hours for mechanical clot disruption. The recently published DAWN trial showed that the time window for endovascular thrombectomy may be extended to 24 hours with certain selection criteria.⁷⁵

Patients presenting with acute stroke can range in presentation from relatively stable to severely compromised. Often the anesthesia team has little time to gather preoperative information. Evidence from studies suggests that

anesthetic choice may have an impact on neurological outcomes. General anesthesia may provide comfort and an immobile patient; however, it can also prolong time to treatment and produce unfavorable hemodynamic perturbations. Monitored anesthesia care, on the other hand, allows for quicker intervention and fewer hemodynamic swings; however, patients may be uncooperative and at risk of aspiration as the airway is not protected. To date there are no randomized controlled trials, but retrospective studies suggest that sedation may offer improved neurological outcomes.⁷⁶ Anesthetic choice should first and foremost be guided by the patient's condition and tailored to each individual situation.

Invasive blood pressure monitoring is preferable and can be obtained after the procedure is started as long as it does not delay time to treatment. If intracranial pressure is an issue, a bolt or extraventricular drain may be necessary to measure intracranial pressure during the procedure.

Interventional Cardiology Procedures: General Considerations for the Electrophysiology and Catheterization Laboratories

For the past 20 years, medicine has witnessed a crescendo of new procedures in electrophysiology and interventional cardiology. In parallel, the need for anesthesiology involvement has increased. For instance, the electrophysiology laboratory now offers expanded treatment options for patients with late-stage heart failure and complex arrhythmias. Because many of these procedures are long and involved, most are performed with general anesthesia or a combination of sedation and general anesthesia. Similarly, percutaneous treatment of structural heart disease has become part of the repertoire of interventional cardiologists creating new and exciting opportunities for cardiac anesthesiologists. The opportunity to provide real-time echocardiographic guidance represents a new horizon for cardiac anesthesiologists who can now care for structural heart disease patients as co-proceduralists (further discussed in the addendum to this chapter).

Many patients in both the electrophysiology and catheterization laboratories have significant comorbidities. The proceduralists involved may be unaware of the ramifications for procedural success. In this new and challenging arena, collaboration and planning between interventionalist and anesthesiologist are required to ensure patient safety and optimize outcome. A clear understanding of the procedure to be performed, possible pitfalls, and unique patient characteristics is necessary for the formulation of a safe and effective plan. As always, a common knowledge base and vocabulary facilitate integration of care.

THE ELECTROPHYSIOLOGY LABORATORY ENVIRONMENT: UNIQUE CHALLENGES FOR ANESTHESIOLOGISTS

This section presents an overview of electrophysiology laboratory environments, the evolution and future pathways of current practices, cases performed in each venue, and

current anesthetic approaches. Common electrophysiology laboratory procedures include the following (see also [Chapter 38](#)):

1. Electrophysiology studies
2. Atrial and ventricular ablation procedures
3. Implantation and removal of cardioverter-defibrillator and pacing devices

Invasive cardiology procedures performed in the cardiac catheterization laboratory include the following:

1. Diagnostic cardiac catheterizations and coronary interventions
2. Peripheral vascular diagnostic and therapeutic procedures
3. Implantation of intraaortic balloon pumps (IABPs) and percutaneous left ventricular assist devices
4. Amelioration of structural heart disease by the placement of intracardiac devices

These procedures potentially require the involvement of anesthesiologists if the patient has significant comorbidities. However, some ablations and electrophysiology studies and some device implants and removals can be performed with nurse-administered sedation. Some procedures are lengthy and technically demanding and require that the patient be still; in such situations, preservation of hemodynamic stability and need for a motionless field may indicate the need for a general anesthetic.

The electrophysiology and catheterization laboratory environments differ significantly from the OR. It is important for anesthesiologists to recognize the limitations of the venue and understand the flow of cases and responsibilities of ancillary personnel. Innovation and flexibility are necessary with respect to equipment availability and positioning, and the nature and tempo of the anesthesiology-cardiology interface.

Room Configuration and Equipment Layout

Electrophysiology and catheterization laboratories are built with separate control stations and procedure rooms. The control area is shielded from radiation and is the vantage point from which the progress of the procedure can be recorded. An operator may record procedural and patient monitoring data as well as video and audio information. The operator may also engage in digital record keeping. The ability to manipulate anesthetic equipment is typically not included in the array of controls in the station.

Within the procedure room itself, cardiologists, anesthesiologists, nurses, and radiology technicians contribute to the care of the patient during the procedure. It can be daunting to know who is who and who is responsible for what; thus, it is best to ask if unsure. In an emergency, understanding who is in charge of a life-saving therapy (i.e., the defibrillator) can eliminate confusion and save lives.

The procedure room includes fluoroscopy equipment (x-ray tube and C-arm), which usually surrounds the patient's head making access difficult. The procedure table is mobile and screens for viewing the procedure are typically at 90 degrees to the anesthesiologist. Sterile tables for the cardiologist, closets or portable storage units for various catheters and wires for the procedures, and blood analysis machines may take up a significant amount of space, which

can make the inclusion of anesthesia equipment (machine, cart, pumps, monitors) challenging. Ceiling lead screens and procedure table lead skirts are typically not available to the anesthesiology team and thus protection from radiation often requires the use of portable lead screens wheeled between the anesthesia area and the fluoroscopy equipment.

The anesthesiologist should become familiar with the contents of each procedure room. Gas outlets and suction, monitors for vital signs, the cardioverter-defibrillator, emergency medications, and airway equipment are critical and may not be optimally or even obviously placed. Longer tubing or extensions may be needed for ventilator hoses, intravenous lines, and suction. Electrical outlets may not be sensibly located, requiring the use of extension cords. Other equipment frequently found in these rooms may include ventricular assist devices, IABP, device programmers, and echocardiography machines. Space can become an issue during complex cases when a plethora of equipment is needed.

The fluoroscopy table and fluoroscopy equipment are controlled by radiology technicians and cardiologists. These move during the procedure to facilitate imaging, sometimes with no warning. As with all NORA locations, the local availability of extra equipment and an emergency airway cart becomes essential when the anesthesia workroom is not nearby. With cardiac patients, time can be especially critical. An anesthesia cart stocked with intravenous lines, airway equipment, and essential medications is important in the electrophysiology and catheterization laboratories. All personnel in the laboratory should be informed about the location and names of emergency equipment, particularly when an anesthesiologist is working alone.

Anesthesiologists in the Electrophysiology Laboratory

Clinical electrophysiology has redefined itself over the past 20 years (see also [Chapter 38](#)). Advanced technology and increased demand have driven exponential growth in the number of electrophysiology procedures. Additionally, the scope of these procedures has also dramatically changed from simple diagnostic procedures to major life-saving therapeutic interventions. More than 14 million Americans are affected by arrhythmias and approximately 6 million are affected by heart failure,⁷⁷ many of whom require hospitalization and complex medical care. ICDs reduce mortality and morbidity in those with malignant tachyarrhythmias as well as in patients with a reduced ejection fraction,⁷⁸ and as a result, implantations and revisions of these devices have skyrocketed.⁷⁹

The performance of many of these procedures frequently mandates the administration of general anesthesia because of procedure duration and patient comorbidities that increase the difficulty of tolerating a procedure with sedation alone. Optimal anesthetic planning requires the anesthesiologist to integrate patient comorbidities, the nature of the arrhythmia, and the tempo and framework of electrophysiology procedures. This section reviews the most commonly performed electrophysiology procedures.

DIAGNOSTIC ELECTROPHYSIOLOGY STUDIES

Abnormal heart rhythms occur from many etiologies and range from being asymptomatic to creating hemodynamic instability and cardiac compromise. In general, these rhythms result in uncoordinated or ill-timed contractions and can be too slow or too fast. Bradyarrhythmias arise from either abnormal impulse generation or abnormal impulse propagation, and the disease may occur at the level of the sinus node, the atrioventricular node, or the His-Purkinje system. Tachyarrhythmias that are regular with a normal QRS include supraventricular tachycardias (SVT) such as atrial flutter, atrioventricular nodal reentry tachycardia (AVNRT), atrioventricular reciprocating tachycardia (AVRT), and atrial tachycardia. Supraventricular tachyarrhythmias with a normal QRS that are irregular include atrial fibrillation and multifocal atrial tachycardia. Tachyarrhythmias with a wide QRS may still be reflective of a supraventricular tachyarrhythmia but with aberrancy due to a preexisting bundle branch block or may originate within the ventricle as a ventricular tachycardia (VT).^{80,81} Arrhythmias can have many etiologies including overactive electrical foci or structural heart disease leading to scar-triggered electrical activity. Common electrophysiologic generators of arrhythmias include abnormal automaticity, anatomic reentry, and triggered activity.

These abnormalities can be identified with diagnostic electrophysiology studies, which are usually undertaken in conjunction with a therapeutic procedure to either treat a specific arrhythmia or place a device (see also [Chapter 38](#)). Diagnostic studies can determine the electrophysiologic etiology of specific symptoms or events. Intracardiac recordings are made from catheters placed via femoral venous access into the high right atrium, bundle of His, coronary sinus, and right ventricular apex or right ventricular outflow tract. Arrhythmias are induced by programmed stimulation.⁸² For these studies, sedation with benzodiazepines and short-acting opioids is usually sufficient. Drugs that may affect inducibility of certain arrhythmias should be avoided.

CATHETER ABLATION

Treatment of certain arrhythmias may be accomplished using percutaneous catheter-based ablation techniques. Radiofrequency energy (thermal injury) and cryotherapy (cold-induced injury) are most commonly used for ablation; both energy sources can be painful when delivered to target tissues. Ablation techniques are used for arrhythmias that are refractory to pharmacologic therapy. These arrhythmias may include SVTs such as AVNRT, Wolf-Parkinson-White syndrome (antidromic AVRT), atrial flutter, and atrial fibrillation. With regard to atrial fibrillation: recent American College of Cardiology (ACC) and American Heart Association (AHA) Atrial Fibrillation Guidelines state that in patients with little or no left atrial enlargement, catheter ablation is a “reasonable alternative to pharmacologic therapy” to help prevent recurrence of atrial fibrillation.⁸³ Atrial fibrillation may be treated with pulmonary vein isolation or, if complicated by an uncontrollable rapid ventricular response, ablation of the atrioventricular node and

placement of a permanent pacemaker. In select patients, VT can be treated with ablation as well, such as that arising from coronary artery disease or arrhythmogenic right ventricular dysplasia.⁸⁴

During ablation procedures, catheters are placed throughout the cardiac chambers and programmed stimulation is performed from different sites to induce tachyarrhythmias. Complex mapping techniques localize the source of the arrhythmia to identify the exact intracardiac location to which the energy must be applied. Because of the precision required for mapping and the application of energy, a still field is required. Many catheter ablation procedures, such as atrial flutter ablations, can be performed with sedation; sedation may, in fact, be preferred as arrhythmias can be suppressed with general anesthesia. However, procedures such as atrial fibrillation ablations can require 4 to 6 hours of procedure time followed by a 30-minute observation time after ablation with repeat stimulation (sometimes with the application of pharmacologic agents such as isoproterenol or adenosine) to ensure success of the procedure.⁸⁴ These longer procedures may be challenging to conduct with monitored anesthesia care as undersedation may result in back pain and patient movement, and oversedation may result in snoring or partial airway obstruction with resultant swinging of the intraatrial septum making transseptal catheter placement difficult; hence, general anesthesia may be required for optimal procedural conditions and patient comfort.

The quest for a near static field has led to the rising use of HFJV, particularly in atrial fibrillation ablations because sustained contact between the catheter and the area around the pulmonary veins is often required. HFJV aims to eliminate cardiac translation in the thoracic cavity due to tidal ventilation and reduce the potential for catheter instability⁸⁵; this technique may decrease procedure time,⁸⁶ though patient and proceduralist characteristics such as ejection fraction and case volume performed by the electrophysiologist may be influential.⁸⁷ HFJV typically requires monitoring of arterial CO₂ either via arterial blood gas analysis or with intermittent traditional mechanical ventilation to obtain an end-tidal CO₂ measurement. Hypercarbia refractory to adjustments in jet ventilation settings may require a transition back to traditional ventilation. Due to the unpredictable delivery of volatile anesthetic with HFJV, total intravenous anesthetic techniques are typically necessary.

The anesthetic management of electrophysiologic ablation procedures involves several other concerns.^{88,89} Paralysis should be avoided during ablation so that phrenic nerve stimulation and activity can be used as an alert to avoid its injury; remifentanil or sufentanil infusions can be administered in this setting. The esophageal temperature should be monitored for conductive heat transfer to the esophagus, which can result in esophageal injury; the correct position of the temperature probe can be verified easily with fluoroscopy. Radiofrequency (as opposed to cryotherapy) ablation may require irrigation, which can result in the administration of a substantial amount of fluid to the patient over the duration of the case; a careful tally and regular assessment of fluid balance may alert the anesthesiologist to the potential need for diuretic administration. Finally, cardiac tamponade may rarely occur as a result of ablation or wire

perforation; this uncommon complication should be considered in the differential of hypotension of unknown origin or with narrowing of the pulse pressure. A diagnosis of tamponade can be confirmed with ultrasound (transesophageal, intracardiac, transthoracic) and requires reversal of heparin with protamine, placement of a pigtail catheter for drainage, and the potential involvement of a cardiothoracic surgeon.

Arterial line monitoring may be necessary for VT ablations due to the nature of the arrhythmia being induced. Arterial lines may not be required for other ablations (atrial fibrillation and other SVTs) unless desired for HFJV or for monitoring of patients with ventricular dysfunction, who may also require inotropic and vasoactive agents to maintain hemodynamic stability during arrhythmia induction. Close communication with the cardiologist is necessary in these situations. Frequently, electrical cardioversion is necessary during these cases.

ELECTROPHYSIOLOGIC DEVICES

Devices for the treatment or control of arrhythmias have diminished in size and increased in sophistication over the past 10 years (see also [Chapter 38](#)). More patients qualify for device implants, and hence the number of procedures for implantations, revisions, battery changes, and upgrades of devices has grown. The two most common types of devices are ICDs and pacemakers.

Implantable Cardioverter-Defibrillators

ICDs have been demonstrated to be efficacious and safe in a number of large, prospective multicenter randomized trials in patients with and without coronary artery disease. ICDs have been found to be particularly beneficial in patients with depressed left ventricular ejection fractions (35% or less).⁹⁰ The ACC, AHA, and the Heart Rhythm Society (HRS) guidelines detail the indications for ICD implantation and the conditions for which these devices prolong life and decrease the risk of sudden cardiac death.⁹¹ With the advent of smaller biphasic, transvenous ICDs and experience gained over the years, it is now feasible for electrophysiologists to implant ICDs safely in the pectoral position in the electrophysiology laboratory. Local anesthesia combined with conscious sedation is frequently used for these procedures. Defibrillation threshold testing may be performed, and in these instances the role of the anesthesiologist may be crucial, particularly if patients have significant comorbidities. Testing the device requires deep sedation or general anesthesia and can be accomplished without an arterial line. External cardioverter-defibrillator pads are placed on the patient at the beginning of the procedure and serve as backup if the implanted device fails during the test. Defibrillation threshold testing is sometimes omitted due to elevated risk of the procedure in patients who may not have adequate physiologic reserve (such as those with untreated coronary artery disease). In addition, the newer ICDs may obviate the need for such maneuvers.

Subcutaneous ICDs (S-ICDs), which eliminate the need for transvenous leads, are also available for implantation. Although these devices detect and treat malignant VT and VF, they are incapable of providing anti-tachycardia pacing, advanced diagnostics, or radiofrequency interrogation

with remote monitoring, and therefore are not appropriate for all patients. Implantation of these devices requires tunneling of a relatively large lead, which can be painful enough to require deep sedation or general anesthesia.⁹²

Pacemakers

Pacemakers may have one lead (typically right ventricular), two leads (right atrial and right ventricular), or three leads (right atrial, right ventricular, and left ventricular via the coronary sinus) for the purpose of providing coordinated biventricular pacing for cardiac resynchronization therapy (CRT). CRT with and without defibrillation systems is prescribed for both primary and secondary prevention of sudden cardiac death in patients with heart failure associated with both an ischemic and nonischemic etiology. The ACC/AHA/HRS guidelines gave CRT with or without an ICD a class I indication for those with a left ventricular ejection fraction 35% or less with a QRS duration 120 ms or greater and drug-refractory New York Heart Association functional class III or IV heart failure who are receiving optimal medical therapy.⁹¹

While single and dual lead pacemaker placements may be accomplished with conscious sedation and standard monitors, the anesthetic strategy for the implantation of biventricular ICDs requires greater thought. CRT implantation may be successfully accomplished with sedation but could require general anesthesia for a number of reasons. For example, the indications for CRT also function as significant patient comorbidities (e.g., ejection fraction less than 35% secondary to coronary artery disease or valvular heart disease that could be associated with pulmonary hypertension and right ventricular dysfunction), which may impact on the safety of performing sedation. These procedures may be complex and lengthy because of difficulty in positioning the left ventricular lead into the coronary sinus and great cardiac vein in the setting of distorted ventricular anatomy due to cardiac dilatation and advanced heart failure. In addition, valvular regurgitation can complicate lead positioning. Finally, lead dislodgement may occur immediately after lead placement, especially in patients with a large coronary sinus, further prolonging these procedures.

During any device placement, pneumothorax or coronary sinus perforation related to lead placement is possible. Coronary sinus perforation can immediately be recognized by contrast extravasation. Perforation of the coronary sinus or cardiac perforation related to right atrial or ventricular lead placement may cause cardiac tamponade, necessitating immediate pericardiocentesis. Paralytics should be avoided as well, so that lead placement resulting in diaphragmatic pacing can be immediately identified and avoided.

Anesthesiologists in the Catheterization Laboratory

Anesthesiology in the catheterization laboratory reflects the evolving range of therapies performed in this venue. Catheterization laboratories—initially the workplace of interventional radiologists (who were the “original” angiographers)—are now home to interventional cardiologists, vascular surgeons, and others who practice a broad range of therapies. All of these practitioners use fluoroscopy and a

host of ever more sophisticated interventional technologies. Procedures can be peripheral or cardiac and range from the stenting of narrowed vessels to the implantation of prosthetic heart valves. Anesthesiology involvement ranges from providing monitored anesthesia care to providing a full cardiac anesthetic and performing transesophageal echocardiography (TEE) during the case.

PERCUTANEOUS CORONARY INTERVENTIONS

Percutaneous coronary interventional procedures for patients with both stable coronary artery disease and acute coronary syndromes have grown in the past 10 years. Percutaneous coronary interventions (PCIs) include coronary angioplasty (mostly performed immediately before coronary stenting) with both bare metal stents and drug-eluting stents, atherectomy procedures, and intracoronary thrombectomy procedures. PCI procedures are commonly performed in patients with 70% or greater intracoronary luminal atherosclerotic obstruction and myocardial ischemia in the context of stable coronary disease. The major benefit of PCI is to reduce or relieve symptoms of ischemic heart disease and increase aerobic capacity.⁹³ No significant difference in total mortality, nonfatal myocardial infarction, or other major cardiovascular events were demonstrated between patients randomized to aggressive medical therapy versus aggressive medical therapy plus PCI angioplasty with bare metal stenting.⁹⁴ But for patients who presented with acute coronary syndromes, PCI decreased mortality and recurrent myocardial infarction in contrast to medical treatment alone.⁹⁵

PCIs can be performed with mild to moderate nurse-administered sedation under the direction of the cardiologist. Anesthesiologists are usually involved only when patients present with known severe comorbidities (e.g., oxygen-dependent COPD, opioid tolerance) or with the development of respiratory or hemodynamic compromise. If acute respiratory or hemodynamic decompensation occurs, anesthesiologists are often called emergently. In these circumstances, clear and direct communication with the cardiologist is required and management decisions usually need to be made expeditiously. Information such as medications given, intravenous access, and stage of the procedure must be communicated. As mentioned previously, access to the patient's head can be difficult due to x-ray equipment. If an airway needs to be established, it may be necessary to temporarily move the table and fluoroscopy equipment. Placement of an endotracheal tube is preferred to a LMA even in an elective situation because constant movement of the equipment can dislodge the LMA; however, an LMA can serve as a temporizing measure if placement of an endotracheal tube is difficult. During PCI, patients can be in a highly anticoagulated state, and a bleeding difficult airway is a nightmare in this context.

INTRAORTIC BALLOON PUMPS AND PERCUTANEOUS VENTRICULAR ASSIST DEVICES

The IABP is a mechanical device inserted percutaneously into the aorta that increases myocardial oxygen delivery and cardiac output. The balloon, sitting approximately an inch distal to the subclavian artery, inflates and deflates in diastole and

systole, respectively, thereby delivering counterpulsation. This increases coronary blood flow and myocardial oxygen delivery and decreases afterload resulting in a rise in cardiac output. The balloon pump is controlled by a programmed console, which inflates the balloon at time intervals linked to either an electrocardiogram trace or a pressure transducer at the distal tip of the catheter. The placement of an IABP is usually successful under conscious sedation unless the patient is compromised from a hemodynamic or respiratory standpoint, in which case the team may seek assistance from an anesthesiologist.

Percutaneous ventricular assist devices (PVADs) can provide cardiac output support during high-risk PCI or cardiogenic shock associated with myocardial infarction. Several types of PVADs are available. The TandemHeart device (CardiacAssist, Philadelphia, Pennsylvania) is a percutaneous left-atrial to femoral arterial bypass system consisting of a transseptal cannula, an arterial cannula, and an externally located centrifugal blood pump, which can deliver flow rates of up to 4 L/min.⁹⁶ An alternative percutaneous-based left ventricular assist device is the Impella (Abiomed, Danvers, Massachusetts), which comes in three sizes: 2.5, CP, or 5.0; cardiac outputs of either 2.5 L/min, 4.3 L/min, or 5.0 L/min can be achieved with these devices, respectively.⁹⁷ The Impella uses a cannula inserted retrograde via the femoral artery into the left ventricle across the aortic valve. These pumps do not require transseptal puncture, are smaller and easier to implant, and incorporate a microaxial pump into the catheter system thereby eliminating the need for extracorporeal blood. Anesthesiologists are often consulted for placement of these devices because the patients are unstable and/or present with a high likelihood of hemodynamic compromise. Depending on the procedure and state of the patient, either sedation or general anesthesia can be used. These devices achieve cardiac outputs that can completely replace left ventricular function; blood flow may not be pulsatile, so pulse oximetry and noninvasive blood pressure cuffs may not work properly. However, invasive monitoring is available via the arterial cannulation used during the procedure and arterial blood gas analysis can provide information on gas exchange. The choice of anesthetic, likely postprocedural care, and prognosis should be discussed with the cardiologist before the start of the case, if possible.

PERCUTANEOUS CLOSURE OF SEPTAL DEFECTS

The percutaneous closure of septal defects includes closure of PFOs and secundum atrial septal defects (ASDs). Initial studies assessing the efficacy of percutaneous closure of PFOs in patients who have suffered from a cryptogenic stroke showed no benefit.⁹⁸⁻¹⁰⁰ However, these studies have recently been supplanted by several multicenter randomized controlled trials showing decreased rates of recurrent stroke, particularly in young patients with large shunts.¹⁰¹⁻¹⁰⁴ The Food and Drug Administration (FDA) approved use of the Amplatzer PFO Occluder (St. Jude Medical Inc., St. Paul, Minnesota)¹⁰⁵ based on the results of one of those studies, the RESPECT trial, which showed a 50% reduction in the rate of new strokes in patients using the occluder plus blood-thinning medications compared with blood-thinners alone.¹⁰³

The Amplatzer Septal Occluder is used in clinical practice for closure of secundum ASDs. This occluder is a two-sided “clam shell” made up of two flat discs with a middle or “waist.” The discs are made of nitinol (nickel and titanium) wire mesh and polyester fabric inserts, the latter of which create a nidus for tissue growth after placement.¹⁰⁶ The closure of PFOs tends to be simpler than the closure of ASDs. In patients with ASDs, it is important to clarify right ventricular function, pulmonary arterial pressures, and shunt fraction to formulate an optimal anesthetic plan. Success rates for PFO and ASD closure range from 79% to 100%.¹⁰⁷

These occluder devices can also be used to close other types of defects such as paravalvular leaks and muscular or perimembranous ventricular septal defects (VSDs), either congenital or acquired. Reportedly, VSDs can be closed 96% of the time, with a 2% major complication rate with these devices.¹⁰⁸ In patients with traumatic (postmyocardial infarction) VSDs, hemodynamic instability is not unusual and complications are common during closure attempts. Tissue integrity is frequently compromised making placement of closure devices difficult. Visualization of the defect and guidance of device placement can also be challenging. Patients with postmyocardial infarction VSDs are more likely to have complications during closure of the defect.¹⁰⁹

Complications of any device placement in the cardiac catheterization laboratory include air embolism, device embolization, malposition, thrombosis, arrhythmias, hypotension, valve dysfunction, cardiac perforation, and injury to non-target cardiac structures. It is critical that these complications be recognized and dealt with expeditiously. Rapid and effective communication is critical. Untoward events may be evident initially to anesthesiologists if they are guiding the procedure with TEE.

Echocardiography is often used during the placement of intracardiac septal occluder devices to help guide placement and confirm a successful result. TEE can be performed by cardiologists, anesthesiologists, or ultrasound technicians depending on institutional preference and availability of personnel, and if used, requires general anesthesia (see also [Chapter 37](#)). Although two-dimensional (2D) echocardiography is the most widely used imaging technique for pre-procedural patient evaluation, multidetector row CT and cardiac MRI can also help to delineate structural intracardiac details. Intraprocedural three-dimensional (3D) TEE is also available.¹¹⁰ Intracardiac echocardiography (ICE) can be used to guide the procedure, but this must be performed by the cardiologist because the controls are at the groin in the field. In cases in which TEE is not available or cannot be performed because of patient comorbidities, ICE is a reasonable alternative, in which case general anesthesia may not be needed.

PERIPHERAL ARTERIAL DISEASE

Peripheral arterial disease affects approximately 8 million Americans (see also [Chapter 56](#)). The prevalence of this disease increases with age and occurs more commonly in African Americans. Intermittent claudication and rest pain are the principal symptoms. Claudication occurs as a result of insufficient arterial blood flow and leg ischemia and is often described as pain, aching, or a sense of fatigue that is

relieved at rest. Symptoms are most often experienced in the muscle bed supplied by the most proximal stenosis. Buttock, hip, or thigh claudication is related to obstruction of the aorta or iliac flow, calf claudication is commonly a result of either femoral or popliteal arterial stenosis, and ankle or pedal claudication is typically caused by either tibial or peroneal disease.¹¹¹

According to ACC and AHA guidelines, percutaneous revascularization in patients with intermittent claudication should be considered when any one of the following circumstances is encountered:

1. Claudication symptoms significantly disable the patient.
2. The patient would benefit from an improvement in exercise.
3. Rehabilitation and pharmacologic therapy have not provided an adequate response.
4. A favorable risk-to-benefit ratio to performing the procedure exists.
5. The characteristics of the lesion permit appropriate intervention at low risk with a high likelihood of initial and long-term success, and/or the patient has limb-threatening ischemia, as manifested by rest pain, ischemic ulcers, or gangrene.¹¹²

The majority of cases are performed with sedation. The anesthesiologist may be critical to the interventional cardiologist during a peripheral vascular intervention because many of these patients are unable to lie still during the procedure because of rest pain symptoms and other related comorbidities. In addition, the procedure itself may create painful transient ischemia resulting in patient movement that may reduce the likelihood of success. Anesthesia care may also be required when the procedure is technically difficult and the patient is unable to cooperate or when vascular injury has occurred (i.e., formation of a hematoma).

PERCUTANEOUS VALVE REPAIR AND REPLACEMENT

Percutaneous technologies for the treatment of mitral regurgitation and aortic valve disease are presently available with ongoing development of devices and approaches. These procedures are a major addition to the repertoire of interventional cardiologists and represent an exciting new overlap of surgical and medical therapies for structural heart disease.

PERCUTANEOUS MITRAL VALVE REPAIR

Surgical repair is typically indicated for the treatment of symptomatic mitral regurgitation (with LVEF >30%) or asymptomatic mitral regurgitation with impaired left ventricular ejection fraction (EF 30% to ≤60%).¹¹³ However, alternate techniques of percutaneous mitral valve repair are under investigation including leaflet repair, direct annuloplasty, and coronary sinus annuloplasty.¹¹⁴

Mitral regurgitation can be percutaneously repaired by placement of a MitraClip (Abbott Vascular, Abbott Park, Illinois), a clip-like device that creates an Alfieri edge-to-edge repair. After a transatrial septal puncture, the clip is positioned in the center of the mitral valve orifice. The clip is opened, passed into the left ventricular cavity, pulled back

to contact the mitral valve leaflets, and then closed to create a double-orifice mitral valve.¹¹⁴ Direct mitral valve annuloplasty such as with the Cardioband system (Valtech Cardio, Inc., Or-Yehuda, Israel) mimics a surgical annuloplasty but delivers the device transseptally and implants on the atrial side of the annulus using multiple anchor elements.^{115,116} Devices that use the coronary sinus as a method of cinching the mitral annulus are investigational, and the safety and efficacy of this approach remains undetermined. General anesthesia, fluoroscopy, and TEE are used to help guide placement of these devices.¹⁰⁷

Percutaneous Aortic Valve Replacement (Transcatheter Aortic Valve Replacement)

Percutaneous aortic valve replacement or transcatheter aortic valve replacement (TAVR) is a relatively new treatment in the U.S. for aortic stenosis. During the procedure, a replacement valve is crimped into a catheter and passed through the femoral artery to the aortic annulus. Rapid ventricular pacing is employed to minimize cardiac output while the prosthesis is deployed into the appropriate position after a balloon valvuloplasty. Transaortic and transapical insertions of transcatheter valves can also be performed by a multidisciplinary team in a hybrid OR setting. In the future, other variants of this procedure will likely evolve for placement of valves in other positions.

The concept of a transcatheter valve for percutaneous placement was initially presented in the early 1990s, and the first percutaneous heart valve for human use was developed by Cribrier and implanted in Europe in 2002.^{117,118} Two devices currently exist for percutaneous implantation: the Edwards Lifesciences SAPIEN (Edwards Lifesciences, Irvine, CA) and the Medtronic CoreValve (Medtronic, Minneapolis, Minnesota). The Edwards SAPIEN valve received FDA approval in November 2011 and the CoreValve in January 2014.^{119,120} The SAPIEN valve is a bovine pericardial prosthesis sutured into a balloon-expandable tubular metal stent, while the CoreValve is a porcine pericardial self-expanding valve prosthesis sutured into a nitinol stent.

The population of patients eligible for TAVR has expanded from patients who are not surgical candidates¹²⁶ to those who are high-risk surgical candidates,¹²¹ and now encompass patients who are considered only intermediate-risk.¹²² In high-risk patients with severe aortic stenosis, TAVR was found to be noninferior to surgical aortic valve replacement at 1 year in terms of survival. However, the transcatheter procedure was associated with a higher risk for stroke than the surgical replacement at 1 year and a higher risk for major vascular complications at 30 days. More patients undergoing TAVR demonstrated improved symptoms at 30 days, but no significant between-group difference was seen at 1 year.¹²¹ In intermediate-risk patients, the rates of both death and disabling stroke at 2 years were comparable to those who underwent surgical aortic valve replacement; however, similar to the trial studying high-risk patients, the TAVR group had more major vascular complications and also showed improved symptoms compared with the surgery group at 30 days but not at other time points.¹²² The use of TAVR for treatment of failing aortic bioprostheses (with valve-in-valve therapy) due to either stenosis or

regurgitation has also been increasing. The rapid expansion of indications for TAVR has prompted a task force examining appropriate use criteria of this technology.¹²³

CTs are typically obtained before the procedure to define valve size and anatomy. Patients are frequently elderly with severe valvular disease and attendant comorbidities; thus, planning for expected difficulties related to patient comorbidities and technical challenges is well worth the extra time. A team meeting before the procedure is worthwhile because elements of the patient's history often warrant interdisciplinary scrutiny and discussion.

Transfemoral TAVR can be performed in a cardiac catheterization laboratory or hybrid OR. At our institution, all percutaneous valve repairs are performed under general anesthesia with fluoroscopic and TEE guidance. As technology improves, the flow of cases will change. Presently, however, at our institution, the following list constitutes the framework for transfemoral cases:

Critical Procedural Steps During Transfemoral Transcatheter Valve Replacement

1. Place intravenous line and arterial line, induction.
2. Place PA line, larger access, cerebral SvO_2 .
3. Conduct TEE, discussion of expected and unexpected findings with entire team.
4. Access femoral vasculature: arterial sheath, contralateral transfemoral aortic occlusion balloon, and place transvenous pacer.
5. Perform standard balloon aortic valvuloplasty: refine sizing and enlarge orifice.
6. Assess adequacy of rapid ventricular pacing.
7. Upsize sheath to (27 Fr) or appropriate introducer.
8. Advance transcatheter valve; assess position by fluoroscopy and echocardiography.
9. Deploy valve during rapid ventricular pacing.
10. Assess valve position and function.
11. Remove sheath and complete vascular closure.

Large peripheral intravenous lines should be placed for volume administration. Invasive arterial pressure monitoring is important because noninvasive blood pressure cuffs may not work when the patient is rapidly paced. Central access is useful for infusions and a Swan-Ganz catheter is recommended in compromised patients.

TEE plays a critical role in the management of patients undergoing TAVR (also see [Chapter 37](#)). Before any intervention, aortic stenosis with a trileaflet valve should be confirmed—TAVR cannot be performed with bicuspid valves. The degree of aortic insufficiency should be assessed before valvuloplasty, as the presence of preoperative mild to moderate aortic insufficiency may be protective in severe new-onset cases after balloon aortic valvuloplasty. Ejection fraction, degree of mitral and tricuspid regurgitation, presence of mitral annular calcification and mitral stenosis, estimated pulmonary artery pressures, and coronary artery takeoff location are also useful measurements. Accurate measurement of the aortic annulus aids in the choice of prosthetic valve size.

During the placement of the valve, real-time echocardiographic guidance, either 2D or 3D, can assess positioning of

the prosthesis. Multiple attempts may be needed to ensure proper catheter and device placement with an acceptable result. Following valve deployment, rapid assessment of valve position, function, and perivalvular and central leaks is crucial; verification of the patency of the coronary ostia and absence of new ventricular wall motion abnormalities is critical as well. Communication and visual accessibility to all imaging during the procedure is vital to successful placement of the device. Patients may develop hemodynamic instability, myocardial ischemia, or significant arrhythmias during the case, so constant communication between anesthesiologist and cardiologist is critical. Planned extubation is reasonable assuming the patient's comorbidities and the course of the procedure warrant it.

Multiple aspects of this procedure may evolve in the future. For instance, the percutaneous femoral approach requires adequate endoluminal diameters, but as technology develops, smaller sheaths and more flexible valves will become available. Thus, in the future, tortuous iliac vessels or high athermanous burden may not preclude a femoral approach. In addition, the merits of intraprocedural TEE versus transthoracic echocardiography or fluoroscopy alone are under active debate.¹²⁴ Similarly, while general endotracheal anesthesia is preferred, institutions in the U.S. and Europe have reported successful outcomes with conscious sedation.¹²⁵

Common Complications and Remedies

Vascular Avulsion, Perforation, or Dissection. A number of vascular problems can occur during insertion and removal of the introducer sheath. Vascular dissection or perforation, while rare, are known complications. Femoral vascular avulsion is possible on removal of the introducer sheath. Temporization of hemorrhage can be achieved with the distal aorta occlusion balloon residing in the contralateral femoral artery. This can prevent fatal hemorrhage in the event of a vascular catastrophe. If percutaneous access cannot be obtained, cut-downs or surgical access to the aortic bifurcation is possible. Vascular surgical repair is necessary in this situation.

Pacing Malfunction. Transvenous pacing is used to establish rapid ventricular pacing and a near-zero cardiac output state during ballooning of the aortic valve. If atrioventricular node dysfunction occurs after valvuloplasty or valve deployment, postdeployment pacing may be necessary. Poor communication during rapid ventricular pacing may be catastrophic. Loss of pacer capture during balloon valvuloplasty can place excessive traction on the native valve during balloon inflation, and unexpected ventricular ejection can embolize the valve from the annulus during deployment.

Valve Deployment. Patients respond idiosyncratically to balloon valvuloplasty; new-onset aortic insufficiency may require significant support and necessitate rapid valve introduction and deployment. Inotropic support may be necessary to maintain systemic blood pressure as balloons and crimped valves traverse the valve orifice.

Invasive monitors typically reflect low cardiac outputs, falling cerebral Svo₂s, and high pulmonary artery pressures. The authors routinely have boluses of epinephrine, norepinephrine, and vasopressin available in a variety of concentrations.

Valves left prepared on the balloon but not deployed for significant amounts of time may open improperly, causing significant aortic insufficiency. Deployment of an additional device (valve-in-valve) may be necessary in this case.

Device Embolization. Embolization into the aorta can occur as a result of ejection because of inadequate pacer capture or inappropriately high deployment. Once a valve is in the aorta, it is irretrievable endovascularly. Valves lodged in the descending aorta have been reported and are tolerated; however, a second valve must still be deployed in the aortic position. Valve loss into the ventricle may occur if deployment is too low. This result requires surgery for retrieval and may be fatal if comorbidities are significant.

Coronary Occlusion. Coronary occlusion is a potential problem if calcium or native aortic valve tissue occludes a coronary ostium. Prior coronary artery bypass graft with patent grafts is partially protective. Coronary guidewires may be placed in patients who are at higher risk. Skilled intervention is required to reopen occluded coronary arteries. Clear interdisciplinary communication is essential in the management of regional wall motion abnormalities, ST-segment changes, or hemodynamic compromise.

Need for Cardiopulmonary Bypass. Cardiovascular collapse during transfemoral procedures may require cardiopulmonary support. Institutional variability exists regarding the type of support planned. Some institutions have a primed cardiopulmonary bypass pump in the room, even if the case is in a catheterization laboratory outside of the OR; others have percutaneous VAD support on standby.

Neurologic Events. Acute stroke is potentially detectable with unilateral changes in cerebral oximetry readings. The higher stroke rate of cohort A patients in the PARTNER trial was felt to be a result of both the introduction of a large balloon and valve apparatus across the aortic arch and ballooning of the calcified native valve. Anesthetics allowing for early neurologic assessment are preferred.

As patient acuity increases, safe and efficient care for the target population in the cardiac catheterization and electrophysiology laboratories is a concern for all anesthesiologists and cardiologists. Anesthesiologists are uniquely trained to care for this complicated patient population while permitting cardiologists to focus on the interventional procedure. Anesthesiologists, in collaboration with cardiologists, must establish guidelines for the interdisciplinary care of patients with complex issues. The goal is to enhance patient safety, procedural efficiency, and outcomes while advancing the frontiers of medical care in venues outside of the OR.

Interventional Echocardiography Anesthesiologists as Co-Proceduralists—The Road Ahead

As percutaneous interventions for structural heart disease increase in number and broaden in scope, the need for multidisciplinary input grows. Cardiac anesthesiologists traditionally perform TEE in the OR before and after cardiopulmonary bypass to diagnose structural problems and assess surgical repair. In the catheterization laboratory, growing usage of general anesthesia to support patients during complex procedures ideally positions cardiac anesthesiologists to perform this service in a new context.

Diagnostic echocardiography is important in the catheterization laboratory, as it is in the OR. However, the novel feature of TEE performed in the catheterization laboratory (interventional TEE) is the need for step-by-step guidance of intricate and highly technical intracardiac manipulations (see also [Chapter 37](#)).¹²⁶ Fluoroscopy—the traditional imaging modality for interventional cardiology procedures—entails significant radiation exposure, requires the use of intravenous contrast, and can be temporally and spatially imprecise. Interventional TEE provides precise adjunctive imaging for placement or removal of intracardiac devices, placement of transcatheter valves, and repairs of paravalvular leaks or other structural defects. In addition, cardiac anesthesiologists understand imaging in the context of anesthetic care and are capable of manipulating hemodynamics as observation of cardiac function requires. Functional interpretation of structural defects can be critical as repairs are made. In the catheterization laboratory or hybrid OR setting, cardiac anesthesiologists become co-proceduralists providing imaging, hemodynamic control, interpretation, and step-by-step guidance for interventionalists in the context of fixing abnormal cardiac anatomy. Real-time 3D guidance during catheter placement, ballooning, or device implantation is an important and new component of interventional cardiology. This is a time-sensitive, high-acuity undertaking. It is relatively new in intracardiac imaging and for cardiac anesthesiologists; it defines an exciting and important role that goes a step beyond the job of maintaining homeostasis during the stress of surgery.

Interventional TEE is performed during septal occlusion, paravalvular leak repair, and transcatheter valve replacement. As in the OR, comprehensive interventional TEE examination begins with assessment of cardiac structure and function in the context of the proposed procedure, including the primary defect and any associated pathology. Effective communication among team members is critical because the value of interventional 2D and 3D TEE is lost if mutual understanding is absent. To this end, information from fluoroscopic and echocardiographic images can augment each other when unusual anatomy or clinical circumstances are observed. Data from each imaging modality should be discussed if contradictory interpretations arise.

Interventional TEE includes both 2D and Doppler imaging complemented by 3D and real-time 3D assessments. It may be important to alternate between 2D and 3D imaging to clarify temporal and spatial details^{127,128} so that accurate

placement of wires and catheters can occur. Closure of paravalvular leaks or stenting of stenotic pulmonary veins, for example, may require both types of imaging. Real-time 3D imaging can clearly depict the proximity of equipment and devices to targeted defects by permitting rotation of acquisitions in all directions, thereby delineating structures in their native orientation. Although in the OR it is possible to correlate actual anatomy with TEE images while the chest is open and the patient is on bypass, this is not the case during percutaneous procedures. The accuracy of imaging and interpretation is therefore critical.

During TAVR, interventional echocardiography is important for optimization of valve placement and diagnosis of problems when they occur. After TAVR deployment, a comprehensive TEE is performed. Valve position and function is assessed, gradients are calculated, the absence of coronary ostial occlusion is confirmed, and the need for any remedial activity is discussed. This requires the input of proceduralists and cardiologists alike.

As technology evolves, percutaneous procedures for structural heart disease will become more sophisticated. As devices improve, the target populations will grow. Patients with congenital, acquired, and surgically created defects will become eligible for treatment by interventional cardiology procedures. Interventional TEE has emerged as the newest evolutionary phase of cardiac anesthesiology.¹²⁹ The development of collaborative relationships between interventional cardiologists and anesthesiologists provides the foundation for a robust, multidisciplinary interface, thus establishing a basis for advancement of clinical practice and a place for anesthesiologists at the forefront of medicine.

The Road Ahead: Toward a Comprehensive Strategy

As technology evolves, medical procedures performed in locations outside of the traditional OR environment will continue to increase and both the procedures and the patients who undergo the procedures will be more complex. As the population ages and medical therapies achieve increased effectiveness, more patients who in the past would not have been candidates for any intervention will be offered procedures that either prolong life or improve its quality. The current expansion of minimally invasive, non-surgical approaches to disease will continue and, as a result of these changes, demand for anesthesiology services will escalate.

The experience with NORA procedures has taught us many lessons. Perhaps the most significant lessons include our understanding of the needs of the patients and proceduralists—and the expectation that the same standards of care will be required wherever anesthesia care is provided. As a result, anesthesiologists must be flexible, while also ensuring that the usual safeguards provided in the OR environment are extended to every other location in which we provide care. Inclusion of procedural areas within our practice requires a new model of service delivery. Over the past 30 years, anesthesiologists revolutionized safety, reliability, and the scope of perioperative practice. We must extend the same safety and quality to the care we provide in the non-OR locations. Seeing beyond the traditional role of

anesthesiologists in the OR, we can create a niche as innovators of NORA in the same way that we have broadened our services by providing critical care coverage inside and outside the ICU and by widening the integration of care provided by acute and chronic pain management teams.

SOME ADDITIONAL CONSIDERATIONS

Operational Effectiveness

Operational effectiveness is a crucial component of providing clinical care in any setting. It is also required to ensure that each health system can successfully compete and remain financially solvent. For anesthesiologists providing care outside of the OR, we are critical participants in defining how care is provided and what resources are necessary to optimize care, while also being cognizant of the economics of our practices. We must provide more efficient and, in many cases, more flexible services in nontraditional settings as long as we remain attentive to patient needs and safety considerations. We also need to communicate when an anesthesia provider is required for some procedures, what equipment, supplies, and other needs must be met, and how to do so cost-effectively. To do so requires that we document our services and outcomes and evaluate alternative approaches to care in a thoughtful and evidence-based manner.

Costs, Uniqueness, and Value-Added

Anesthesiologists have the training and experience to deliver superior, integrated, and cost-effective services outside the OR. In an era of increasing medical specialization and fragmentation of care delivery, particularly in the context of accountable care organizations and bundled payments, these are the critical indices of success.

Proper variable cost accounting demonstrates that the cost of patient care involving an efficiently deployed anesthesiologist is less than the cost imposed on the whole system by those procedures that start without anesthesia personnel and end with an urgent, unanticipated call. The expense of (1) delaying a procedure, (2) stopping a procedure for inadequate or excessive sedation, (3) hospitalizing a patient, and (4) rescheduling or redoing procedures is forbidding. However, the costs are not always obvious because they are spread over multiple cost centers.

Strategic Positioning

For anesthesiologists, strategic positioning occurs when the needs of customers are satisfied with minimal cost to the anesthesiologists. The customers are not just patients—they are also medical proceduralists and third-party payers. If we can provide a safer and more comfortable, time-efficient, and cost-effective environment for proceduralists, the value of anesthesiologists will be clear. If we develop a bridge between medical and surgical treatment by facilitating hybrid procedures and interdisciplinary approaches, the overall value of our presence will be incontrovertible to proceduralists, patients, insurance companies, regulatory bodies, and government agencies.

Financial Silos and Teamwork

The increased requirements by third-party payers to provide value-based care requires that anesthesiologists work collaboratively with our colleagues to define new models of

care and integrated care requires collaboration and interdisciplinary effort. As accountable care organizations and value-based care models expand, we will have to demonstrate the value the anesthesiologist provides for the NORA procedures to justify our “piece of the economic pie.” Our success will depend on the strength of relationships we forge with health systems and our physician colleagues. Team building requires communication and coordination based on common experience and vocabulary. In many cases, this process will be most effective if we align anesthesiologists and other providers by service lines which collaboratively define standard approaches to care for specific patient populations. The integration of medical and surgical perspectives can facilitate innovative solutions, improve the delivery of cost-effective and efficient care, and avert mistakes outside of the OR.

Sustainable Strategy: Key Points

An effective strategy is one that maintains a dynamic and profitable market presence. Anesthesiologists have two related parallel sets of priorities: creating and maintaining a stable but flexible customer base, and achieving financial sustainability.

Operational effectiveness will ensure that appropriate resource allocation permits innovation. Enhanced core competencies resulting from expanded medical training and presence outside of the OR will provide a basis for the already needed enrichment of services. Team building will ensure that proceduralists understand the rationale for close cooperation and generate a foundation for better integrated finances. Reframing boundaries and elimination of silos will enhance integration, productivity, and the quality of care across the board. The overall strategy must be to make our specialty indispensable to customers and potential customers while enhancing the lives of patients by improving outcomes and stimulating progress.

Our expertise will generate consistent reimbursement if we have the data to demonstrate the benefit of that presence. Our participation in non-OR procedures can stimulate and advance medicine just as development of the OR environment advanced the practice of surgery. As technology continues to proliferate and diversify, the distinction between medical and surgical approaches to treatment becomes blurred. The pursuit of innovation has always been characteristic of anesthesiologists. We must continue this work in new venues and work to build bridges to continue to strengthen our specialty.

The need is urgent for anesthesiology to adopt a broader perspective. If this opportunity and its associated intellectual challenges are ignored, the status of anesthesia, a key medical subspecialty, may be threatened. If the challenge is accepted, the practice of anesthesiology will be on the front lines of changing and advancing medical science. An unprecedented crescendo of emerging technology and ongoing innovation continues to defy status quo approaches to NORA cases. Proceduralists, locations, and equipment will continue to evolve. Regardless of the venue or the technique, anesthesiologists remain a critical and constant guardian of the integrative medical perspective, patient safety, and efficient procedural processes. As we move beyond the OR, constant vigilance, dedicated teamwork, mutual respect, and effective communication will continue to be the fundamental keys to success.

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Complete references available online at expertconsult.com.

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KEY POINTS

- High altitude or space environments present a number of extreme physiologic challenges that must be overcome in order to survive.
- Given sufficient time, humans can adapt to both hypobaric hypoxia and microgravity.
- Lack of adaptation can lead to environment-specific illnesses, such as acute mountain sickness, high-altitude pulmonary edema, decompression illness, or the acute worsening of comorbid conditions.
- These conditions can rapidly become fatal if not treated appropriately (e.g., with either descent to lower altitudes or returning to the Earth's surface).
- Providing critical care or anesthesia in such environments is further complicated by their extreme levels of remoteness.
- Exploratory missions to such environments depend on the development and vetting of robust and simple health care protocols.

Introduction to Altitude and Explanation of Hypobaric Hypoxia and Its Effect on Physiologic Performance

An estimated 140 million individuals live at altitudes over 2500 m,¹ whereas sojourns to altitude are undertaken by large numbers of individuals each year for leisure, work, and religious reasons.²⁻⁴ It can be expected that a significant proportion of these individuals will require medical care, either directly related to altitude or for any other reason. As such, there is a clear need for medical practitioners to appreciate the specific environment, physiology, and pathologic conditions at altitude.

At high altitude, a number of environmental changes may be observed. These include decreased temperature, increased ultraviolet exposure and, particularly in mountainous environments, remoteness combined with challenging access and egress, and challenging weather patterns. Overall, the area of primary focus to the critical care and anesthetic practitioner is hypobaric hypoxia and the resultant physiologic changes associated with altitude exposure.

As altitude (i.e., vertical height above sea level) increases, the barometric pressure (P_B) decreases in a non-linear manner (Fig. 74.1), resulting in a P_B at the summit of Mount Everest (8848 m) approximately one third that

of sea level. The relative concentrations of gases, including oxygen, remain static but because of the falling P_B , the partial pressure of each gas decreases. The resultant hypoxia is of great clinical significance and results in many physiologic changes. These physiologic changes vary with the time course of exposure and a number of long-term adaptations in high-altitude populations have been observed.⁵ This chapter considers the high-altitude environment directly, and the consequences of it on clinical practice; however, it should be noted that many consider the hypoxia encountered at altitude to be of translational value to hypoxia at sea level, for example, in critically unwell patients.

Physiologic Responses to Hypoxia/Acclimatization

CARDIOVASCULAR RESPONSES

Initial cardiovascular changes occur rapidly. Following the initial ascent, however, more gradual changes may be observed over a period of weeks (Fig. 74.2). On exposure to hypoxia at altitude, peripheral arterial chemoreceptors are stimulated, triggering increased sympathetic activation. The resultant increased heart rate (HR) leads to a rise in cardiac output.⁶ A concurrent systemic vasodilation is seen

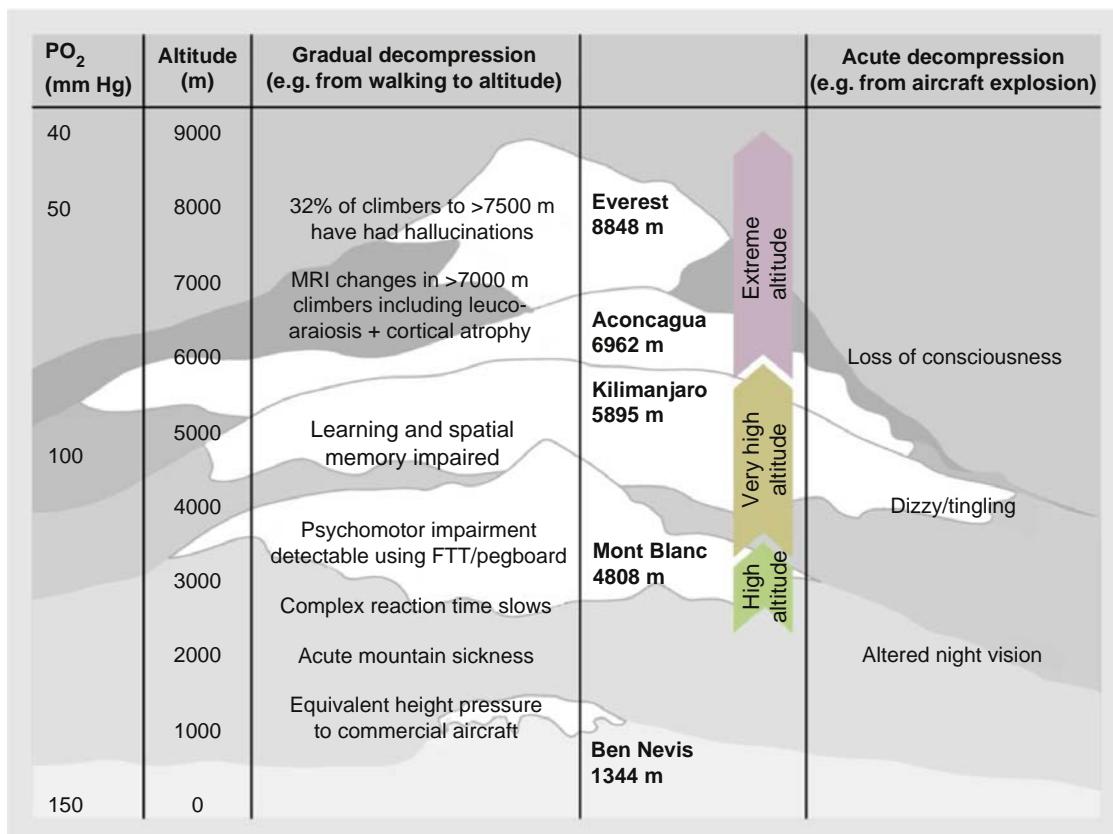


Fig. 74.1 The symptoms and clinical effects associated with the nonlinear decrease in barometric pressure at increasing altitude. *MRI*, magnetic resonance imaging. (From Wilson MH, Newman S, Imray CH. The cerebral effects of ascent to high altitude. *Lancet Neurol*. 2009;8:175–191.)

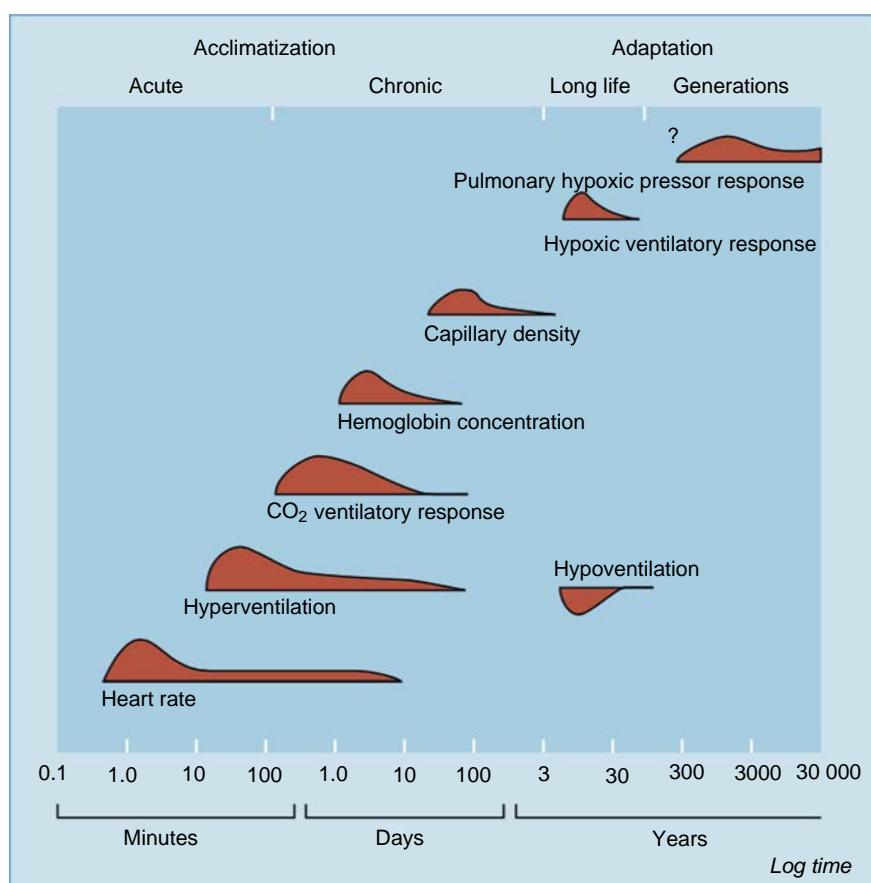


Fig. 74.2 The time course of acclimatization and adaptive responses to hypobaric hypoxia with the curve of each response representing the relative rate of change (note the log time scale). (From Peacock AJ. Oxygen at high altitude. *BMJ*. 1998;317:1063–1066.)

on ascent to altitude. This is antagonized by increased sympathetic tone and the overall effect is one of increased blood pressure (BP), although in the early hours of exposure vaso-dilation may predominate.⁷ After several days, cardiac output returns to baseline but with a lower stroke volume (SV) and higher HR,⁸ while BP continues to rise for several weeks.

This pattern of increased HR and reduced SV persists across exercise states at altitude.⁹ In both athletes and nonathletes,¹⁰ maximal oxygen consumption ($\text{VO}_2 \text{ max}$) decreases with increasing altitude, estimated at approximately 1% per 100 m above 1500 m.⁷

Hematologically, a rise in hemoglobin (Hb) concentration is seen in response to altitude exposure. Over the initial days, this is related to a fall in plasma volume of approximately 20%,¹¹ followed by a rise in red cell production secondary to increased levels of erythropoietin (EPO; which begins to rise within hours of ascent).¹² This change in Hb concentration increases arterial oxygen content (CaO_2) and theoretically improves oxygen delivery (DO_2) to tissues.

However, this may be compromised because there is a marked increase in hematocrit and plasma viscosity. Viscosity has been observed to increase by 38% in healthy volunteers on ascent to 5800 m.¹³ Changes in microcirculation, important for the final phase of DO_2 , have been observed *in vivo* at altitude with a significant reduction in microcirculatory flow seen in healthy volunteers during altitude exposure, although this does not seem to be directly related to the increase in hematocrit and viscosity.¹⁴ Subsequent studies have shown that this flow is significantly greater in the highly altitude-tolerant Sherpa population,¹⁵ raising the possibility that such microcirculatory adaptation may play an important role in optimizing DO_2 and adaptation to high altitude.

RESPIRATORY RESPONSES

The falling P_B at altitude results in a decreased atmospheric partial pressure of oxygen (PO_2). This in turn results in reduced alveolar (PAO_2) and arterial (PaO_2) partial pressures of oxygen. However, the reduction in PAO_2 is accentuated because the saturated vapor pressure of water ($P_{\text{SVP Water}}$) is unchanged (6.3 kPa) at altitude. Examining the alveolar gas equation, we can see that a proportionally higher saturated water vapor at body temperature ($P_{\text{H}_2\text{O}}$) will result in a decreased PAO_2 .

$$\text{PAO}_2 = \text{FiO}_2 (P_B - P_{\text{H}_2\text{O}}) - (\text{PaCO}_2 / R)$$

This decrease in PAO_2 leads to the hypoxic ventilatory response (HVR), which is the most important aspect of acclimatization to high altitude. Studies have found that successful climbers demonstrate an improved HVR.¹⁶ The decrease in PaO_2 leads to hypoxic stimulation of peripheral arterial chemoreceptors,¹⁷ which in normoxia are normally suppressed by central chemoreceptors responding to changes in carbon dioxide (CO_2). The peripheral arterial chemoreceptors trigger rapid increases in minute volume (V_E) over seconds to minutes. A resulting decrease in PaCO_2 also helps increase the PAO_2 , as explained by the alveolar gas equation, which demonstrates that any fall in PaCO_2 will result in an increased PAO_2 .

The resultant hypocapnia following HVR leads to a leftward shift in the oxygen dissociation curve (ODC). This shift

improves oxygen uptake at the lungs, but the increase in affinity may have consequences for DO_2 at end organs.¹⁸ A leftward shift and increased oxygen affinity of Hb are key components of the adaptive response in a number of animals who live in hypoxic conditions.¹⁷ However, with altitude exposure in humans, this leftward shift is opposed by an increase in 2,3-diphosphoglycerate, over several days, causing a rightward shift. The final position of the curve varies depending on altitude exposure and level of acclimatization, but in sojourners it appears to equilibrate at almost sea level values, whereas certain groups of high-altitude natives are able to sustain a leftward shift through hyperventilation.^{19,20}

As PaCO_2 decreases, a respiratory alkalosis develops in both arterial blood and cerebral spinal fluid (CSF). This alkalosis initially antagonizes HVR; however, after several hours and continuing for over 2 weeks, the body begins to correct the alkalosis through bicarbonate (HCO_3^-) excretion, as well as the increased concentrations of protein anions (such as phosphate and albumin). These processes allow the continued increase in V_E (and thus improved acclimatization) to progress throughout this period.^{21,22}

The pulmonary circulation is also modulated at altitude. In response to the reduced PAO_2 , hypoxic pulmonary vasoconstriction (HPV) occurs within minutes.²³ The mechanism is a contraction of pulmonary smooth muscle cells. This process is independent of any external regulation and has been demonstrated in the laboratory setting in pulmonary smooth muscle cells completely isolated from all other tissues.²⁴ The exact mechanism of oxygen sensing is a source of ongoing research, but it is known that the smooth muscle contraction itself, as in other tissues, relies upon a rise in intracellular Ca^{2+} . Although the contraction occurs in isolation, it is modulated by both the endothelium and systemic factors such as sympathetic activation. The process is biphasic in nature, with an initial contraction reaching its maximal effect between 2 and 15 minutes. A secondary phase occurs between 30 and 60 minutes, causing further vasoconstriction in sustained hypoxia. This secondary phase appears to be dependent on the presence of endothelial cells.^{7,24}

In contrast to HPV in localized hypoxia (as seen in many pathologies found at sea level, such as pneumonia, atelectasis) where this response is beneficial for correcting ventilation-perfusion (V/Q) mismatch, the global alveolar hypoxia seen at high-altitude HPV can be significantly deleterious. Widespread vasoconstriction increases pulmonary vascular resistance 50% to 300%,²³ with a consequent precipitous pulmonary arterial pressure (PAP) increase that may be responsible for altitude-specific pathologies such as high-altitude pulmonary edema (HAPE) (see later in this chapter).⁷ This rise in PAP is further exacerbated by physical exercise with chamber studies reporting a PAP of 54 mm Hg on maximal exercise at a P_B equivalent to 7620 m.²⁵

RENAL AND ENDOCRINE CHANGES

Renal responses play a key role in altitude acclimatization and have long been observed. The hypoxic diuretic response (HDR) was first observed in 1944.²⁶ It is characterized by both natriuresis and diuresis and is seen in humans and many other mammals.^{27,28}

The earliest phase of the HDR occurs within hours of ascent and is in fact a diuresis alone, with a static fractional sodium clearance. Hypoxia and hypocapnia appear to be the driving factors (although the exact mechanism remains uncertain)²⁹ and natriuresis soon follows. During the HDR, a total water loss of approximately 3 L is possible during initial exposure³⁰ and a decrease of approximately 40% plasma volume.¹¹

A number of studies suggest that HDR undergoes humoral regulation.^{31,32} The renin-angiotensin-aldosterone system is one of the major systems regulating fluid balance at sea level. Renin and aldosterone promote retention of both water and sodium. However, although renin activity and aldosterone levels are observed to decrease in response to altitude,^{28,33,34} this response has not been consistently shown to be directly related to the level of natriuresis observed, suggesting there may be a mediation driven by chemoreceptor activation.²⁸ It is also of note that although the aldosterone exercise response (leading to an increase in plasma aldosterone) remains present at altitude, it appears to be reduced.³³ Indeed, further elements of the hormonal response also appear inconsistent. An increase in serum osmolality is reported with altitude ascent and although this may be expected to produce a concomitant increase in arginine vasopressin (AVP), such a response is often not observed, suggesting a change in AVP regulation at altitude in favor of a diuresis.³⁵⁻³⁷

The other side of the coin, from a fluid homeostasis perspective, is atrial natriuretic peptide (ANP). It is produced by cardiomyocytes in response to atrial distension and plays an important role in fluid balance; an increase in ANP will induce a natriuresis.³⁸ It has been observed to increase in response to both pure hypoxia and altitude ascent and may play an important role in the initial diuresis,^{34,38,39} although any direct causal relationship between ANP levels and the observed diuresis/natriuresis have been questioned.²⁸

Although controversy remains around the exact relationship between any hormonal changes and the observed diuresis/natriuresis, a number of studies have reported an association between a picture of increased fluid retention, or hormonal changes promoting fluid retention, and altitude pathologies such as acute mountain sickness (AMS) and HAPE.^{34,40} This suggests that, regardless of the underlying regulation, diuresis remains an important part of successful acclimatization.

In addition to fluid balance, the renal system is also important in mitigating the pH changes generated by the HVR, as discussed previously. Urinary bicarbonate excretion increases over a period of hours to more than 2 weeks, in a process that appears to be unrelated to the natriuresis previously discussed.⁴¹ This reduces blood pH, and may play a role in facilitating the ongoing increase in V_E and, therefore, acclimatization to altitude.

Additional endocrine changes may also be observed following altitude exposure. Cortisol, a stress hormone secreted by the adrenal glands, appears to increase at altitude,^{33,42,43} although exceptions are found in the literature.⁴⁴ It may be that this variation is related to duration of exposure, exercise state, and other stress factors, such as coexisting pathology.³⁷

As previously discussed, sympathetic activation forms an essential part of the response to acute altitude exposure, which drives many other physiologic changes. As expected, levels of norepinephrine and epinephrine increase,^{42,45} as does nerve fiber activity.⁴⁶ However, after prolonged exposure and despite persistently elevated catecholamine levels, maximal HR and response to chronotropic drugs (e.g., isoproterenol) are both reduced, which suggests that a degree of desensitization is also occurring.⁴⁷

CENTRAL NERVOUS SYSTEM

Several central nervous system (CNS) changes are found at high altitude. Many of the most frequently observed were eloquently described by John West, one of the leading figures in respiratory and high-altitude physiology.

On ascending to altitude, unacclimatized lowlanders typically complain that they take longer to get to sleep, wake frequently, often have unpleasant dreams and do not feel refreshed in the morning. The resultant difficulties are not confined to the night because, as a result of poor sleep, people often feel somnolent and fatigued during the following day, their productivity is reduced and they are more liable to make errors.⁴⁸

This quote encapsulates two separate changes observed at altitude: sleep disturbance and cognitive changes.

Sleep disturbance is a frequently occurring symptom, with incidences of up to 65% reported on ascent.^{49,50} Indeed, a network analysis of symptom scores in altitude sojourners identified the largest single cluster of symptoms to be one primarily characterized by sleep disturbance.⁵¹ Subjectively, individuals report reduced general sleep quality, difficulty in falling asleep, frequent wakening, as well as temperature-related discomfort.⁵²

At high altitude, the sleep architecture is altered. The duration of light sleep, and non-rapid eye movement (NREM) sleep stages I and II, is increased. Deep sleep and NREM stages III and IV are reduced dramatically,⁵³⁻⁵⁵ whereas rapid eye movement (REM) sleep duration appears to be more variable in duration.⁵⁴ Frequent awakenings are also observed, which appear to be closely linked to another phenomenon seen during sleep at altitude: periodic breathing.^{53,55,56}

Periodic breathing, as described by John Cheyne and William Stokes in the 19th century and named eponymously for them,^{57,58} has long been observed at altitude. Reports date back as early as 1857 before it was first described fully by Angelo Mosso in 1894.^{59,60} Characterized by periods of crescendo-decrescendo hyperpnea followed by apnea at altitude, periodic breathing is seen most commonly during NREM stages I and II and appears to be largely absent during REM sleep.⁵⁴ Periodic breathing may be responsible for the frequent awakenings seen at altitude that often occur at the transition from apnea to hyperpnea.⁵³

This breathing pattern is caused largely by hypocapnia, which is itself a result of HVR. Although this hypocapnia during wakefulness does not adversely affect patterns of breathing during sleep, both the rate and depth of respiration can decline, culminating in apnea. During this apnea, the partial pressure of carbon dioxide (PCO₂) increases

as PO_2 falls, ultimately leading to a return of ventilation with hyperpnea.⁵⁵ This theory is supported by the observation that those who demonstrated the most brisk HVR also experienced the highest rates of apnea,⁶¹ along with the efficacy of supplemental oxygen to improve sleep quality.⁶² Periodic breathing tends to increase with ascent⁵⁵ and may even occur during REM sleep at extremes of altitude.⁶³ With acclimatization, periodic breathing can be seen to decrease.⁵⁴

The previous quote from John West also alludes to cognitive changes, which are frequently observed at altitude. Studies have demonstrated deficits across a wide range of domains under hypoxic conditions including arithmetic, memory, language, and motor skills.⁶⁴⁻⁶⁷ In addition to direct cognitive impairment, there are adverse changes in mood state and even new onset anxiety disorders secondary to high altitude.^{68,69} The exact etiology of these cognitive changes has not been fully elucidated, although fatigue does appear to be correlated with a number of cognitive domains, and as such, sleep disturbance may be contributory.⁷⁰

GASTROINTESTINAL

On ascent to altitude, anorexia is frequently observed but not fully understood.^{71,72} Leptin, a hormone with elevated levels that are associated with satiety, has been hypothesized as playing an important role but the literature is conflicting; elevated, reduced, and unchanged levels have all been reported.^{42,44,73,74} Cholecystokinin, another satiety hormone, has been less widely studied but has been found to be elevated, particularly in those with marked anorexia at altitude.⁷⁵

In concert with anorexia, weight loss of both fat and muscle occurs in response to prolonged exposure.^{73,76,77} This may be related primarily to reduced intake,⁷⁸ although a modest increase in basal metabolic rate is observed, and may be partly attributable to sympathetic drive.⁷⁹

Altitude Illness

Several distinct pathologies are observed in association with both acute and chronic altitude exposure. Although each is considered separately here, some share pathologic features. In addition, the hypoxic environment can also affect individuals with other ongoing health considerations, such as comorbidity or pregnancy.

ACUTE MOUNTAIN SICKNESS

AMS is the most common acute altitude pathology. It is a clinical syndrome of nonspecific symptoms, occurring on ascent to altitude (>2500 m). The onset is usually seen between 4 and 12 hours after ascent.⁸⁰⁻⁸²

The prevalence of AMS is closely linked to altitude attained—approximately 25% at moderate altitude (<3000 m)⁵⁰ and approximately 50% above 4000 m.⁸³ Other factors exerting a strong influence are rate of ascent, degree of acclimatization, and individual susceptibility.⁸⁴ It is relevant to note that physical fitness appears to confer no risk reduction.^{85,86} Physical exertion at altitude may increase risk, although studies remain conflicted.^{85,87,88}

The pathophysiology of AMS is not yet fully understood. A number of theories have been suggested and current opinion appears to favor CNS dysfunction as the primary cause.^{80,81,89} Imaging studies in moderate-severe AMS have suggested some degree of cerebral edema,⁸⁹ and increased intracranial pressure (ICP) has also been observed.⁸⁰ In one remarkable study by Brian Cummins in 1985, three individuals, including Cummins himself, were fitted with invasive telemetric ICP monitoring. On ascent, two subjects remained well but one developed symptoms of AMS, including headache. This individual was also the only subject to demonstrate a raised ICP. The symptoms were seen on minimal exertion; turning his head increased ICP from 14 to 24 mm Hg, and a press up led to an ICP of 51 mm Hg.⁹⁰ This study has never been, and is unlikely to be, replicated but suggests elevated ICP may be pathologically significant and potentially related to reduced intracranial compliance.^{81,89,90} Cerebral blood flow (CBF) is known to increase transiently on ascent⁹¹ and, although wide interindividual variations have been observed, it may play a role. A unifying hypothesis has been proposed whereby hypoxia and hypoxemia result in increased CBF, which alongside changes in blood-brain barrier permeability, leads to brain swelling. Finally, in those with reduced intracranial compliance, this leads to AMS.⁹² This hypothesis, however, remains speculative, with some believing venous outflow may be more significant than intracranial compliance.^{80,93}

The diagnosis of AMS is clinical. The symptoms are variable in presentation but may include headache, nausea, anorexia, dizziness, sleep disturbance, and fatigue.^{80,81} Headache is the most frequently observed indication and remains a mandatory symptom for diagnosis in a number of research tools.^{82,94} Several scoring systems^{51,82,94-96} of AMS exist for research purposes. A number of these have been applied to clinical practice, although they are not validated formally for this use. The most widely used, the Lake Louise Score,⁸² is ubiquitous in the literature and consists of five simple, self-reported symptom-related questions. This scoring system was revised in 2018⁹⁴ with the removal of sleep disturbance after studies suggested that it is likely to be a separate phenomenon unrelated to AMS (Table 74.1).^{51,97} Laboratory testing and clinical examination in AMS are both unremarkable.⁸¹ Oxygen saturation (SpO_2) monitoring has been suggested as a useful tool but although SpO_2 is seen to fall with ascent, there appears to be no independent relationship with AMS.⁹⁸

Optimal clinical management of AMS begins with prevention. The most significant measure should be a slow ascent, with a limit of 300 m gain in sleeping altitude per day at altitudes above 3000 m generally accepted as best practice,^{80,89} although 600 m is proposed as an alternative.^{80,81} The sleeping altitude is generally accepted to be the most important consideration and the mantra of “climb high, sleep low” can be found widely in the literature. Other nonpharmacologic measures suggested, with some evidence, include: preacclimatization, avoidance of exercise, adequate hydration, and oxygen supplementation.^{81,89} Pharmacologic prophylaxis has been widely studied with acetazolamide the most recommended at an adult dose of 125 mg twice daily.⁹⁹ Higher doses of acetazolamide remain efficacious; however, they may be associated with more deleterious effects.¹⁰⁰ Dexamethasone (2 mg every 6 hours

TABLE 74.1 Lake Louise Consensus on Acute Mountain Sickness 2018

2018 Lake Louise Acute Mountain Sickness Score		
Symptom	Description	Score
Headache		
None at all		0
A mild headache		1
Moderate headache		2
Severe headache, incapacitating		3
Gastrointestinal symptoms		
Good appetite		0
Poor appetite or nausea		1
Moderate nausea or vomiting		2
Severe nausea and vomiting, incapacitating		3
Fatigue and/or weakness		
Not tired or weak		0
Mild fatigue/weakness		1
Moderate fatigue/weakness		2
Severe fatigue/weakness, incapacitating		3
Dizziness/light-headedness		
No dizziness/light-headedness		0
Mild dizziness/light-headedness		1
Moderate dizziness/light-headedness		2
Severe dizziness/light-headedness, incapacitating		3
AMS Clinical Functional Score		
Overall, if you had AMS symptoms, how did they affect your activities?		
Not at all		0
Symptoms present, but did not force any change in activity or itinerary		1
My symptoms forced me to stop the ascent or to go down on my own power		2
Had to be evacuated to a lower altitude		3

From Baillie JK. Lake Louise Consensus on Acute Mountain Sickness 2018. In: [altitude.org](http://www.altitude.org). Apr 2019 [cited 16 Apr 2019]. Available: http://www.altitude.org/lake_louise_AMS_score_2018.php

or 4 mg every 12 hours) has also been shown to be beneficial,^{49,101} but remains a second-line chemoprophylaxis.¹⁰⁰ Individual risk is highly variable based on both personal (e.g., previous history of AMS or High-Altitude Cerebral Edema [HACE]) and environmental (e.g., rate of ascent, highest altitude attained) factors. Prescribing of prophylactic medications and indeed any recommendations regarding individuals should consider this personalized risk.

When treating AMS, because of the nonspecific nature of the symptoms, consideration must be given to other causes. There may be more severe altitude pathologies such as HACE, or common conditions related to the nature of much travel to altitude such as dehydration, exhaustion, hypothermia, hypoglycemia, or infection.¹⁰⁰ In cases where AMS is diagnosed, then the single most efficacious treatment is descent. This may present other dangers, given the terrain often found in the high altitude environment; however, in severe cases, descent until resolution of symptoms (which typically occurs after a descent of as little as 300 m) remains the gold standard treatment.¹⁰⁰ Measures aimed at correcting hypobaric hypoxia, such as supplemental oxygen and hyperbaric chambers, can offer possible alternatives to descent but

in a remote high-altitude setting these treatments present marked logistical challenges, may only offer temporary benefit, and also carry their own risks.^{100,102} Dexamethasone has been shown to be an effective treatment,¹⁰²⁻¹⁰⁴ but it does not aid acclimatization and further ascent is not recommended until the patient is asymptomatic without dexamethasone.

HIGH-ALTITUDE CEREBRAL EDEMA

HACE is a severe, life-threatening pathology. It is rare, with a prevalence of 0.28% to 1%.^{4,105} Because of its rarity, there is limited systematic evidence regarding risk factors.⁸¹ However, (not yet conclusively proven) HACE is now considered to be a severe form of AMS and may share the same pathophysiology and risk factors.^{89,93,106} It is important to note though that while AMS may rapidly progress to HACE if left untreated, HACE may also present suddenly without any preceding symptoms of AMS.

Both animal studies and postmortem examinations have demonstrated gross edema in HACE sufferers,^{107,108} with magnetic resonance imaging (MRI) studies suggesting this is likely vasogenic in nature.¹⁰⁹ In contrast to AMS, in HACE there is evidence of microhemorrhage, primarily within the corpus callosum. The presence of microhemorrhage may indicate venous obstruction as a key pathologic process, which may differentiate AMS from HACE.⁹³

HACE may be clinically differentiated from AMS by the presence of ataxia, confusion, psychiatric changes, or altered consciousness that may progress rapidly to coma and death.^{81,89,93,110} Investigations offer limited benefit on acute presentation; however, lumbar puncture may reveal elevated ICP,¹¹¹ whereas MRI and computed tomography may reveal changes associated with edema.¹⁰⁹

Prevention of HACE should be guided by the same principles as AMS, with slow ascent, preacclimatization, and pharmacologic strategies as previously described.¹⁰⁰ The diagnosis should consider other possible causes for the observed presentation, but it is important to remember the mantra that any illness at altitude should be treated as altitude-related until proven otherwise. When HACE is diagnosed, its severity should not be underestimated and prompt management is essential. Immediate actions include supplemental oxygen (aiming for an SpO₂ > 90%), administration of dexamethasone (initial dose of 8 mg by mouth, or intravenous or intramuscular injections; and immediately followed by a dose of 4 mg every 6 hours) and, where logistically possible, descent.^{81,100} If descent is not possible, and the airway is adequately protected, then a hyperbaric chamber is an acceptable temporary alternative.^{81,93}

High-Altitude Pulmonary Edema

HAPE is a form of noncardiogenic pulmonary edema that occurs in unacclimatized individuals on ascent to altitude (>2500m).⁸¹ The condition was first described in South American lowlanders on ascent to altitude in 1955,¹¹² and subsequently in 1960 by two separate American physicians.^{113,114}

The condition generally occurs within 2 to 5 days of ascent and is more common with greater altitude. It remains relatively uncommon under 3000 m and after more than 1 week at altitude.^{115,116} As with many altitude pathologies, the rate of ascent, altitude, and individual

susceptibility are the most significant risk factors for the development of HAPE.⁷ There is evidence of other predisposing factors including: male sex,¹¹⁷ preexisting respiratory infection,¹¹⁸ and cold temperatures.¹¹⁹ Cardiorespiratory diseases, including anatomical abnormalities affecting pulmonary blood flow, have also been shown to increase risk of HAPE and it should be noted that altitude dwellers may suffer from “re-entry” HAPE following a sojourn to lower altitudes.¹¹⁵ The prevalence of HAPE varies greatly depending on the aforementioned risk factors. For example, in the general population prevalence of HAPE is estimated at less than 0.2% when climbing to 4500 m in 4 days. However, for a 1- to 2-day ascent to the same altitude, the prevalence rises dramatically to 6%. In those with a known susceptibility to HAPE, this could reach as high as 60%.¹¹⁶

The pathophysiology of HAPE is closely related to HPV and the increase in PAP. Pulmonary hypertension is seen on ascent to altitude prior to the development of HAPE.¹²⁰ Individuals who are susceptible to HAPE tend to have a brisk HPV response, and often a relatively blunted HVR which further drives HPV. This accentuated rise in PAP of approximately 60 mm Hg in untreated HAPE on ascent may also be partly related to decreased nitric oxide (NO) bioavailability.¹²¹ The subsequent edema appears to be directly related to this increase in pressure, with bronchoalveolar lavage in early HAPE showing little inflammatory change, while pulmonary capillary pressure exceeds values shown in animal models to cause edema.¹²¹

Early clinical presentation is most commonly exertional dyspnea, often associated with a dry cough. This results in reduced exercise performance. Dyspnea is normally progressive, leading to dyspnea at rest, while the cough may become productive of pink frothy sputum—with hemoptysis of frank blood being rare.¹¹⁵ Orthopnea is additionally seen as edema progresses. Symptoms of AMS may coexist, but around 50% of sufferers display none.¹¹⁷ Examination findings typically include tachycardia and tachypnea. Cyanosis may be present and, although not universal, crepitations are invariably audible on auscultation of the lungs.⁷ SpO₂ and blood gas analysis show more profound hypoxia than in healthy controls, while radiographic findings demonstrate patchy edema, generally starting peripherally.¹²²

As with AMS, if appropriate steps are taken, the incidence of HAPE can be significantly reduced. Gradual ascent remains the single most effective means of reducing HAPE occurrence.¹⁰⁰ Individuals with a history of HAPE should take additional care and in such cases pharmacologic prophylaxis may be warranted. Nifedipine, a calcium channel blocker, has been shown through randomized control trial¹²⁰ and clinical experience¹⁰⁰ to be effective in high-risk individuals, delivering significantly lower PAP and improved prophylaxis of clinical HAPE over a placebo. Other medications, such as salmeterol¹²³ and tadalafil,¹²⁴ have shown promise in clinical trials but clinical experience remains limited. Further research is required, although salmeterol is considered as an adjuvant to nifedipine in high-risk cases.¹⁰⁰ Dexamethasone, which is used widely in AMS/HACE, is not as regularly utilized in HAPE. There is some data supporting its use,¹²⁴ but again further study is advised to confirm.¹⁰⁰

As with AMS/HACE, descent remains the most effective treatment for HAPE. Improvements may be seen after

only minimal descent, although descent of 1000 m or until symptoms resolve is advocated. The degree of exertion on descent should be minimized as much as possible to reduce further rise in PAP.¹⁰⁰ Supplemental oxygen and hyperbaric chambers are further measures to consider when descent is not possible. Nifedipine continues to have a role in treatment, with a single unblinded trial showing some clinical improvement¹²⁵ and extensive clinical experience supporting its role.¹⁰⁰ Phosphodiesterase inhibitors and dexamethasone may both confer some benefit and case reports of their use exist.^{126,127} It is important to point out that unlike other forms of pulmonary edema, the use of diuretics is not advocated in HAPE, particularly as patients may have concurrent hypovolemia.¹⁰⁰ In the hospital setting it may be possible to manage HAPE without descent using supplemental oxygen and close observation. The use of continuous positive airway pressure has been advocated but remains unreported.¹⁰⁰

CHRONIC MOUNTAIN SICKNESS

Chronic mountain sickness (CMS), also known as Monge disease, is a syndrome affecting lifelong altitude dwellers and native populations. First described by Carlos Monge in 1928 in Peru,¹²⁸ it is characterized by excessive erythrocytosis (EE), which may lead to pulmonary hypertension, cor pulmonale, and congestive cardiac failure.¹²⁹

CMS prevalence varies widely among high-altitude populations around the world. Tibetans have a low prevalence with 1.2% reported, while with the Han Chinese in the same region the rate is 5.6%. The rates in South America are also generally higher with a prevalence of 4.5% in the general population,¹³⁰ and increasing up to 33.7% in minors 60 to 69 years of age.¹³¹ These ethnic variations may be explained by significant differences in adaptation to high altitude. Tibetan natives have been dwelling at altitude for significantly longer than Andean natives and have adapted very differently. Andeans show lower HVR and stronger HPV than Tibetans and even in health show a preponderance for higher Hb than is observed in Tibetans.⁵ Other than ethnic variation, there appears to be a direct correlation with altitude; a study in North India observed no cases of CMS below 3000 m, yet a prevalence of 13% above this elevation.¹³²

The underlying cause of the EE is not yet fully understood. It is generally accepted that chronic hypoxia, potentially exacerbated by a loss of ventilatory acclimatization leading to central hypoventilation, results in an erythrocytosis. The EE may be mediated by EPO, which is produced in response to hypoxia; however, the correlation between EPO levels, SpO₂, and Hb is not consistent, suggesting that it is not the sole factor.¹²⁹ Recent gene studies have highlighted the potential role of SENP1, a gene involved in EPO regulation. Individuals with CMS SENP1 appear to show a higher transcriptional response to hypoxia¹³³⁻¹³⁵ and the gene is the subject of ongoing research in this field.

Clinically, CMS may be identified by the excessive erythropoiesis (females Hb \geq 19 g/dL; males Hb \geq 21 g/dL) and severe hypoxemia.¹³⁶ Symptoms of this include headache, dyspnea, fatigue or sleep disturbance, and a burning sensation in the hands and feet. Meanwhile, signs include cyanosis (particularly marked in mucous membranes), finger

clubbing, and dilatation of blood vessels. Further investigations may demonstrate pulmonary hypertension and cardiac failure. Of clinical relevance are family history, obesity, and sleep apnea, which are all risk factors for the development of CMS. The gold standard tool for diagnosis is the Qinghai score for CMS.¹³⁶ It is important to note that the diagnosis of CMS should only be made in the absence of other systemic disease that may explain hypoxemia, such as chronic airway diseases.

The optimal management of CMS is permanent relocation to a lower altitude; however, CMS will dissipate with the resumption of normoxia. When permanent relocation is not possible, sojourns to lower altitudes may help to stop Hb from hitting excessive levels.¹²⁹ Venesection, with or without isovolumetric hemodilution, is used widely in clinical practice.^{129,136} However, supportive literature is of limited quality^{137,138} and there are concerns about a rebound effect on Hb, although these are unproven.¹²⁹ In addition, recent evidence suggests that iron deficiency caused by venesection may worsen pulmonary hypertension and advocates the use of iron supplementation to ameliorate this effect.¹³⁹ Numerous pharmacologic compounds have been studied with limited success including: ACE inhibitors, ventilatory stimulants, and dopaminergic antagonists. Recently, more focus has been given to acetazolamide with positive results, suggesting it is safe, able to reduce erythrocytosis, and improve pulmonary circulation, although side effects associated with long-term use remain unknown.^{140,141}

COMORBIDITY AT ALTITUDE

The acute altitude pathologies described previously have been largely studied in healthy populations and there is a limited body of evidence to characterize how existing disease may be affected by ascent to altitude.¹⁴² At the same time, travel to remote, high-altitude destinations is becoming easier, and people are living longer with a higher burden of chronic disease¹⁴³; as a consequence, the challenges of managing chronic disease at altitude are likely to become increasingly relevant.

It is recommended that individuals with significant pre-existing disease should consult an experienced altitude physician and undergo a risk assessment before travel. The assessment should consider existing conditions as well as details of the proposed trip, including ascent profile and level of exertion.¹⁴⁴ The conditions most likely of concern at altitude are those affecting the cardiorespiratory system because these may cause additional difficulty in adapting to the hypoxic environment. Consideration should be given to two separate issues: whether chronic disease will predispose individuals to the development of acute altitude pathologies and whether altitude exposure will exacerbate chronic disease.¹⁴²

Ischemic heart disease is a pathology that may be worsened by altitude exposure. Acute altitude exposure increases cardiac output, and thus myocardial oxygen demand, while in the presence of reduced arterial oxygen content.¹⁴⁵ Estimates of myocardial perfusion in healthy subjects suggest that there may be some reduction at altitude, which may be partly ameliorated by acetazolamide.¹⁴⁶ However, several studies have exposed patients with stable coronary artery disease (CAD), who are deemed to be low risk and who

have exercised at altitude with no adverse effects.^{147,148} A single study of eight patients with moderate-risk disease demonstrated that compensatory mechanisms of coronary circulation may be exhausted at even moderate altitude.¹⁴⁹ Current recommendations advise cautious ascent to a maximum of 4200 m by low-risk patients, who have had a minimum of 6 months postmyocardial infarction or revascularization before travel. These recommendations also advise moderate-risk patients not to ascend above 2500 m, with only light exercise undertaken, while those at highest risk should avoid altitude entirely. Consideration should be given to acetazolamide, as it may aid coronary perfusion, but this has not been verified in patients with CAD.¹⁴⁵

Patients with heart failure may pose a significant challenge at altitude, particularly as the condition is often closely linked to other comorbidities. However, studies on patients with stable disease (New York Heart Association Class II-IV) have demonstrated moderate altitude may be tolerated without significant compromise, although those with the most severe disease were significantly limited in their exercise tolerance.^{150,151} Medications used to manage heart failure should also be closely reviewed. Use of diuretics must be monitored, as fluid status is likely to alter at altitude and particular care should be paid to concomitant use of acetazolamide. Studies suggest that selective β 1 receptor antagonists may improve exercise performance when compared to nonselective beta blockers and are advised where practical.^{145,152} In summary, those with the most severe disease should abstain from travel to altitude whereas those with mild to moderate disease should proceed with caution.¹⁴⁵

In the presence of the hypobaric hypoxia found at altitude, there is concern for exacerbation of respiratory disease. Counterintuitively, however, observational data suggest that asthma is less common, and less severe, in those living at altitude.^{153,154} One likely reason for this is the reduced population of dust mites at altitude secondary to the cold, dry, and hypoxic conditions¹⁵⁵ that result in a significant improvement in many pathologic features of asthma.¹⁵⁶ However, such studies do not provide evidence regarding acute altitude exposure. There have been a number of observational studies exploring acute altitude exposure¹⁵⁷⁻¹⁶⁰ with conflicting results for physiologic measurements (e.g., peak expiratory flow, forced expiratory volume in 1 second [FEV1]), but all have demonstrated safe travel for patients with mild asthma to altitudes of up to 6410 m. Caution is advised, however, as upper airway infections, particularly in remote environments, remain a risk for asthmatic patients.¹⁶¹ Hence, while travel to altitude is safe for well-controlled asthmatics, adequate supplies of rescue inhalers and oral steroids are advised.¹⁴² Measures may also be taken to limit cold, dry air exposure, which often exacerbates asthma.¹⁵⁷ These can be as simple as covering the nose and mouth during outdoor exposure.¹⁴² Those with poorly controlled or severe asthma are at high risk because of the remoteness of the environment and variability of medical facilities, and travel should be avoided where possible in this group.¹⁴²

Chronic obstructive pulmonary disease (COPD) poses a particular challenge at altitude. Studies of altitude dwellers with COPD demonstrate increased mortality and cor pulmonale.^{162,163} A number of studies simulating altitude as a

model for commercial air flight have shown marked hypoxemia in response to moderately simulated altitude.^{164,165} A similar drop in PaO₂ was observed in mild to moderate COPD sufferers on ascent to 1920 m, with a mean PaO₂ fall from 8.8 kPa at sea level to 6.9 kPa.¹⁶⁶ However, no adverse clinical events were reported in these studies and, given the chronic nature of the hypoxia, there is likely to be some degree of preexisting adaptation.¹⁴² Particular care must be taken in COPD patients with pulmonary hypertension. As previously discussed, the pathophysiology of HAPE indicates that preexisting pulmonary hypertension may increase susceptibility to HAPE.¹⁴² When assessing risk of hypoxemia at altitude, the use of formulae derived to predict PaO₂ during flight may be helpful.¹⁶⁷ In general, there are limited data on the safety of travel to altitudes for patients with COPD, and no data for their travel above 3048 m. Patients with COPD, and in particular those with pulmonary hypertension, should seek medical advice prior to traveling to high altitude.

Special Situations at Altitude

CHILDREN

Children represent an understudied group at altitude. While many of them either live at or sojourn to higher elevations, comparatively few studies have examined this. Children born and living at altitude are at increased risk of hypoxemia either secondary to acute pathology or congenital abnormalities. However, the risk and responses to living at altitude vary greatly among different ethnic populations as a result of the variations in adaptation as previously discussed.¹⁶⁸

Studies on acute exposure to altitude suggest that children show similar patterns of acclimatization as adults.^{169,170} Altitude pathologies meanwhile present a significant problem in children. A study in Colorado at 2835 m estimated a 28% prevalence of AMS in children.¹⁷¹ However, the diagnosis of AMS remains problematic in children, as many symptoms of AMS may be associated with any travel in children. The same holds true for more serious altitude pathologies of HAPE and HACE, which may be overlooked in children (especially of younger age). As a result, extreme caution and descent is advised when a child becomes unwell at altitudes above 2500 m.¹⁷² Pharmacotherapy is less widely advocated in children, particularly for mild cases of AMS. In severe cases or where HAPE develops, there may be a place for weight-appropriate doses of acetazolamide or nifedipine.¹⁷³

PREGNANCY

Maternal hypoxia may develop as a consequence of travel to high altitude (>1800 m) with obstetric guidelines identifying this as potentially hazardous for the fetus,^{174,175} although evidence suggests a number of pregnant women will travel to altitude.^{50,176} There are limited data available on this subject, with only a small number of studies exploring on sojourners to altitude.^{176,177} There is evidence of an increased rate of neonatal intensive care admission and oxygen administration at birth in infants of altitude

residents.¹⁷⁶ In addition, multiple population studies demonstrate a significant reduction in birth weight that is proportional to altitude gain above 2000 m. This is not due to increased prematurity but rather intrauterine growth restriction (IUGR).^{178,179} The effect of altitude on birth-weight in these populations varies among different populations. It is more pronounced in recently arrived populations, such as the Han Chinese and Europeans, and least pronounced in groups such as Tibetans, who have resided at altitude for much longer.¹ This suggests any results derived from sojourners or permanent residents are unlikely to be entirely transferable.

The limited number of physiologic studies on the fetal effects of maternal hypoxia suggest changes in the placental villous membrane facilitate increased gas exchange.¹⁸⁰ With these changes, the fetuses of women exposed to short administrations of 10% oxygen show no signs of distress with no significant change in fetal heart rate, HR variability, or Doppler velocimetry in the umbilical artery.¹⁸¹ However, studies on altitude dwellers have demonstrated a reduction in the pregnancy-associated increase in uterine artery blood flow,¹⁸² which may account for IUGR.

Additional research is required in this field and the paucity of evidence makes any firm recommendation challenging. There are clear physiologic sequelae for both mother and fetus in response to altitude, which in the chronically hypoxic mother appear deleterious. Consequently, any travel to altitude during pregnancy must be with caution, although conclusive data for sojourners are unavailable.

Anesthesia at Altitude

GENERAL PRINCIPLES

Most surgical facilities are not situated at extremes of altitude. However, a number of centers perform operations at high altitude,^{183,184} while at any altitude there may be an emergent need for general anesthesia.¹⁸⁵ Practice under these conditions is guided largely by clinical experience, the setting, and select published case reports.

The anesthetic practitioner at altitude should be aware of the physiologic and pathologic changes, discussed previously, which may affect individuals. They should endeavor to assess on an individual basis how these changes can impact each patient. Consideration should be given to the altitude at which anesthesia is performed, the level of acclimatization of the individual, and any concomitant pathology. When logistically feasible, it may be advisable, particularly in unacclimatized individuals, to descend before administration of anesthesia.¹⁸⁶ At extremes of altitude, the risks associated with anesthesia are only outweighed by life- or limb-saving procedures.¹⁸⁵

It is also important to establish the environment in which anesthesia will take place. The operating environment in a hospital with formal operating theaters and associated equipment is very different to emergency surgery undertaken in a remote and rural setting, regardless of altitude.

Several aspects require particular consideration, the most obvious of which is the increased risk of perioperative hypoxia. Medications used during anesthesia, notably opiates, depress both the tachycardia and tachypnea

associated with the physiologic response to altitude.¹⁸⁶ Slowed recovery from anesthesia has been reported,¹⁸⁷ as has increased sensitivity to anesthetic medications.¹⁸⁵ These factors combine to create a prolonged period where an individual may not be able to enact the full range of compensatory mechanisms to tolerate hypobaric hypoxia. Some of these consequences may be reversed by the administration of supplemental oxygen¹⁸⁷ and certainly oxygen therapy at altitude is advised when possible.¹⁸⁶ Care with analgesic agents in the postoperative period is necessary to ensure ventilation and oxygenation is not compromised; analgesia-induced respiratory depression was implicated in the death of a Sherpa who underwent a debridement at 4300 m.¹⁸⁸

The second area of particular note in the perioperative period are reports of increased bleeding and challenging hemostasis during surgery at altitude.^{183,187} This is attributed to increased venous pressure and increased capillary density¹⁸⁶ and, while not conclusively proven, still warrants consideration.

ANESTHETIC EQUIPMENT

The most routinely considered implication of high altitude on anesthetic equipment is in relation to anesthetic vaporizers. As variable bypass vaporizers rely on the saturated vapor pressure of anesthetic agents, the partial pressure of anesthetic gas delivered remains constant regardless of altitude, although the F_{IAA} will rise. This should in theory mean the same clinical effect.¹⁸⁹ Chamber-based studies on vaporizers have confirmed a constant partial pressure delivery;¹⁹⁰ however, several caveats to this exist. First, desflurane vaporizers operate by using a measured flow principle.¹⁸⁹ Such vaporizers will deliver a constant F_{IAA} and, therefore, in hypobaria will deliver a reduced partial pressure. Second, consideration must be given to the monitoring and targeted dose of anesthetic gas. The minimum alveolar concentration is often used to guide dosing of anesthetics but it is not appropriate for use at altitude. Instead, practitioners should consider their administration as a partial pressure rather than a fraction, or concentration, as it is the partial pressure that determines depth of anesthesia.¹⁹¹ This is most apparent when considering nitrous oxide, which when delivered at a given concentration is less effective at altitude, proportional to the drop in partial pressure.¹⁹²

This recommendation regarding the use of partial pressure should also be considered for all forms of gas monitoring. Modern anesthetic machines may interchangeably state partial pressure or concentrations for gas monitoring.¹⁹¹ However, the analyzers themselves physically detect partial pressure, not concentration. The reported concentration is derived mathematically and, for example, an oxygen analyzer set to measure 21% in air at sea level will read 17.4% in air at 1500 m, unless recalibrated.¹⁹⁰ Once again, the physiologic significance is in the partial pressure of oxygen. Therefore, direct measurement of partial pressure allows greater understanding of the physiologic effect of the gas mixture being delivered to the anesthetized patient.¹⁹¹

Flowmeters are also affected at altitude. Flowmeters rely on the density of gas to measure flow. Studies examining the floating flowmeters showed that with reducing P_B , and

therefore density of gas, these flowmeters were liable to be under-read.¹⁹⁰ The percentage of error observed was not constant but reached a peak error of 21%, making adjustments challenging. Studies have not been conducted to observe the impact of high altitude on flowmeters found in more modern anesthetic machines such as hot wire anemometers. Caution is advised when examining readings from flowmeters and where possible gas analyzers directly measuring partial pressure should be used to corroborate.

GENERAL ANESTHESIA

Several considerations for anesthesia at altitude have already been discussed, including perioperative hypoxia and the effects of anesthetic drugs on mechanisms of acclimatization. As such, when considering anesthetic agents, the maintenance of these mechanisms, including tachycardia and hyperpnea, may be desirable. This is particularly relevant in the austere environment where supplemental oxygen may not be available. In such environments, the use of ketamine has been advocated in both emergency¹⁸⁵ and elective¹⁹³⁻¹⁹⁶ settings. These reports have varied in their approach, with some using entirely ketamine anesthesia, whereas others have supplemented with inhalational anesthesia or benzodiazepines. Without supplemental oxygen, some degree of desaturation may be observed in the spontaneously breathing patient, but this was felt acceptable and could be managed with monitoring and simple airway maneuvers.¹⁹⁴ However, total apnea may be seen with smaller doses of ketamine than would be expected at sea level, with a report of deep general anesthesia and apnea at a dose of only 0.5 mg/kg;¹⁸⁵ however, other studies have successfully used higher doses without any adverse outcome.¹⁹⁶ Further caution is advised when using ketamine, as it may increase pulmonary vasoconstriction, with a single study at 1600 m suggesting certain susceptible patients may develop increased pulmonary vascular resistance with ketamine use.¹⁹⁷ This may make it an undesirable agent for use in patients with active, or high risk of developing, HAPE.

Any anesthetic at altitude, particularly emergency remote surgery, remains comparatively high risk because there are limited data on which to base practice. There is some literature suggesting that ketamine may be used safely (either alone or in combination). Adequate monitoring, airway equipment, and appropriately trained practitioners are advised, alongside a careful risk-benefit analysis and consideration of alternative courses of action.

REGIONAL ANESTHESIA

Spinal anesthesia may be desirable at altitude, as it allows the individual to maintain his or her own ventilatory parameters and reduces much of the risk surrounding perioperative hypoxia. Reports of very high rates of postdural puncture headache (PDPH) do exist;¹⁸⁷ however, these predate the use of modern spinal needles with narrower gauges and pencil-point needles now routinely used in modern practice.¹⁹⁸ A single study examining spinal anesthesia at moderate altitude (1890 m) found that at altitude spinal blocks took longer to perform, and block duration was shorter than at sea level.¹⁹⁹ They also observed a higher

rate of PDPH (7.14 vs. 2.85%; $P < .05$) at altitude. Despite these limitations, spinal anesthesia provided adequate analgesia for lower extremity surgery in all patients and no significant complications were reported. Based on this limited evidence, spinal anesthesia may be the first choice for such procedures at high altitude but further study is advised.

APPLICATION TO FLIGHT, INCLUDING AIR TRANSPORT OF CRITICALLY UNWELL PATIENTS

The contents of this chapter remain relevant when considering air travel. Cabin pressure in commercial air travel is regulated but studies have shown peak cabin altitudes do vary, with an average value of 1933 m and the highest recorded being 2606 m.²⁰⁰ The physiologic changes are equivalent to those experienced by visitors to high altitude but with the caveat that ascent happens much more rapidly with less time to acclimatize. A small drop in SpO_2 may be observed, and symptoms of AMS have been reported. Despite this, air travel is generally physiologically well tolerated.²⁰¹ Greater concern may be associated with prolonged immobility and the risk of thromboembolic phenomena.²⁰²

In contrast, patients with significant comorbidity may not tolerate air travel because of the rapid altitude gain and relative hypoxia. Extensive guidelines exist to guide the decision on flying with health conditions.²⁰⁴ In the rare event of cabin decompression, risks are considerably higher. In addition to acute hypoxia, which at altitudes above 13,716 m may induce unconsciousness in as little as 15 to 20 seconds, there are dangers posed by sudden air movement, cold, and debris.²⁰³

The transfer of an unwell patient is a significant undertaking that relies on careful planning, adequate infrastructure and equipment, and a thorough understanding of the patient's physiology and pathology.²⁰⁵ In addition to hypoxia, there should be an awareness for gas expansion within body cavities.^{205,206} This expansion may affect pathologic processes, such as pneumocephalus, pneumothorax, or intestinal gas, which is particularly significant in cases such as volvulus. The presence of any of these pathologic processes is a relative contraindication for aeromedical evacuation,²⁰⁵ but the decision must be ultimately be balanced against the need for ongoing treatment not available at the patient's location. Gas expansion also changes the volume of air within medical devices, such as endotracheal cuffs. Ascent to 2500 m from sea level increases the volume in an endotracheal cuff by approximately 35%,²⁰⁷ which should be considered and accounted for both on ascent and descent. There are additional working challenges related to the enclosed space and moving of patients.^{205,207} A large cohort (19,228) of aeromedical evacuations in Canada reports a critical event on 5.1% of evacuations at a rate of 1 per 12.6 hours of transport time.²⁰⁸ Critical events were more likely to occur in older patients, those with greater hemodynamic instability, and those requiring assisted ventilation. The most common critical event was hemodynamic deterioration and the need for intubation was the most common major resuscitative procedure required. The mortality in the cohort remained very low at 0.1%.²⁰⁸ These results demonstrate that with appropriately trained practitioners, aeromedical evacuation can be performed safely and with great benefit to patients.

Space Medicine

Atmospheric pressure decreases exponentially with increasing distance from the Earth's surface and becomes progressively hostile to human survival. At the cruising altitude of commercial airliners (approximately 39,000 feet), the atmospheric pressure outside the aircraft is only approximately 20% of the pressure at sea level. The International Aeronautics Federation defines the boundary of outer space, where the Earth's atmosphere stops and space starts, as an altitude of 100 km above the Earth's surface.²⁰⁹ However, at any particular time, astronauts on board the International Space Station (ISS) are 350 to 450 km above the Earth's surface as they circle our planet at velocities of up to 17,500 mph. Yet, these extreme altitudes are still considered to be relatively low Earth orbits and future astronauts will travel much farther away from the protective environment of the Earth.²¹⁰

INTRODUCTION TO SPACE EXPLORATION AND MEDICINE

On November 5, 2015, the National Aeronautics and Space Administration (NASA) announced it was looking for astronauts for long-duration space flights, including extended missions on the ISS and possible journeys to Mars.²¹¹ In recent times, both the United States and Russia have announced their intentions to construct a new spaceport on the moon and to use this lunar base as a stepping stone to send their own astronauts to Mars. Private billionaire entrepreneurs (such as Richard Branson and Elon Musk) have outlined similar visions and promised to revolutionize air travel by transporting passengers using rockets traveling through space instead of traditional airplanes traveling through the earth's atmosphere. An international "space race" is undoubtedly already well underway.

Technology, skills, and knowledge have all developed rapidly since humans first entered space in 1961 when Yuri Gagarin orbited the Earth for the first time during a flight lasting less than 2 hours in total.²¹² Yet since then, only 12 men have ever walked on the moon and over four decades have passed since the last Apollo mission (Apollo 17) left Earth.²¹¹ A future that includes successfully leaving low Earth orbit again and sending astronauts on more distant missions, as well as making spaceflight safe for commercial purposes, poses many challenges, including how best to identify and manage any potential health issues among future crewmembers and passengers.

RISK OF DISEASE AMONG ASTRONAUTS DURING SPACE TRAVEL

Although the absolute chance of a medical issue arising during spaceflight is low, the risk remains significant. Current conceptual plans for future missions to Mars from NASA predict crewed missions lasting up to 1100 days (approximately 3 years).²¹³ Given the rate of emergencies among the general population is around 0.06 events per year, a crew of 6 astronauts would expect to encounter at least one medical emergency during a 3-year space mission ($0.06 \times 6 \times 3 = 1.08$ events).²¹⁴

Astronauts can be affected by illness or disease just as any other human. For example, concern about possible exposure to the German measles virus meant that NASA Astronaut Thomas K. Mattingly was famously removed from the crew of the ill-fated Apollo 13 mission just 72 hours prior to launch (Mattingly never actually developed measles and went on to successfully fly future missions including both Apollo 16 and STS4).²¹⁵ However, the unique environmental conditions associated with spaceflight can also modify an astronaut's susceptibility to such illnesses. Identifying these effects remains an active focus of research, such as the Longitudinal Study of Astronaut Health that NASA has been operating since 1992.²¹⁶ This cohort study is generating data about all-cause astronaut mortality and morbidity, such as the reassuring finding that cancer mortality among astronauts is not significantly increased (as might be expected from increased exposure to harmful doses of radiation, as later discussed), suggesting the many preventative measures employed to mitigate these risks during spaceflight appear to be effective.²¹⁶

Similarly, the spaceflight environment can also cause a number of specific health concerns to astronauts that are not normally experienced by the general population and which can affect the physiologic and psychologic performance of crewmembers. One survey of astronauts returning from 79 U.S. space shuttle missions showed that as many as 94% of crewmembers took some form of medication at some stage during the flight and often to treat conditions not normally expected among similarly physically fit cohorts on Earth. These conditions included space motion sickness (SMS), sleeplessness, headache, or backache.^{217,218}

The Environmental Challenges Posed by Spaceflight

EXTREME ACCELERATIONS/DECELERATIONS

Takeoff and landing (including re-entry to the Earth's atmosphere) are two of the most important and dangerous periods of any spaceflight. Every human fatality during spaceflight to date (Challenger, Columbia, Soyuz 1, and T11) has occurred during one of these critical periods.²¹⁰ Astronauts routinely experience extreme accelerative forces of around 4 to 5 G during takeoff and re-entry but these can be much higher; Yuri Gagarin remained conscious while experiencing forces of around 8 G during re-entry in his spacecraft Vostok 1 in 1961, and the Apollo astronauts typically experienced landing forces of around 17 G and tolerated them remarkably well.^{211,212} Current ISS crews returning in Russian Mir spacecraft use seats with specially designed shock absorbers and liners to decrease these forces by 20% to 30% and bring them down below 22G.²¹¹

These accelerative and decelerative forces are more than capable of dislodging incorrectly stowed items of equipment (causing trauma from the impact of flying objects or hard landings a real hazard), and also generating extreme temperatures from friction with the surrounding air. During re-entry, the outside of the U.S. space shuttle reached temperatures in excess of 15,000°C. This was high enough to ionize air and remove electrons from the outermost atoms on the protective heat tiles around the Shuttle spacecraft

surface, generating significant amounts of electromagnetic disturbance that prevented any radio contact with the on-board crew for 17 minutes. On February 1, 2013, damage to one of the heat tiles during takeoff led to a weakness in the Space Shuttle Columbia's critical heat-protective layer, leaving the vehicle unable to withstand these extreme temperatures on its return to Earth and causing the vehicle to burn up on re-entry, resulting in the loss of all seven crew-members on board.²¹¹

RADIATION

Solar radiation exposure (i.e., galactic cosmic rays, high-energy photons, high-energy and charge (HZE) neutrons and nuclei, and solar particle events) has always posed a major health concern for astronauts. These risks of both acute (mission-critical) and chronic (post-mission) radiation-related exposure are only going to increase on longer-term exploratory missions deeper into space.²¹⁹ Crewmembers have not completely left the protection of the Earth's magnetic field (i.e., gone beyond the Van Allen belts) since the Apollo missions, but crewmembers on any future mission to either the moon or to Mars will be at risk of direct exposure to full solar radiation doses for the first time in over 40 years and currently no adequate shielding strategy has been fully developed and tested.²²⁰ Chronic exposures of less than 1 sievert (Sv) per year are still thought to have long-term effects on tumor rates; acute exposures of 0.5 to 1.0 Sv could be sufficient to cause symptoms of acute radiation exposure. Some estimates predict exposure rates could almost nearly reach such levels during a 940-day Mars mission.²²¹ Other estimates have even projected radiation exposure levels during a simulated Mars mission, that would for the first time even exceed the strict occupational career limit NASA currently employs (i.e., upper confidence interval [CI] for risk of exposure-induced death [REID] of 3%), using the recommendations by the National Council on Radiation Protection.²²² During a 1-year deep-space mission at minimum average solar radiation levels, the total risk of exposure-induced cancer in a 45-year-old male who has never smoked is predicted to be approximately 2% (CI 0.53%–7.84%), with the risk anticipated to be highest for lung cancer followed by colorectal cancers.²¹⁹ However, our overall understanding of the long-term health risks from radiation exposure during spaceflight is still relatively limited and marked differences between current predictions and previously observed effects remain.²²³ Besides malignancy, other chronic radiation exposure health risks have been noted among astronauts. For example, increased rates of cataract formation have been reported in those exposed to greater than 8 millisievert (mSv) of radiation after a 20-day space mission,^{216,224} reduced fertility (and/or increased numbers of birth defects in animal studies),²¹¹ and a slightly (but not statistically significant) increased risk of developing clinical thyroid disease.²¹⁶ Initially, the CNS was thought to be relatively resistant to the effects of radiation; however, widespread CNS changes have been reported including memory impairment, changing synapse plasticity, impaired executive function, and cognitive dysfunction.^{225–229} Moreover, many of these effects may be even further compounded by the significant neuropsychologic challenges of spaceflight.

ISOLATION, CONFINEMENT, SLEEP DISTURBANCE, AND OTHER PSYCHOLOGICAL CHALLENGES

Traveling at over 17,000 km/h, the crew of the ISS travel completely around the Earth—what we usually define as a typical “day”—every 90 minutes. This means that in every 24-hour period, the ISS crew experience no fewer than 16 sunrises and 16 sunsets; in other words, crewmembers could easily see 365 sunrises (a whole year’s worth) in just a 23-day space mission. The sleep-wake cycle is closely linked to biologic circadian rhythms regulated by the solar light,²³⁰ but astronauts also face many other challenges to sleeping comfortably, such as constant noise, physical discomfort (astronauts usually sleep in sleeping bags fixed tightly to the walls of the space craft), and hypercapnia. Sleep deprivation and fatigue are common complaints among crewmembers, with studies suggesting that on average astronauts experienced just 5.96 hours (SD 0.56) sleep during space shuttle missions, 6.09 hours (SD 0.67) during ISS missions, and less than 6.5 hours during their 3-month pre-launch period.^{231,232} Similar levels of sleep disturbance have been reported to impair cognitive performance and worsen long-term health outcomes.^{231,233} The constant stresses posed by extreme isolation and prolonged periods of confinement can also increase sleep disturbances and affect individual and team behavioral performances.²³⁴ Interestingly, though, these effects seem much more variable between different individuals and would also appear to be trainable. In the Mars 500 study, 6 males were confined for 520 days in a 550 m³ chamber simulating a high-fidelity Mars mission. One crewmember reported depressive symptoms throughout 93% of the mission, whereas two other crewmembers had no symptoms of psychologic distress at any point in the study.²³⁵ Similarly, after reviewing how their astronauts performed during missions on the ISS, all crewmembers participating in the study displayed unusually high levels of self-awareness and were generally positive about their time on the ISS, leading NASA to conclude that their training programs regarding interpersonal relationships, teamwork, and psychologic support were effective.²³⁶

DECOMPRESSION AND CHANGING OXYGEN CONCENTRATIONS

Foreign space objects pose a constant hazard to any manned space vehicle, as any penetrating impact could cause sudden depressurization of the internal cabin environment. NASA estimates that there are now more than 21,000 orbital debris objects (usually human made objects with no further usable purpose or the remains of such objects) in the Earth’s atmosphere, and approximately 200 kg of meteorite material (rocky material passing through the Earth’s atmosphere while orbiting the sun) is likely to be within 2000 km of the Earth surface at any particular time.²¹¹ Sudden loss of the crew’s artificial environment can cause acute hypoxia, decompression sickness (DCS), and ultimately death if the problem is not rapidly resolved or contained. According to the Federal Aviation Administration, the time of useful consciousness (i.e., the amount of time a person can effectively or adequately perform flight duties with an

insufficient supply of oxygen) after rapid decompression at 50,000 feet is just 5 seconds.²³⁷

DCS (commonly known as “the bends”) arises when gases usually dissolved are forced out of solution by sudden pressure changes to form generalized bubbles (a process called *ebullism*, body fluids boiling as a result of ambient pressure being less than the saturated vapor pressure of water). Soviet Cosmonaut Alexei Leonov reportedly gave himself DCS in 1965 as he finished making the world’s first space-walk—he needed to reduce the size of his malfunctioning spacesuit in order to fit back through the airlock door into his space craft.²³⁸ Space suit design has since improved massively but the dangers associated with performing extravehicular activities (EVAs) remain significant.

American and Russian spacesuits maintain an internal environment of 100% oxygen at either 30 or 40 kPa, respectively. It is a major engineering challenge to build flexible suits durable enough to withhold higher pressures against the vacuum of space.²³⁹ Astronauts undergo pre-EVA procedures before leaving the main spacecraft to minimize the risk of developing DCS during a particular EVA, but despite being relatively time-consuming in spaceflight terms, these pre-EVA activities represent extremely rapid decompression times. Atmospheric pressures between 30 and 40 kPa are equivalent to standing on the summit of Mount Everest at 8848 m. While most climbers would typically take around 60 to 70 days to reach the summit of Mount Everest,²⁴⁰ astronauts are decompressed to these values within minutes to hours, thus making supplemental oxygen essential to prevent any of the altitude illnesses described earlier in this chapter. However, oxygen represents a major fire hazard to any spacecraft and no manned space programs currently use spacecraft with elevated oxygen levels for this reason. Therefore, some form of decompression procedure currently remains essential prior to any EVA.²³⁹ Although this may not be much of a concern to routine commercial passenger travel into space (passengers will not need to routinely exit their spacecraft), how best to manage these conflicting issues on longer missions to the moon or Mars remains unclear.

MICROGRAVITY

The human body has carefully evolved over millions of years to perform optimally in an environment with gravity. In fact, the effects of gravity on our environment are so ubiquitous that it is challenging to contemplate just how significant a role gravity plays on human health and performance. Without gravity, just attempting to function and interact appropriately with our surrounding environment becomes immensely difficult, and simple phenomena that we take for granted on earth no longer occur. Without gravity, there is also no convection, making temperature control difficult. As an example, burning flames are spherical and blue rather than yellow and pointy; there is no downward soot deposition or upward heat transfer and the flame burns as soon as it reaches any oxygen and in all directions. Without gravity, there is no effect of buoyancy—bubbles do not rise to the surface but remain suspended in fluids (Fig. 74.3). In other words, to remove any bubbles from fluid in a syringe requires the application of an external accelerative force. Weightlessness has an impact on almost every organ

system in the body, posing a number of both acute and chronic health risks to astronauts. A future mission to Mars raises further challenges as astronauts will need to be able to transition from weightlessness to functioning in a gravitational environment again within minutes after landing.²¹¹

Cardiovascular Physiology During Space Flight

The cardiovascular system is particularly susceptible to the effects of microgravity. Shortly after takeoff, an acute “fluid shift” quickly occurs as fluid usually held in the venous

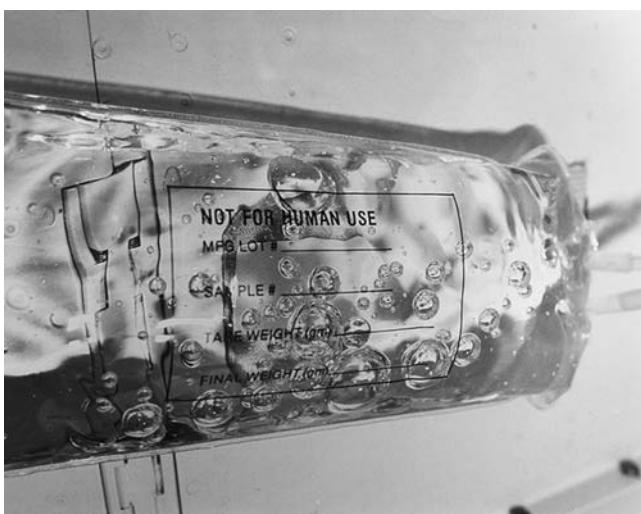


Fig. 74.3 A 1-L bag of 0.9% saline during an orbital flight with air bubbles clearly visible throughout the bag because of the lack of gravitational forces. (From Norfleet WT. Anesthetic concerns of spaceflight. *Anesthesiology*. 2000;92(5):1219–1219.)

(high capacitance) side of the circulation starts to rapidly redistribute throughout other tissue beds (Fig. 74.4). This effect is most marked in the upper body with up to 2 L of the blood normally pooled in the venous system in the legs by gravity is released upward into the central circulatory system within minutes of launching.²⁴¹ Astronauts quickly develop facial edema and a so-called “chicken leg” syndrome as a result of this shift.²¹⁰

Different studies suggest that cardiac output increases between 18% and 30% acutely in response to weightlessness and that this increase persists for at least 8 days.^{242–244} This increase is driven predominantly by increases in stroke volume as overall HR appears to remain relatively unchanged.^{243–245} Systemic vascular resistance (SVR) also decreases by 14% to 35%, leaving systolic BP relatively unchanged,^{244,245} although some studies suggest that resting diastolic and mean arterial pressures might both decrease slightly in response to microgravity but still increase as normal in response to exercise.^{243,245} These decreases may turn out to be even more pronounced, however, on longer-duration space missions.²⁴⁵ Paradoxically, central venous pressure (CVP) acutely decreases after takeoff, possibly as a result of increased atrial distension.^{246,247} One study of space shuttle astronauts suggested that baroreflex sensitivity at rest might actually increase briefly initially before returning to baseline levels a few days later,²⁴⁸ but the baroreflex response seems to be chronically reduced after longer (e.g., 9 months) duration missions.²⁴⁹

As time in space increases, adaptation to microgravity slowly decreases SV (and cardiac output) again and allows ejection fraction to increase.^{250,251} This is presumed to be driven by anatomical changes to cardiac tissue, as left ventricular mass and mean sphericity index may decrease by 8.0% and 9.6%, respectively, together with a drop in total body fluid.^{252,253}

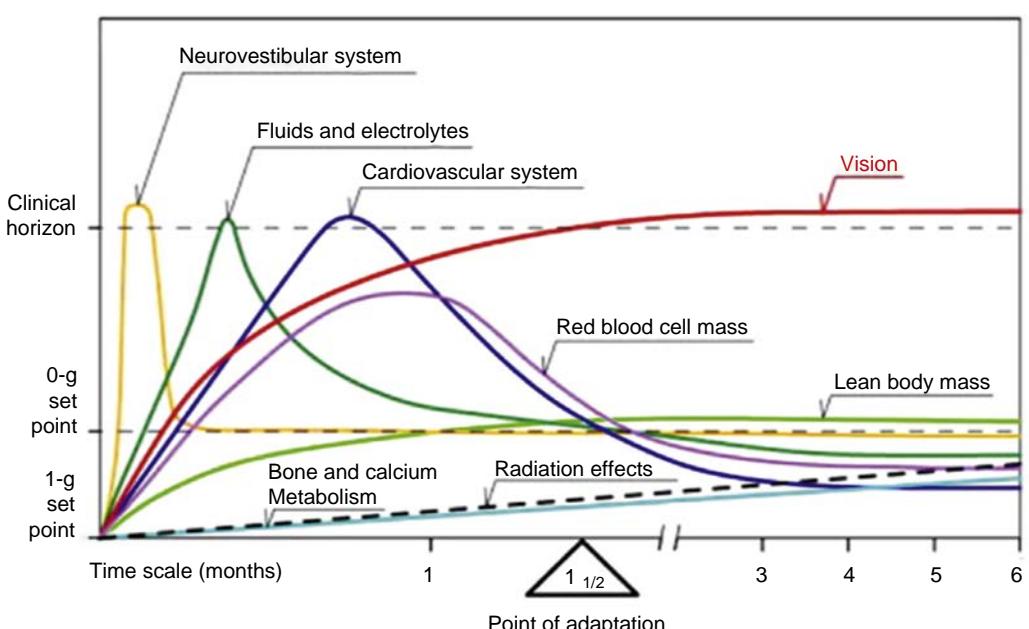


Fig. 74.4 The time course of physiologic adaptation and acclimatization to microgravity. (From Komorowski M, Fleming S, Kirkpatrick AW. Fundamentals of anesthesiology for spaceflight. *J Cardiothorac Vasc Anesth*. 2016;30(3):781–790.)

Plasma volume decreases of up to 15% have been reported in both bedrest and spaceflight studies,²⁵⁴⁻²⁵⁶ accompanied by similar decreases in total red cell mass.^{254,257} Whereas plasma volume decreases within 24 hours, red cell changes take a week to become apparent, suggesting different mechanisms behind each change, but the exact cause of the decrease in red blood cells (RBCs) remains unclear.^{210,257} Elevated ferritin levels have been measured after space shuttle missions, but decreased reticulocyte counts suggest this process is because of reduced RBC production and not increased destruction/consumption.²⁵⁷ But this could also be a result of changes in tissue oxygen levels, particularly in the kidney, as a result of fluid shifting from the lower limbs toward the central (and renal) tissue beds.²¹⁰

Although these fluid changes reverse within 2 to 3 weeks after returning to Earth, initially hypovolemia and orthostatic intolerance still cause astronauts significant problems when they arrive back on Earth. Current protocols require astronauts to “fluid load” with salt water approximately 1 hour before landing, which significantly reduces these risks.²⁵⁸

Microgravity itself does not appear to affect cardiac electrophysiology directly. However, a large number of arrhythmias have been reported during spaceflight and particularly during EVAs, possibly due to the many fluid shifts described above and the changes in catecholamine levels and adrenergic receptor sensitivity.^{210,259,260} Every one of the nine Skylab astronauts suffered some form of rhythm disturbance during their mission, NASA recorded multiple arrhythmias during its many space shuttle missions, and in 1987 one of the crew-members on board the Russian MIR space station recorded a 14-beat run of ventricular tachycardia (VT).^{210,211}

Pulmonary Physiology During Space Flight

Human lungs are normally exquisitely sensitive to gravity, which induces relevant gradients to both ventilation distribution and pulmonary blood flow. Consequently, it is not surprising that pulmonary function alters during spaceflight away from the Earth’s normal gravity environment.^{242,261} However, adaptive changes remain remarkably short lived and, unusually, no pulmonary recovery or rehabilitation is commonly necessary when astronauts do return to Earth.²⁶² Whether this would also remain true after future space missions with durations longer than 6 months currently remains unproven.

More specifically, respiratory rate increases by around 9% in microgravity but tidal volume decreases by up to 15%, meaning that minute alveolar ventilation remains essentially unchanged overall.^{210,242,263} Other respiratory measurements don’t alter significantly either with space flight. Measurements suggest that although vital capacity, forced vital capacity, and FEV1 may all decrease marginally (by around 2%-5%) within 24 hours of entering microgravity (Fig. 74.5), by the fourth day of spaceflight all have returned to pre-flight values.^{211,264} Residual volume decreases by around 18% in space (approximately 320 mL) and consequently functional residual capacity also reduces by around 15% (approximately 500 mL) in microgravity, possibly because of cranial movement of the diaphragm,

more uniform alveolar expansion, and increased intrathoracic blood flow.²⁶³ However, although ventilation and blood flow are more uniform throughout the lung in microgravity, a small and clinically insignificant degree of ventilation perfusion mismatch still remains even in space.^{211,265}

On average, ISS astronauts’ exercise capacity (as measured by $\dot{V}O_2$ peak) decreases in the initial stages of their space flight (by 17%) but then continues to gradually normalize again throughout the remainder of their mission. Although some astronauts were able to reach their pre-flight value, others were not, suggesting considerable interindividual variability in exercise-responses to spaceflight.²⁶⁶ The fact that aerobic capacity increasingly recovers as flight durations lengthen suggests this is a successful response to exercise countermeasures employed during and throughout each ISS mission.²⁶⁷ All astronauts undergo an individually tailored daily exercise regime whilst in space to counter any aerobic deconditioning, but this countermeasure program has continued to evolve over the years as both knowledge and the equipment available for use on the ISS has changed and improved. While the relative contribution of both treadmill running and cycle ergometry has steadily decreased over the last 10 years of ISS missions to just 30 minutes of each on average per day, the number of resistance exercises in these programs has gradually increased to around an hour a day.²⁶⁸ HR only increases marginally on return to Earth after long duration space flights, suggesting that these programs can successfully maintain astronauts’ cardiovascular fitness to enable them to meet the demands of daily mission activities.²⁶⁹ Another one of the main aims of this rigorous exercise regime is to counter the significant muscle atrophy and bone demineralization that occurs under conditions of microgravity (Fig. 74.6).

Musculoskeletal Physiology During Space Flight

Marked bone demineralization starts immediately after entering space and leaving Earth’s gravity. Urinary and



Fig. 74.5 British European Space Agency (ESA) Astronaut Tim Peake performs pulmonary function tests while on the International Space Station. (Image courtesy ESA.) (From European Space Agency. http://m.esa.int/spaceinimages/Images/2016/02/Taking_Tim_s_breath_away. Published 2016.)



Fig. 74.6 European Space Agency (ESA) Astronaut Samantha Cristoforetti exercising on the International Space Station. (Image courtesy ESA.) (From European Space Agency. http://m.esa.int/spaceinimages/Images/2015/09/Samantha_running_in_space. Published 2015.)

fecal calcium excretion increase by 60% to 70% in the first day of space flight, and continues throughout the mission's duration along with notable increases in urinary levels of bone resorption markers and decreases in blood levels of both parathyroid hormone and 1,25 dihydroxy vitamin D.²⁴¹ On Earth, the average loss of bone density as a result of aging is approximately 1% per year, whereas in space, bone density decreases an average 1% per month and the rate can be double in the pelvic bones.^{210,211} Exercise countermeasure programs (particularly resistive exercise elements) can mitigate these effects and are improving each year, but they are not able to curtail these effects and the risks of fragility fractures and renal stones during space flight remain high among astronauts (and are major concerns for future Mars mission planners), as do long-term health risks such as osteoporosis.^{210,270,271}

Similarly, studies of astronauts and cosmonauts on both U.S. space shuttle missions and the Russian Mir missions of 16 and 28 weeks' duration demonstrated significant decreases (5%-17%) in muscle volume in all muscle groups except the neck.²⁷² Muscle groups normally required to maintain an upright posture are usually most affected (i.e., antigravity muscles). For example, muscle volume loss in ISS crewmembers was greatest in the calves (10%-16% reduction) and in the thighs (4%-7% reduction), whereas no change was seen in upper limb muscle volume.²⁷³ Vastus lateralis muscle biopsies taken from 8 astronauts on early space shuttle missions up to 11 days long confirmed that relative losses were greatest in type IIB and then type IIA (fast twitch) muscle fibers, with type I (slow twitch) fibers changing the least.²⁷⁴ Functional muscle impairment also occurs alongside these structural muscle changes in response to microgravity, with increased muscle fatigability and decreased muscle-fiber strength also seen most extensively in antigravity muscle groups.²⁷³ It is notable that decreases in muscle function during space flight are out of proportion with the loss of muscle structure alone. Other factors, including neuronal muscle control, may also contribute.²⁷⁵ A study by Antonutto found that maximal explosive power decreased between 45% and 65% in spaceflights of 1 to 3

months' duration, while muscle mass only decreased by 9% to 13% during the same period.²⁷⁶ Electromyographic cycle period and burst durations were decreased in Rhesus monkeys after simulated spaceflight,²⁷⁷ and significant amounts of dendritic remodeling have been noted in rats on board the ISS.²⁷⁸

Central Nervous System and Psychological Challenges During Space Flight

Astronauts commonly experience neurologic changes soon after they arrive in space and also rapidly after their return to Earth, with many of these deficits persisting for long periods after their return. For example, most crewmembers have had some form of locomotion dysfunction after transiting into or out of microgravity, such as ataxia or postural instability. Postural instability may be explained by a number of factors: differential muscle wasting affects postural tone; unloading of the spine means astronauts can gain 2 to 3 inches in height within 10 days of arriving in space, causing stretching of spinal nerve roots and altering the usual length-tension relationship of different muscle compartments (including antigravity muscles most affected by wasting in microgravity); and changes to vestibular feedback loops (the cerebellum and the vestibular system are usually finely tuned to the Earth's gravity) can also significantly impair normal postural reflexes.²⁷⁵

The vestibular system, composed of the semicircular canals and otoliths that sense distant angular and linear forces, respectively, is constantly updating the brain about the head's three-dimensional orientation and movement. However, this system has evolved and developed over thousands of years to be finely tuned to the Earth's gravitational field and not a microgravity environment, making vestibular problems in space extremely common.²⁷⁵ Between 60% and 80% of all astronauts will experience "space motion sickness" within 48 hours of arriving in space, a condition characterized by symptoms of pallor, anorexia, nausea, sometimes vomiting, increased body warmth, and cold sweating.²⁷⁹ It is usually a short-lived phenomenon, with most cases either resolving spontaneously or with minimal pharmacologic treatment within 48 to 72 hours, but occasionally symptoms can persist longer. Rarely has this condition led to crew members being incapacitated for an entire space shuttle mission.²⁴¹ It poses a real challenge to astronauts contemplating missions of long duration to either the moon or to Mars, where they may need to function normally in a new gravitational environment very shortly after landing in order to survive.

Terrestrial motion sickness commonly results from discrepancies between visual and vestibular perceptions of motion. Similarly, lack of any vestibular sense of "up or down" in the unique, weightless environment of space may also contribute to the development of space motion sickness.²⁴¹ Microgravity affects other sensory systems too. American and Russian astronauts have reported that foods taste and smell different in space with requests for spices to

enhance many foods tasting more bland, as well as having less of a desire for coffee and sweets.²¹¹ Similarly, astronauts are constantly affected by noise during spaceflight with life support systems operating constantly. While ear plugs can block out the noise (typically at levels of 70 to 100 dBA running constantly in very close proximity, 24 hours a day), they do not attenuate the vibrations caused by these machines. However, the headward fluid shifts associated with microgravity may also impair middle ear function and may attenuate the sense of vibration to some degree.²¹¹ Microgravity also impairs proprioceptive sense of limb position and modifies tactile sensitivity with a significant degree of interindividual variability.²⁸⁰

The visual system is particularly affected by spaceflight. Anatomical and functional changes, including disc edema, cotton wool spots, choroidal folds, nerve fiber layer thickening, globe flattening, and consequent hyperopic shifts in vision have all been reported in seven astronauts examined after returning from long-duration spaceflights on the ISS.²⁸¹ In one of these astronauts, who had initially only experienced relatively mild changes after his 6-month flight (unilateral choroidal folds and a single cotton wool spot in the right eye), these changes continued to progress during a second 6-month mission and he developed disc edema and more widespread choroidal folds in the same eye.²⁸² Soon after returning from this second mission, globe flattening and moderate increases in optic nerve sheath diameters were noted bilaterally. Twenty-one months later, widespread choroidal folds remained in the right eye and spontaneous venous pulsations were also absent.²⁸³ Choroidal folds in astronauts were thought to be caused by increased ICP during spaceflight (possibly secondary to higher rates of resistive exercise, higher atmospheric levels of CO₂ on board the spacecraft, or the cephalad fluid shifts associated with spaceflight), which are transmitted to the eye through increased levels of CSF transiting along the optic nerve sheath and putting more posterior pressure on both globes. In fact, this is “visual impairment intracranial pressure syndrome” as seen in spaceflight and it has similarities to some effects experienced by people visiting high-altitude regions.²⁸⁴ However, the long-term asymmetry of these findings in this particular subject suggests that ICPs may not be elevated over prolonged periods in space. Instead, visual impairment during spaceflight may be caused by localized changes to CSF flow within the intraorbital portion of the subarachnoid space—in effect causing an optic nerve sheath “compartment syndrome.”^{285,286}

Unsurprisingly, the effects of these changes on vision during spaceflight are widespread, and particularly during longer duration missions. Almost 30% of astronauts reported deteriorations in both near and distant visual acuity during short spaceflight missions, with this number increasing to 60% on long-duration missions.²⁸¹ Older astronauts are more likely to notice changes as lens accommodation declines with age, and astronauts over the age of 40 are now routinely prescribed “Space Anticipation Glasses” to compensate for their new farsightedness in space. Anecdotal changes in visual fields and changes in intraocular pressure were also reported during the early years of the American space program and substantial



Fig. 74.7 A small winter-over crew at the European Space Agency's (ESA) remote Concordia station in Antarctica. This crew experienced complete isolation, 24-hour darkness, and extremely cold temperatures (down to -80°C) for many months of the year. (Image courtesy ESA.) (European Space Agency. http://m.esa.int/spaceinimages/Images/2016/07/Concordia_crew_2014-2015. Published 2016.)

amounts of evidence now show that transitioning to or from microgravity also impairs ocular movements and reflexes too.²¹¹

In addition to coping with changes to their perception, astronauts also experience numerous psychologic challenges before, during, and after their mission. Astronaut selection is extremely competitive and the intensive international training schedule for crewmembers preparing for launch puts intense stresses on all members of the family unit even before the astronaut leaves Earth. Long periods of isolation have been shown to increase levels of stress as measured by activation of the hypothalamic-pituitary-adrenal axis (resulting in increased levels of cortisol production) and a degree of sleep impairment.²⁸⁷ The increased levels of insomnia astronauts experience is likely multifactorial and not simply explained by isolation alone. For example, low-earth orbit is associated with circadian desynchrony, increased levels of noise, hypoxia, hypercarbia, and extremes of temperatures. However, identifying how best to manage the psychologic stress caused by long-term isolation is critical to the success of any future long-term space missions. International space agencies now run a number of ground-based spaceflight research analog programs specifically to research this (and other) challenges to long-duration spaceflight. For example, the European Space Agency's ground-based research analog program is based at the Concordia station situated high on the Antarctic plateau, which is completely inaccessible for half of the year, completely isolating the dozen crewmembers who “winter-over” there annually (Fig. 74.7). Reports from the Mars 500 project, the first high-fidelity simulated mission to Mars isolating a multinational crew of 6 in a 550 m³ chamber for 520 days, recently suggested that appropriate selection of crewmembers is key. Substantial interindividual differences were seen in behavioral responses: two crewmembers with the highest ratings of stress and exhaustion accounted for more than 85% of all the perceived conflicts.²³⁵

The Effect of Spaceflight on Other Physiologic Systems (Including the Immune and Gastric Systems)

Infectious diseases have been a major concern since the earliest days of space travel. Astronauts were at increased risk of catching infectious disease in the 1960s and 1970s. During that time, approximately 50% of all Apollo astronauts reported suffering from bacterial or viral infections either during or soon after spaceflight.²⁴¹ Concerns about how microgravity affects the immune system's responsiveness, and the likelihood of crewmembers becoming increasingly immunocompromised during spaceflight, will continue to grow as we look toward longer-duration missions in the future.²⁸⁸

Studies have shown that even short-duration spaceflights impair immune responsiveness with significant increases in inflammatory cytokine production (e.g., IL-4, IL-10, IL-12, and tumor necrosis factor- α [TNF α]) during space shuttle missions, and reduced virus-specific T-cell functionality during spaceflight and soon after landing.²⁸⁹ The reductions in T-cell function persisted in astronauts participating in ISS missions lasting up to 6 months in duration. Crewmembers on longer missions were more likely to show chronic and persistent reductions in interleukins and TNF α .²⁹⁰ Impairments in cell-mediated immunity and associated reductions in delayed-type hypersensitivity responses have also been observed in crewmembers on board the Russian Space Station Mir.²⁹¹ Reactivation of latent virus activity is also seen in otherwise healthy astronauts; increased shedding of varicella-zoster virus, cytomegalovirus, and Epstein-Barr virus DNA have all been reported during spaceflight.²⁹²⁻²⁹⁴ Interestingly, an episode of thoracic zoster, typically only seen in either elderly or immunosuppressed patients (e.g., following organ transplant/acquired immune deficiency syndrome), has been observed in an otherwise fit and healthy 47-year-old astronaut 2 days before launch, suggesting the chronic stress of astronauts' rigorous training program may affect their immune responsiveness even before they leave the Earth's atmosphere.²⁹³ Spaceflight may also increase the virulence of infective organisms in animal models, which could compound the problems of immunosuppression developing in crewmembers during longer missions.²⁹⁵ Ground-based analog research programs (e.g., the Mars 500 project) have suggested that the long-term confinement of space travel could reduce overall microbial diversity and lead to increased selection of opportunistically pathogenic microorganisms.²⁹⁶ Microbiome changes were also observed during the Mars 500 study, although interestingly even prolonged periods of confinement were not able to compromise individual specificity of different microbiotic compositions.²⁹⁷ Similarly, changes to the balance of gut bacterial compositions have been seen in astronauts in space but initial findings suggest that overall gut microbial diversity does not alter,²⁹⁸ although the gastrointestinal system does undergo a number of other changes during spaceflight.

Assessment of nutritional status among astronauts shows that Mir crewmembers undergoing a 4-month mission could lose more than 10% of their pre-flight body mass, and often only manage to eat between 40% and

50% of their predicted energy requirements.²⁹⁹ ISS crewmembers also lost weight during long missions (128-195 days in duration) and only consumed a mean of 80% of their recommended energy intake. In this study, hematocrit, serum iron, and transferrin levels all decreased, whereas ferritin levels increased even though other acute phase proteins remained unaltered.³⁰⁰ Serum ferritin levels appear to increase early in spaceflight but transferrin levels do not reduce until later on in the mission, suggesting iron is being mobilized and moved into storage tissues.³⁰¹ Overall, gastric motility is significantly reduced for the first 72 hours of spaceflight, nausea and vomiting tends to increase in astronauts during the same time period, and increased levels of gastric acidity have also been reported.^{210,214}

Potential Medical Scenarios During Manned Space Missions

Despite all the physiologic challenges with spaceflight, mortality rates among astronauts have continued to steadily decline over the last 30 years,³⁰² possibly due to improved screening, selection, and training of future astronauts. However, this could also represent a steady improvement in our understanding and ability to manage physiologic problems associated with spaceflight. Astronauts' risk of dying from cardiovascular disease and cancer are now greatly reduced, yet they continue to be at increased risk of accidental death when compared to the general population.³⁰² However, Apollo astronauts who flew to the moon (the only humans to have ever completely left the Earth's atmosphere) experienced four to five times higher cardiovascular mortality rates than all other astronauts, suggesting that longer distance missions (with increasing radiation exposures) will pose even greater health risks to future crewmembers flying to the moon or Mars.³⁰³

Throughout 70 years of manned spaceflight, most fatalities and near misses have occurred during takeoff or re-entry/landing. Although increased rates of "in-flight" emergencies must be expected on longer deep space missions, astronauts are relatively young, highly screened individuals with very few medical comorbidities. When "space tourism" becomes more commonplace and members of the paying general public start entering low-earth orbits, then the need to be able to manage chronic conditions in space will become more of a concern. Until that time though, medical emergencies in space are likely to either be acute medical events (e.g., sudden onset cardiac arrhythmia or traumatic injuries following a burn or explosion) or other conditions related to specific physiologic changes caused by spaceflight (e.g., space motion sickness/vision impairment intracranial pressure syndrome or radiation exposure).^{210,214} Astronauts may experience different health care needs for many years after spaceflight too. For example, astronauts may have long-term or permanent visual changes as discussed earlier and astronauts are more likely to develop atrial fibrillation at younger ages than the general population, possibly because of transient changes in left atrial structure that can occur after as little as 6 months in space.³⁰⁴

Because of the extreme distances involved in deep space missions, any crew will have to be totally autonomous in a medical emergency. Although “telemedicine consultations” with an appropriate physician back on Earth might be possible for minor ailments, the transmission delays would render this useless if an acute event happened on the far side of the moon. Interestingly, when asked about future Mars missions, most American astronauts said they expected health problems to occur during any such mission and would want their crew to include an appropriately trained physician (with 4-6 years of experience including management of acute medicine, emergencies, and aerospace physiology).³⁰⁵ Anesthesiologists and critical care physicians should be well placed to manage space medical issues, both because of their familiarity with acute emergencies of this nature and their excellent understanding of human physiology and pharmacology. The Exploration Medical Capability (ExMC) arm of NASA’s Human Research Program has developed a list of at least 17 conditions that may potentially require general anesthesia or critical care techniques to successfully treat during an exploratory deep space mission. These include traumatic head injuries that require burr hole excision; cellulitis/abscess requiring incision and draining; or reducing a shoulder or elbow dislocation (Table 74.2).³⁰⁶ The European Space Agency estimates that there is approximately a 2.5% chance that a crew traveling to Mars may need to use general anesthesia to manage a medical emergency en route—a highly challenging (and potentially mission limiting) situation for a completely autonomous team to manage without an anesthetically trained physician on board.³⁰⁶

Thoughts and Considerations for Anesthetic Provision in Space

GENERAL PRINCIPLES

It is currently possible to evacuate a crewmember from the ISS and return them to Earth for treatment within 24 hours; however, this will not be possible on an exploratory mission deeper into space. No human has yet required general anesthesia to be performed in space and it is not ethical or appropriate to test protocols on healthy crewmembers in space, making it difficult to plan appropriate contingencies for future longer-duration missions.³⁰⁷ However, Earth-based models and accounts about the provision of anesthesia in remote and isolated environments do exist, such as at high altitude.¹⁸⁵ Lessons can be extrapolated from these to plan for how best to deal with a medical situation that requires anesthesia during long-duration spaceflight. Common themes include a lack of space and medical equipment; limited skillsets and lack of support; little monitoring; need for flexibility and the ability to improvise appropriate solutions quickly; and increased levels of stress with potential negative impacts on performance.³⁰⁷ However, with adequate training and planning to ensure appropriate redundancy in skills and equipment, providing basic but safe anesthetic care should theoretically be possible in a deep space environment in an emergency.³⁰⁷

TABLE 74.2 A List of Possible Medical and Surgical Conditions That Could Potentially Require Anesthetic Intervention During Deep-space Flight

Condition	Example of Surgical Anesthesia	Suggested Anesthesia
Abdominal injury	Splenectomy, bowel excision	GA ETI
Back injury, lumbar spine fracture, neck injury	Fracture reduction, halo traction application, osteosynthesis	GA ETI
Burns	Dressing, fasciotomy	GA SV
Cellulitis	Incision and drainage	GA SV
Chest injury/ pneumothorax	Thoracotomy for hemostasis	GA ETI
Compartment syndrome	Decompressive laparotomy	GA ETI
Elbow dislocation	Reduction	GA SV
Gastrointestinal bleeding	Hemostasis, ulcer suture, bowel excision	GA ETI
Head injury	Burr hole decompression	GA ETI
Hemorrhoids	Excision	GA SV
Hip/lower extremity fracture	Reduction, osteosynthesis, external fixation	GA SV
Intraabdominal infection (diverticulitis, appendicitis, other)	Bowel excision, appendectomy	GA ETI
Nephrolithiasis	Percutaneous nephrostomy, cystoscopy	GA SV
Shoulder dislocation	Reduction	GA SV
Skin laceration	Suture, dressing	GA SV
Upper extremity fracture	Reduction, osteosynthesis	GA SV

GA ETI, General anesthesia with endotracheal intubation; GA SV, general anesthesia with spontaneous ventilation.

From Komorowski M, Watkins SD, Lebuffe G, Clark JB. Potential anesthesia protocols for space exploration missions. *Aviat Space Environ Med*. 2013;84(3):226–233.

PREOPERATIVE PERIOD

All astronauts undergo extensive selection and screening prior to leaving earth (Fig. 74.8). Most are extremely fit and healthy individuals who would initially appear to benefit little from most preoperative interventions. However, one important consideration might be preventative surgery prelaunch to prevent on-board emergencies later. It is not known whether the physiologic changes associated with spaceflight will alter the relative risks of developing acute appendicitis or cholecystitis in crewmembers undertaking deep space missions. Increased rates of appendicitis and atypical presentations are seen in Antarctica, possibly because of altered immunological responses, so a similar increase could be possible in space as well.³⁰⁸ Similarly, whether space travel might affect rates of gallstone formation (e.g., through altered lipid/cholesterol metabolism and fluid shifts) also remains unknown, although interestingly



Fig. 74.8 European Space Agency (ESA) Astronaut Timothy Peake undergoes practical lessons in medical procedures and techniques at the European Astronaut Centre (EAC) before his mission on the International Space Station. (Image courtesy ESA.) (From Baumbach D. European Space Agency. http://www.esa.int/spaceinimages/Images/2010/02/Timothy_Peake_during_training_at_EAC_January_2010. Published 2010.)

it is becoming more commonplace for patients recognized as being at higher risk of gallstone disease progression (e.g., obese patients undergoing bariatric surgery) to be offered prophylactic cholecystectomy surgery. Whether or not the minimal risks of prophylactic surgery on Earth would outweigh the risks of an emergency occurring during a 900-day mission to Mars remains unclear.³⁰⁸

General Anesthesia in Space

In all probability, the skillset or experience of any crew-member performing anesthesia in space is likely to be limited. Consequently, it seems sensible to encourage simple, protocol-driven techniques that use minimal drugs and equipment for performing general anesthesia in space. Ketamine has been advocated as the induction agent of choice because of its ability to induce dissociative states of anesthesia and provide both analgesia, sedation, and hypnosis via multiple routes (intramuscularly, intravenously, orally, intranasally, intrarectally) while maintaining relative hemodynamic stability even in the relatively hypovolemic states that are likely to be encountered in space. Importantly, ketamine can also be stored in either crystal or powder forms for long periods and remains stable over a wide range of different temperatures. In addition, the relative contraindications to ketamine use (e.g., ischemic heart disease, valvular pathologies, epilepsy, severe arterial hypertension, or pulmonary hypertension) are not likely to be present in highly-selected astronauts.³⁰⁶

Ketamine has been used to manage emergency situations in remote and resource-poor regions and maintains a reasonable safety profile.^{185,196,309-311}

Tracheal intubation has been performed successfully in short flying simulations of microgravity environments, but any attempt at intubation in space is likely to be difficult for multiple reasons. All intubation techniques in microgravity will necessitate both the intubator and the patient being firmly secured, plus the patient is likely to have significant facial—and possibly airway—edema. Use of laryngeal mask airways (LMAs), cuffed oropharyngeal airways, and intubating LMAs have all been demonstrated successfully in a simulated microgravity environment using a waterbath.³¹² However, none of these devices were universally inserted successfully; plus, gastroesophageal reflux is likely more common in space due to increased gastric acidity/decreased motility as described, which makes aspiration a considerable risk during general anesthesia using any supraglottic airway device.

To maximize chances of intubation success, Komorowski and colleagues advocate the use of neuromuscular blocking agents despite the small but potentially serious anaphylaxis risk, and astronauts could always be tested for a possible allergy before launch.³⁰⁶ Depolarizing neuromuscular blocking agents should not be used during spaceflight because of the risk of cardiovascular collapse secondary to hyperkalemia. There is a possibility that increased acetylcholine receptor proliferation will occur in muscles that have atrophied under conditions of microgravity.³¹³ Nondepolarizing muscular blocking agents can be used safely without this risk but there are concerns about the dose; based on findings in similarly immobilized patients and patients with neuromuscular diseases, resistance to these agents is expected and requires increased doses.³¹⁴ However, this has never been tested or validated in astronauts in space and, unlike these cohorts, astronauts are continuously undergoing rigorous resistance exercise regimes during spaceflight to minimize muscle disuse. Rocuronium is likely to be the best choice of neuromuscular blocking agent for many reasons: chiefly, it has a rapid onset of action and a rapid sequence induction is likely to be preferred given the increased aspiration risk³⁰⁶; and it can now be rapidly reversed using sugammadex if needed (e.g., unexpected failed intubation, which is much more likely in space for all the reasons discussed earlier).^{315,316}

Astronauts are likely to be both relatively anemic and hypovolemic, which increases the risk of cardiovascular collapse during any anesthetic induction in space. Available volume resuscitation products are likely to be limited and also need to be prepared and used extremely carefully. All blood products currently have too limited a shelf-life to be carried on all but the shortest space missions, and in microgravity fluids and gases do not separate out based on their different densities (normally on earth, less dense air will always rise to the top of the fluid bag). Consequently, in space a drug vial or fluid bag will contain a fluid more like foam. All intravenous fluid bags will need to be “degassed” before use and likely need to be mechanically pumped in some way as flow will not be aided by gravity.³¹³

Strict environmental controls are likely to enforce totally intravenous methods of maintaining anesthesia (total intravenous anesthesia [TIVA]), as scavenging of volatile gases could be challenging (and traditional vaporizers would not work in microgravity). Relatively simple methods for ketamine-only TIVA have already been described elsewhere and would minimize the need for training in and transporting different agents.³⁰⁶ It would also be essential to use the lowest safe inspired concentration of oxygen, as exhaling large concentrations of oxygen will dangerously increase the onboard fire risk. Other considerations include the need to take care with endotracheal cuff pressures in the microgravity environment.

Regional Anesthesia in Space

Regional anesthetic techniques and approaches could offer many advantages over the many risks associated with performing general anesthesia during spaceflight. In an emergency setting or situation with limited resources, it would be possible to perform almost any limb operation with the knowledge of just three regional blocking techniques. Together, a combined sciatic and femoral nerve block would give complete anesthesia of the leg, and an axillary brachial block would anesthetize the arm below the shoulder.²¹⁰

Large systematic reviews have concluded that using ultrasound-guided techniques to deliver regional anesthesia improves both block safety and success rates.³¹⁷ Astronauts have already successfully performed ultrasound examinations on themselves accurately and safely on the ISS,³¹⁸ showing that they are capable of learning ultrasound techniques and this technology can be used safely in low earth orbit. However, an ultrasound-guided regional block has not yet been performed in space and similar challenges would have to be expected. As for the intubation, both the operator and the patient need to be secured in some way, and success rates could considerably decrease due to neuromuscular and proprioceptive changes associated with spaceflight. Plus, regional anesthetic approaches would not always be suitable for any condition and still require a considerable amount of specialist training to develop reasonable levels of competency, again potentially decreasing their suitability for use by medically inexperienced crewmembers on board an exploratory deep space mission.

The use of telemedicine technology has also been proposed to aid astronauts in space and could theoretically allow a ground-based operator to remotely perform regional anesthesia on board a distant spacecraft in the future. Remotely operated robotic surgery has already been tested in consideration for use in future space missions; for example, over 30 robotic telesurgical procedures have been performed remotely across Canada using internet links with latencies of approximately 140 ms.³¹⁹ However, a radiolink to a deep exploratory spacecraft orbiting Mars could expect to experience delays of nearer to 40 minutes because of the extreme distances involved.³¹³

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Clinical Care in Extreme Environments: High Pressure, Immersion, Drowning, Hypo- and Hyperthermia

RICHARD E. MOON, ANNE D. CHERRY, and ENRICO M. CAMPORESI

KEY POINTS

- Immersion in water causes acute redistribution of blood from the extremities and splanchnic vessels to the heart and pulmonary vessels. This can precipitate pulmonary edema (immersion pulmonary edema [IPE], swimming-induced pulmonary edema [SIPE]) in some individuals, especially during heavy exercise or in the presence of myocardial dysfunction. SIPE usually responds to removal from the water and oxygen therapy.
- Prolonged immersion induces diuresis and plasma volume loss that can predispose to severe postural hypotension after extraction from the water.
- Care of a drowning victim includes resuscitation when necessary, oxygen, and supportive care. All victims of drowning who require any form of resuscitation should be transported to the hospital for evaluation and monitoring, even if they appear to be alert and demonstrate effective cardiorespiratory function at the scene.
- In victims of either hypothermia or hyperthermia optimal temperature measurement should be core (rectal or pre-ingested capsule).
- Extracorporeal life support (ECLS) for both circulatory support and controlled rewarming is usually recommended for core temperature less than 30°C.
- Suspected victims of heat exhaustion or heat stroke should be assessed with rectal temperature measurement. Victims of heat exhaustion (temperature normal or slightly above normal) can usually be treated with minimal external cooling. Heat stroke (core temperature 40°C-47°C) should be treated aggressively, ideally with immersion in ice water until core (rectal) of 39°C or less is reached.
- Hyperbaric oxygen exposure (breathing oxygen at increased ambient pressure, typically 2-3 atmospheres absolute [ATA]) causes an increase in arterial and tissue partial pressure of oxygen (PO₂) and no significant change in arterial pH or partial pressure of carbon dioxide in arterial blood (PCO₂).
- During hyperbaric oxygen therapy cardiac output and pulmonary vascular resistance are decreased; systemic vascular resistance is increased.
- Acute illnesses for which hyperbaric oxygen is indicated include carbon monoxide (CO) poisoning (based on randomized, controlled studies), gas bubble injury (gas embolism and decompression sickness [DCS]), and soft tissue necrotizing infections (the latter two based upon clinical experience and meta-analyses).
- The decision to use hyperbaric oxygen to treat a patient with arterial gas embolism (AGE) or DCS should be based on clinical criteria, including the presence of symptoms, abnormal physical examination, or a history of AGE within a few hours even in the absence of symptoms. Neither neurophysiologic testing nor radiographic imaging are useful except, rarely, to exclude other pathologies.
- The decision to use hyperbaric oxygen to treat a patient with CO poisoning should be based on clinical criteria, including a history of impaired consciousness or other neurologic manifestation, pregnancy, or severe exposure (e.g., peak carboxyhemoglobin [HbCO] more than 25%). The HbCO level correlates poorly with the severity of the illness and is generally useful only to make the diagnosis.
- Oxygen-induced seizures are rare and self-limited. Appropriate management includes discontinuation of inhaled oxygen. Chamber pressure should not be altered during the seizure, as decompression while a seizure is occurring can result in pulmonary barotrauma (pneumothorax or pneumomediastinum) and AGE.
- Recent animal and human data support the notion that pretreatment of patients with hyperbaric oxygen may ameliorate some of the adverse effects of cardiac surgery and invasive cardiac procedures.
- As ambient pressure is altered, anesthetic vaporizers (except for desflurane) deliver a variable concentration but fixed partial pressure of vapor. Therefore, there is no need to adjust vaporizer settings when delivering anesthesia in a hyperbaric chamber or at altitude. Desflurane vaporizers deliver a fixed concentration, requiring upward adjustment at altitude.

Introduction

Anesthesiologists and other intensivists are frequently required to evaluate and treat patients suffering consequences of exposure to high and low temperatures, high ambient pressures, gas embolism, decompression sickness (DCS), and drowning. Administration of oxygen (O_2) at increased ambient pressure (hyperbaric O_2 , hyperbaric oxygen treatment [HBOT]) has been used since the early 20th century for selected conditions. It is an effective modality for treatment of gas bubble diseases and several other acute and chronic conditions. This chapter describes the physiology of immersion and its complications, hypothermia, and the use of HBOT for treatment and its indications for acute treatment.

Physiology of Immersion

ACUTE EFFECTS OF IMMERSION

The upright posture of humans results in gravitational effects on the venous blood pool, which tends to be distributed into the lower half of the body. Because water and blood have almost the same density, immersion in water causes immediate redistribution of blood from the legs and splanchnic bed into the heart and pulmonary circulation. This causes a reduction in lung volumes, a rise in central venous and pulmonary vascular pressures,^{1,2} and an increase in ventricular and stroke volumes.³ These effects are accentuated in cold versus warm water due to peripheral vasoconstriction.^{4,5}

PROLONGED IMMERSION AND RESCUE

Because of atrial stretch, there is an increase in B-type natriuretic protein (BNP) secretion. In conjunction with the increase in cardiac output this induces a diuresis. Prolonged immersion, such as may occur during loss at sea, can result in severe hypovolemia due to lack of fluid intake and prolonged diuresis. Indeed, some marine accident survivors have died during extraction from the water in the vertical position.⁶ It is therefore recommended that victims who have spent significant time in the water be kept in the horizontal position during rescue (Fig. 75.1).

IMMERSION PULMONARY EDEMA

Pulmonary vascular pressures that are elevated due to immersion are increased even further during exercise, particularly in cold water.⁵ Drinking water prior to immersion can activate the osmopressor response^{7,8} and further augment central translocation of venous blood. Blood centralization then raises pulmonary vascular pressures, which in susceptible individuals can be sufficiently elevated to induce acute pulmonary edema. This condition is referred to as immersion pulmonary edema (IPE) or swimming-induced pulmonary edema (SIPE). Individuals with cardiovascular pathology, such as hypertension, left ventricular hypertrophy, cardiac valve disease, and cardiomyopathy are particularly susceptible because of their preexisting elevation of left atrial pressure.⁹ However, healthy individuals can

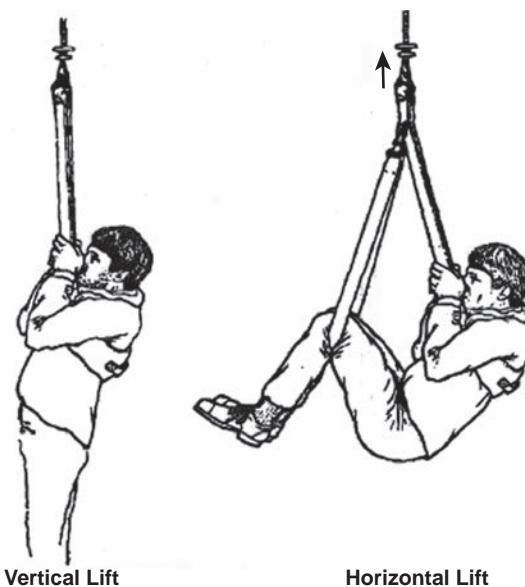


Fig. 75.1 Two methods of extracting a victim from the water. After immersion for 30 minutes in 15°C water, heart rate changes were measured during removal in two different positions. During vertical lift mean heart rate increased by 16% due to reflex response to hypotension versus only a small nonsignificant increase during horizontal lift. Extracting victims in the vertical position has resulted in death, presumably due to hypotension. (From Golden FS, Hervey GR, Tipton MJ. Circum-rescue collapse: collapse, sometimes fatal, associated with rescue of immersion victims. *J R Nav Med Serv*. 1991;77[3]:139–149. [Page 146, Fig. 3] with permission.)

also experience SIPE, particularly during heavy exercise in the water. SIPE has been reported during a long swim in approximately 1.5% of triathletes,¹⁰ 3% to 5% of US Navy special forces trainees,¹¹ and up to 60% of Israel Defense Force recruits.¹² SIPE tends to recur in some individuals and has been linked to higher than normal pulmonary artery (PA) and PA wedge pressures.¹³

The condition usually resolves within a few hours after removal from the water (which immediately reduces intravascular pressure within the pulmonary vessels) and administration of first aid O_2 . Nebulized β_2 -adrenergic agents may be helpful to treat bronchospasm and accelerate water reabsorption from alveoli.¹⁴ Although resolution within a few hours is the norm, SIPE-induced death has been reported.¹⁵

Drowning

DEFINITION

A definition of drowning was proposed and adopted in 2002 by the World Health Organization as follows: *Drowning is the process of experiencing respiratory impairment from submersion/immersion in liquid.*¹⁶ This definition was modified slightly by a consensus of international investigators on guidelines for the uniform reporting of data from drowning studies (Utstein style),¹⁷ which has subsequently been updated.¹⁸ A recent publication has reviewed 14 drowning publications based on this reporting convention.¹⁹

Evolution of the drowning syndrome in a patient depends on the extent of aspiration of fluid into the airways, leading to hypoxemia and cardiac arrest, which can evolve to progressive and irreversible neurologic damage. Death at any time as a result of drowning is described as *fatal drowning*. When the process of drowning is interrupted, it is referred to as *nonfatal drowning*. Any submersion incident without respiratory impairment should be considered a *water rescue* and not a drowning. Other terms such as “near drowning” or “dry” or “wet drowning” or similar distinctions should not be used, in order to standardize appropriate reporting of outcomes.²⁰⁻²³

PREVALENCE

The number of accidental drownings in the world exceeds 500,000 persons per year,²⁴ causing over 370,000 deaths.²⁵ Undoubtedly these numbers are underestimates due to additional unaccounted cases such as the thousands of victims each year from floods, tsunamis, and asylum seekers seeking to flee by sea. Approximately 20% of people who die from drowning are children younger than 15 years of age. From 2005 to 2014, there was an average of nearly 3900 fatal unintentional drownings per year in the United States.²⁶ It is estimated that 4000 children receive emergency department care for nonfatal submersion injuries. At least 50% of drowning victims treated in hospital emergency departments require inpatient care. Nonfatal drowning can lead to severe brain damage and long-term disability.²⁶

These statistics show that drowning is a significant public health issue, surpassing the number of annual traffic accident deaths. However, multiple agencies at a national level follow and attempt to regulate traffic, whereas drowning has not elicited appropriate attention.²⁷

PATOPHYSIOLOGY

After submersion in water when a person cannot maintain a clear airway, water is voluntarily expelled from the nose and mouth and breath-holding is initiated. This usually cannot last more than one minute, because involuntarily inspiratory efforts produce swallowing attempts, water inhalation, and cough. Laryngospasm may occur for some time but will cease during progressive brain hypoxia.

Continued water aspiration leads to hypoxia, loss of consciousness, and deterioration of cardiac function. The hypoxic cardiac insult can rapidly progress through tachycardia, followed by bradycardia, pulseless electrical activity (PEA), and finally asystole. Irreversible damage to the heart and the brain usually occurs within a few minutes. In exceptional but rare circumstances, such as drowning in ice water, cardiac and brain cooling can provide extended hypothermic protection and afford possibility of reversible resuscitation after prolonged submersion times,²⁸ although systematic reviews have failed to find a correlation between water temperature and survival.^{29,30} Drowning in cold water may also be accompanied by several unique aspects related to gasp response, autonomic effects, hemodynamic changes, and hypothermia (see later).³¹

Water aspiration induces pulmonary edema with impairment of pulmonary gas exchange, in part due to surfactant

dilution and dysfunction.³² Although conventional wisdom is that fresh and salt water drowning differ due to osmotically driven fluid exchange across the alveolar-capillary membrane with resulting changes in electrolyte concentrations, animal studies and clinical case reports have not supported differences in clinical course. A study of hemodynamics and pulmonary mechanics in anesthetized dogs using tracheal instillation of 20 mL/kg of fluid with various sodium chloride (NaCl) concentrations (sterile water, 0.225%, 0.45%, 0.9%, 2%, and 3% NaCl) and anoxic controls failed to find any differences among the groups.³³ This is supported by recent clinical series, where outcomes of drownings were similar in fresh and salt water.³⁴

RESCUE AND RESUSCITATION

Enhanced local surveillance by lifeguards has been shown to be highly effective in early rescue and improved outcomes from drowning: the majority of rescued victims in areas of effective surveillance do not need medical attention and only 6% of all rescued persons require emergency medical admission and very few require cardiopulmonary resuscitation (CPR).^{35,36}

Safe rescue techniques comprise reaching the victim with a pole, a rope, or other buoyant life-saving device, avoiding rescuer entanglement with the victim. American Heart Association resuscitation guidelines recommend that rescuers should remove drowning victims from the water by the fastest means available and should begin resuscitation as quickly as possible. Since cardiac arrest is caused by progressive hypoxia, any attempt to institute CPR must include ventilatory maneuvers to attempt to refill the alveoli with air or oxygen. For drowning victims who present in cardiac arrest, a shockable rhythm is predictive of survival, but one series reported that most drowning victims in arrest have asystole or PEA.³⁷

Rescuers should provide CPR, particularly rescue breathing, as soon as an unresponsive submersion victim is removed from the water. Mouth-to-mouth ventilation in the water may be helpful when administered by a trained rescuer, but chest compressions are difficult to perform in water and are often ineffective. Maneuvers to relieve foreign-body airway obstruction are not recommended. It is reasonable for the lone healthcare provider to give 5 cycles (about 2 minutes) of CPR before leaving the victim to activate the emergency medical service (EMS) system. Victims with obvious clinical signs of injury, alcohol intoxication, or a history of diving into shallow water are at higher risk of spinal cord injury, and thus stabilization of the cervical and thoracic spine for such individuals may be considered, although spinal cord injury among drowning victims is uncommon. Often the victim has swallowed variable volumes of water and can vomit early during rescue-breathing; in patients with spontaneous circulation, the lateral position is therefore recommended to minimize the risk of aspiration.³⁸

The clinical presentation of the drowning victim is variable and stratifying risk based on clinical presentation may be useful for initial triage (Table 75.1).²⁰ American Heart Association guidelines recommend that all victims of drowning who require any form of resuscitation (including rescue breathing alone) should be transported to the

TABLE 75.1 Drowning Severity Scale Described by Szpilman With Outcomes of 1831 Cases

Grad	Description	Hospitalization (%)	Mortality (%)
1	Normal pulmonary auscultation with coughing. Insufficient aspiration of water to cause alteration in alveolo-capillary gas exchange requiring medical intervention.	2.9	0.0
2	Abnormal pulmonary alveolo-capillary gas exchange; abnormal pulmonary auscultation with rales in some pulmonary fields.	14.8	4.0
3	Significant alveolo-capillary gas exchange alteration as well as a high degree of pulmonary arterial-venous shunt that generally requires early mechanical ventilation and PEEP. Pulmonary auscultation with rales in all pulmonary fields, in addition to presenting frequently with pinkish foam in the mouth and nose. No hypotension.	44.8	11.5
4	Same as Grade 3 with hypotension.	88.9*	19.4
5	Isolated respiratory arrest.	84.0*	33.3
6	Cardiopulmonary arrest.	12.4	43.5

*Hospitalization < 100% in this group due to several patients reported dead before reaching hospital.

PEEP, Positive end-expiratory pressure.

From Szpilman D. Near-drowning and drowning classification: a proposal to stratify mortality based on the analysis of 1,831 cases. *Chest*. 1997;112(3):660–665.

hospital for evaluation and monitoring, even if they appear to be alert and demonstrate effective cardiorespiratory function at the scene.³⁹

HOSPITAL CARE

The sequence of resuscitation efforts after emergency department admission includes securing a definitive airway, improving oxygenation, reestablishing circulation, insertion of a gastric tube, and rewarming. Previous medical history should be addressed, since trauma, cardiac arrhythmias, or seizures may have precipitated the near-drowning episode. Toxicology evaluation for alcohol or drug intoxication may be helpful to establish causes of impaired consciousness and treatment.

If the patient is unstable, intensive care unit (ICU) admission may be required for observation and weaning from mechanical ventilation, which can usually be accomplished using traditional algorithms. Bronchodilator support may be useful to treat bronchoconstriction and accelerate water clearance from alveoli,¹⁴ but glucocorticoids have not been shown to be effective.⁴⁰

Bronchoscopy might be required for pulmonary toilet or aspiration of solid materials, and secondary pneumonia

can occur.⁴¹ It has been reported that aspiration of swimming pool water rarely results in pneumonia whereas it is more common in salt water aspiration and most common after polluted water aspiration; however other studies have found no relationship between the type of water and development of pneumonia.⁴¹

In a small number of patients admitted to the ICU, pulmonary function can deteriorate beyond the ability of conventional mechanical ventilation to maintain adequate gas exchange. In such cases, administration of surfactant substitutes and nitric oxide has been tried. Case series of extracorporeal membrane oxygenation (ECMO) have also been published.^{40,42} Initiation of such measures is best determined on the basis of individual patient requirements. It has been recommended that ECMO should be considered earlier in the course of therapy (e.g., when arterial pH < 7.2, PCO₂ > 60 mm Hg, SaO₂ < 85%) before progressive respiratory failure leads to cardiovascular collapse.⁴²

Circulation and Renal support

Inotropes may be required to maintain blood pressure. Renal insufficiency or failure has been described and documented in drowning cases,^{43,44} with proposed causative mechanisms including rhabdomyolysis, systemic inflammatory response associated with multiorgan failure, and hypoxic renal injury,⁴⁴ although dialysis is rarely required.⁴⁴

Neuroresuscitation

Neurologic outcome after effective CPR in drowning victims has been shown to be similar to all victims of cardiac arrest from all other causes; however, in the rare cases where hypothermia was established in the rescued drowning subject, survival after prolonged periods of submersion have been demonstrated.^{28,31} Reports⁴⁵ have documented possible beneficial effects of induced hypothermia after resuscitation. It has been suggested that drowning victims with return of spontaneous circulation (ROSC) who remain comatose should NOT be actively rewarmed above 90° to 93°F/32° to 34°C, and victims with ROSC whose core temperature is 93°F/34°C or higher should be cooled to 90° to 93°F/32° 34°C as soon as possible⁴⁶; however recommendations for optimal management of such patients await further studies.

OUTCOME OF DROWNING

If a person is rescued the outcome will depend on submersion duration, EMS response times, volume of water aspirated and its effects, the skill of the providers, and the availability of support systems.^{30,46} Outcomes of 1831 cases of drowning are shown in Table 75.1.²⁰ In a series of 336 drowning-related cardiac arrests, EMS resuscitation was attempted on 154, of whom 27% survived to hospital arrival and 8% survived to hospital discharge. Only 6% were found in a shockable rhythm.³⁷

PREVENTION

Increasing documentation and international interest from institutions supported by coastal and fluvial societies and advocacy groups have demonstrated the value of prevention in drowning.⁴⁷ Use of life vests in the water and

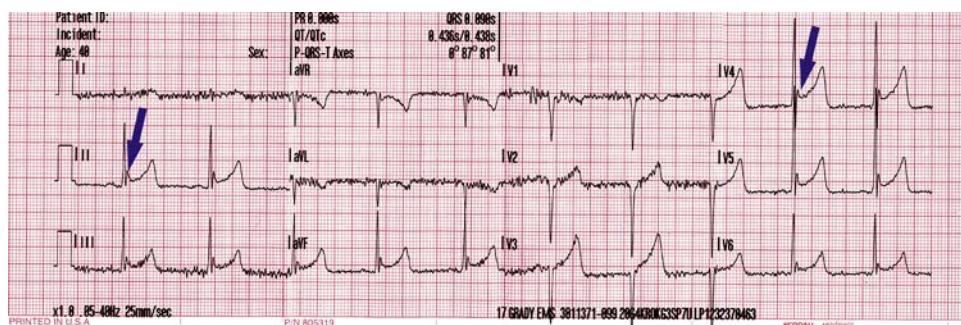


Fig. 75.2 Osborn waves in a hypothermic patient. ECG is from a 40-year-old male found sleeping on the street when ambient temperature was close to 4°C. Rectal temperature on arrival at the hospital was 30.4°C. The 12-lead ECG shows a secondary wave closely following the S-wave (arrows), now referred to as an Osborn wave after the pediatrician/intensivist who first described the pattern as a harbinger of ventricular fibrillation during hypothermia.⁵³ ECG, Electrocardiogram.

instructions teaching swimming and/or floating,³⁸ as well as Dutch, Brazilian, South African, and Australian lifeguard experiences have shown that 85% of drowning cases can be prevented by public education, supervision, and public preparedness.³¹ The recent multiple tragedies of refugees drowning at sea have re-sensitized medical groups to renew efforts to prevent drowning.²⁷

Hypothermia

PHYSIOLOGY OF HYPOTHERMIA

Hypothermia is defined by a low core body temperature (generally less than 35°C, with more conservative perioperative thresholds of 36°C⁴⁸). Thresholds for further categorical breakdown into mild, moderate, and severe hypothermia are not consistent within the literature, and vary depending on context (e.g., trauma, immersion/environmental, therapeutic indication). Extremes of age, sepsis, burns, trauma, some endocrine disturbances, intoxication, exertional fatigue, or malnutrition can place patients at higher risk for developing both hypothermia and complications thereof, with a high degree of variability even among healthy individuals.^{49,50}

On a molecular and cellular level, decreased temperature decreases the speed of chemical and enzymatic reactions, influences intracellular signaling cascades, and alters cellular structure⁵¹; the overall metabolic rate is suppressed to varying degrees for different tissues. As such, cold exposure and hypothermia impact each tissue or organ system differently. The microvasculature of the skin and peripheral tissues manifests a rapid vasoconstrictive sympathetic response to either superficial cold exposure or decreased core body temperature. This response reduces skin blood flow and attenuates cutaneous heat flux, while shifting blood volume to the central compartment. The high surface to volume ratio of the extremities can result in profound decreases in peripheral tissue temperatures with maintenance of the core body temperature.

Superficial peripheral cooling impacts muscle and nerve function,³¹ which can impair a victim's capability for self-rescue or preservation in the case of accidental hypothermia, and has implications for monitoring in clinical settings (see the section on "Clinical Considerations"). Muscle

function declines due to impaired release and diffusion of calcium and acetylcholine, and changes in elastic components. Furthermore, as peripheral cooling progresses and the more superficial muscle fibers become impaired, fatigue occurs more quickly in muscle fibers left to bear the load. Peripheral cooling also impairs nerve conduction velocities and amplitudes, further impacting physical performance. As a final comment on peripheral cooling, accidental hypothermia or improper therapeutic cooling with ice packs or conductive cooling devices can lead to cold injury or frostbite of peripheral tissues (fingers, toes, nose, ears are most susceptible). Treatment is conservative in mild to moderate cases, through protection from mechanical injury, slow rewarming, and consideration of nerve blocks or improving oxygenation when possible. However, tissue salvage in severe injury may also require early therapy with thrombolytics or iloprost.⁵²

The cardiovascular system is impacted in a number of ways. Peripheral sympathetic vasoconstriction leads to increased systemic vascular resistance and blood pressure, as well as increased central venous pressure due to redistribution of blood volume to the central compartment. Shivering increases metabolic requirements; in combination with increased sympathetic tone this leads to increased cardiac output, tachycardia, and a propensity for atrial arrhythmias in mild hypothermia. With more severe hypothermia (<32°C), cardiac conduction delays develop, including J waves (positive deflection at the QRS-ST junction) signaling abnormal early ventricular repolarization (Osborn waves, Fig. 75.2),⁵³ and decreased spontaneous polarization of pacemaker cells, resulting in bradycardia. The likelihood of cardiac arrest increases with cooling below 32°C, with very high risk at 28° to 24°C or below⁵⁴; gentle handling and maintaining horizontal positioning in hypothermic patients can minimize the likelihood of arrhythmia or cardiovascular collapse.

Decreased cerebral metabolism in hypothermia⁵⁵ is useful as the basis of neuroprotection for a variety of therapeutic indications and in accidental hypothermia complicated by hypoxia (particularly if cooling occurs before the onset of hypoxia); however, neurologic and respiratory function also decline with increasing severity of hypothermia. Impaired judgment progresses to hallucinations, delirium, and decreased consciousness as body temperature falls; loss of consciousness is common below 28°C. Reflexes,

pupillary reactivity, and electroencephalographic (EEG) activity decline and become absent with progressive hypothermia, precluding neurologic assessment. From a respiratory standpoint, neurologic impairment can necessitate intervention for airway protection, and with severe hypothermia respiration can even cease. Although decreased metabolic requirements afford some tolerance to hypoxia and decreased ventilation (tidal volume, respiratory rate, and compliance decrease), sensitivity to hypercapnia is diminished, leading to hypoventilation and acidosis, which can exacerbate electrolyte abnormalities and other physiologic changes.⁵⁴

Renal and hepatic impairment have a variety of implications. Hepatic impairment decreases clearance of lactate and other metabolic byproducts and metabolism of some medications (see the section on “Clinical Considerations”). Renal blood flow is increased in mild hypothermia, due to increased blood volume in the central compartment. Increased renal blood flow in combination with decreased antidiuretic hormone activity results in diuresis. However, as hypothermia progresses, renal blood flow and glomerular filtration rate both decrease, although diuresis may persist due to inhibition of tubular water reabsorption.⁵⁴ Additionally, edema that develops in damaged peripheral tissues can exacerbate depletion of circulating blood volume. Respiratory, renal, and endocrine changes result in electrolyte imbalances in both mild and moderate/severe hypothermia. Hypokalemia and hyperglycemia can be present in mild hypothermia, whereas acidosis, increased sodium excretion, and hyperkalemia manifest with progressive cooling.³¹ Hyperglycemia results from decreased insulin sensitivity and secretion, requiring intensive insulin therapy and frequent monitoring of blood glucose levels. Distal tubular transport of sodium is impaired, which also affects acid-base regulation.³¹ Finally, the threshold for cardiac toxicity from hyperkalemia diminishes with progressive hypothermia.⁵⁶ Therapies and medications that increase serum potassium levels (blood transfusion, succinylcholine administration) should be carefully considered in these patients.

Because of increased gas solubility with decreased temperature, arterial partial pressure of oxygen (PaO_2) and arterial partial pressure of carbon dioxide (PaCO_2) decrease and pH increases. Samples corrected to patient body temperature will appear to be alkalotic and hypercarbic, whereas samples left uncorrected at 37°C will correspond to normal reference ranges for these values in the absence of physiologic changes. As such, results should be interpreted in the context of whether temperature correction was or was not performed. As discussed in hypothermia, impaired ventilation and a higher ventilatory threshold for hypercapnia result in hypoventilation, which generally tracks with the reduction in metabolic rate. However, since pH increases and increased carbon dioxide (CO_2) solubility decreases PaCO_2 with decreasing temperature, cerebral blood flow is generally also decreased in proportion to reduced metabolic rate in hypothermia. Clinically, a strategy that has been investigated in hypothermic cardiac surgical patients is correction for known changes in PaCO_2 solubility (known as pH-stat blood gas management, as opposed to alpha-stat management where hypocarbia and alkalosis are permitted), with the theoretical advantage of increasing cerebral blood flow.

Some benefit has been shown in pediatric, but not in adult populations, where there is concern for increased cerebral embolic risk.⁵⁷

Hematologic changes observed in hypothermia are secondary to changes in blood volume, microvascular tone, and coagulation factor function. Contraction of the blood volume due to diuresis (possibly combined with dehydration due to environmental exposure or exertion) increases blood viscosity. In combination with increased viscosity, vasomotor abnormalities in the microcirculation lead to sludging, stasis, and hypoperfusion. Impaired circulation prevents tissue oxygenation, but also clearance of metabolic byproducts, which accumulate in peripheral tissues. Leukocyte and platelet counts fall with severe hypothermia and platelet activation and coagulation factor enzymatic function are highly sensitive to pH and temperature.⁵⁸ This can result in a coagulopathic state with progressive hypothermia, but may also be partially offset by simultaneous inhibition of anticoagulant factors, depending on relative concentrations.⁵⁹

CLINICAL CONSIDERATIONS

In general, hypothermia may impair drug absorption in the bowel. Both core and peripheral cooling, even to a mild degree ($\sim 34^\circ\text{C}$), can have a clinically significant impact on the recovery from, or twitch response to, neuromuscular blockade. This is explained by both impaired neuromuscular function and pharmacokinetic changes (increased plasma concentration) with decreased temperature.⁶⁰ The minimum alveolar concentration (MAC) for volatile anesthetics decreases with hypothermia. With profound cooling ($\sim 20^\circ\text{C}$), anesthesia may no longer be needed to prevent movement,⁶¹ although the precise temperature at which EEG silence is achieved is somewhat lower and demonstrates individual variability.⁶² Plasma concentrations of some intravenous anesthetics increase because of reduced compartmental clearance; the clearance of CYP450-metabolized drugs (including propofol and ketamine) is also reduced in proportion to the decrease in body temperature.⁵⁴ As a result, reduced infusion rates will achieve similar levels of sedation.⁶³ In parallel, general anesthetic and some sedative medications have an impact on thermoregulation (both vasoconstriction and shivering thresholds are reduced by up to $\sim 2^\circ$ to 4°C or more), and can contribute to hypothermia.^{63,64}

There are also considerations for monitoring hypothermic patients, the most obvious being the measurement of temperature itself. Even in thermoneutral conditions there is very high variability in skin temperature at different sites, an effect which is attenuated but persistent for common core temperature measurement locations (Fig. 75.3).⁶⁵ In hypothermia, changes in blood flow distribution exaggerate these temperature variations among site differences. Similarly, rewarming methods can have dynamic effects on temperatures in different tissue compartments (see Treatment of Hypothermia). Apart from the rational yet clinically variable application, the recommendation is “if one’s interest lies with the temperature of a specific body tissue, then measure temperature from that site, or a valid surrogate.”⁶⁵ The guiding principles for measurement of core body temperature are to measure temperature in a location

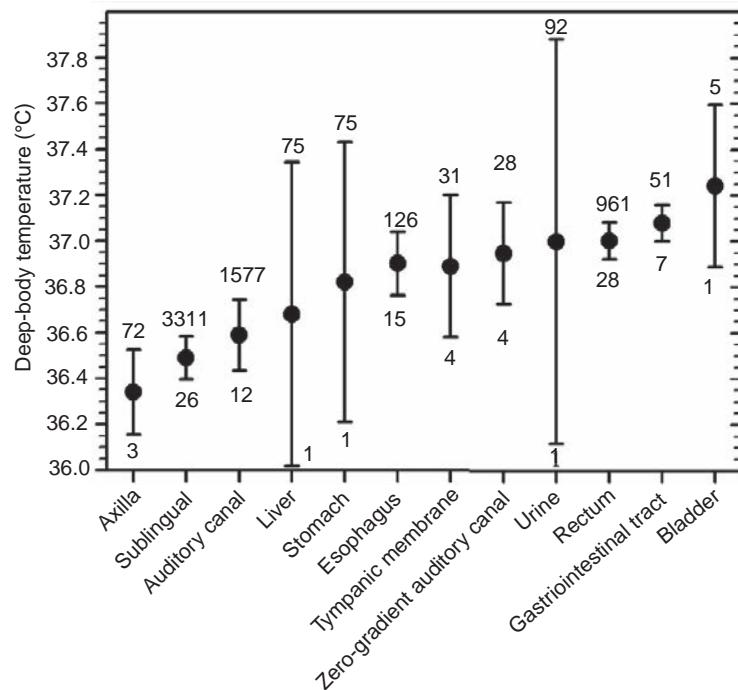


Fig. 75.3 Variations in resting, deep-body temperature in 12 measurement sites from published reports, with means and 95% confidence intervals for each total sample. Numbers above the confidence intervals are the total number of subjects; those below indicate the number of contributing investigations. (From Taylor NA, Tipton MJ, Kenny GP. Considerations for the measurement of core, skin and mean body temperatures. *J Therm Biol*. 2014;46:72–101. [Page 80, Fig. 6] with permission.)

(1) where there is good tissue perfusion, which promotes thermal equilibration with other body sites; (2) that is insulated from the external environment or peripheral tissues, which may be cooled to a greater degree than core tissues; and (3) that is as adjacent as possible to the organ of interest (i.e., the tympanic membrane or nasopharynx for the brain). Blood temperature can be an excellent surrogate for core temperature, with PA blood temperature often cited as a gold standard.⁵⁴ However, this invasive method may also suffer some inaccuracy in the setting of acute mixing of fluids administered via central venous catheters or adjacent placement of invasive warming devices. Esophageal temperature is often used to represent blood temperature due to its proximity to the central circulation.

The response time for pulse oximetry is limited or the signal may fail altogether in conditions of local hypoperfusion, as occurs with peripheral vasoconstriction in hypothermia. Although there have been advances in device algorithms, pulse oximetry often does not give a reliable reading from the digits in even mild hypothermia, with relatively preserved performance for ear or forehead sensors.⁶⁶ Similarly, concerns for exaggerated or prolonged neuromuscular blockade can be complicated by the fact that local or body cooling decreases nerve stimulation (mechanomyography) twitch tensions, even in the absence of paralytic medications.⁶⁰

There are important differences between accidental hypothermia due to environmental exposure and induced hypothermia in controlled, clinical situations such as therapeutic hypothermia for neuroprotection or during cardiac surgery. The most obvious difference is that the mechanism of cooling may vary—environmental exposure results in cooling across the skin and body surface, through radiation, evaporation, convection, or conduction from cold air,

water, or contact surface (with the exception of drowning, where aspiration and swallowing of cold fluid can impart some degree of “internal cooling”). In contrast, in addition to surface cooling, clinical hypothermia may be induced and maintained by more efficient, evenly distributed, and precisely controlled invasive methods, such as intravascular catheters, cold fluid infusion, or cardiopulmonary bypass. Second, clinical support throughout the period of cooling, hypothermia, and rewarming can mitigate some of the major physiologic perturbations that would otherwise limit hypothermia tolerance or resuscitation and allow cooling to temperatures not tolerated outside of the clinical setting. Death is not uncommon in accidental hypothermia with body temperatures of 24° to 28°C, and the lowest documented temperatures from which resuscitation has occurred for accidental hypothermia are ~13°C³¹; on the other hand, recovery from induced hypothermia to 10°C and lower has been reported.⁶⁷ Finally, accidental hypothermia is often complicated by immersion or drowning, prolonged fasting and/or hypovolemia, extreme exertion or exhaustion, trauma, or a variety of other clinically relevant conditions.

TREATMENT OF HYPOTHERMIA

Supportive care for the previously mentioned physiologic perturbations should be provided, and hypothermic patients should be protected from further heat loss with insulation and/or a vapor barrier, and they should be transferred to a controlled clinical setting when available. Intrinsic thermoregulatory responses should be addressed, including the vasoconstrictive sympathetic response in the skin and shivering in the muscles (primarily truncal muscles), which can

both be stimulated by skin or core cooling. Shivering effectively provides heat at the expense of increased metabolic requirements that cannot be indefinitely maintained.⁶⁸ Similarly, after provision of caloric supplementation to support increased metabolic requirements, and taking steps to prevent a further drop in temperature, exercise is recommended to augment rewarming in the case of mild accidental hypothermia where neurologic function is intact.⁶⁹ Physiologically, shivering is blunted by exertional fatigue (termed thermoregulatory fatigue), hypoglycemia, and paradoxically, shivering is markedly attenuated and eventually stops as core temperatures continue to fall (<~31°C).⁷⁰ It may be undesirable in some clinical situations, and can be treated with a number of interventions, pharmacologic and otherwise.⁶⁴

The vasoconstrictive sympathetic response protects from heat loss during cold exposure, but also impairs effectiveness of transcutaneous warming. On application of external heat, local vasodilation does occur despite continued core hypothermia.⁷¹ Cutaneous warming can be applied using large heat packs (primarily in prehospital settings), or with forced air or circulating water devices when more advanced care is available. Radiant or resistive heating devices are less commonly used. Limitations to all of these methods include the potential for tissue damage from heat application (and therefore their maximum safe set temperature), and their reliance on effective peripheral circulation to distribute heat from the periphery to the core. Regarding the latter point, cutaneous warming is significantly more effective when applied to areas of skin with optimal blood flow; that is, in nondependent areas that are not compressed by body weight.

As mentioned, cutaneous warming demonstrates improved heat transfer efficiency with peripheral vasodilation. General anesthesia and some sedative medications can also affect peripheral vasodilation, which can exacerbate cooling in the context of exposure to cold environments, but in the context of cutaneous rewarming can similarly increase the effectiveness of warming, if vasodilation is not already maximal. On the other hand, vasodilation also makes simultaneous cooling across exposed skin possible, even with warming devices covering other locations. Efforts should be made to cover or warm as much exposed skin as possible in patients under anesthesia (and those sedated using vasodilating agents) to prevent this inefficiency.

Administered fluids should be warmed, which is of increasing importance with administration of large volumes such as in severe diuresis, dehydration, or traumatic blood loss. However, administration of warmed fluids rarely actively warms patients to any important extent because of the small amounts given relative to the heat distribution volume in most patients, and because it is unsafe to heat fluids much above normal body temperature. Similarly, airway heating and humidification can result in environmental heat loss. Provision of heated, humidified oxygen can prevent further heat loss, but its capacity for heat exchange is limited and it should only be used in conjunction with other warming methods.

A number of invasive warming methods have been used, including heat exchange through intravascular warming catheters; hemodialysis circuits; and peritoneal, gastric, bladder, or pleural lavage. Increasing invasiveness generally also predisposes to potential for complications;

primarily it should be kept in mind that some of these methods can negatively impact the circulation (i.e., impaired preload, bleeding) and precipitate circulatory collapse in at-risk patients. In general, all of these rewarming methods rely on the circulation for heat equilibration, and prolonged CPR may be logistically difficult or have limited effectiveness. Therefore, in the case of arrested, severely compromised, or at-risk circulation, an increasing number of centers report and recommend the use of extracorporeal life support (ECLS) for both circulatory support and controlled rewarming in patients with profound hypothermia (typically core temperature < 30°C).⁵⁴ As expected, these methods are not without pitfalls, but they can make resuscitation possible in extreme cases.⁷² Rewarming for these methods is relatively rapid, and is primarily limited by standard guidelines for (1) temperature gradients between blood return and patient blood of greater than 10°C, to avoid outgassing and generation of gaseous emboli when blood is returned to the patient; and (2) an upper threshold of 37°C for outlet blood temperature to avoid cerebral hyperthermia.⁷³

Finally, it is worth reviewing issues that present in the setting of hypothermia that may complicate the rewarming process. The most important are the concepts of rescue arrest and afterdrop. Hypothermic patients are likely to be hypovolemic and to suffer from acidosis and electrolyte abnormalities, and are predisposed to significant cardiac arrhythmias. As such, changes in posture that impact preload, or significant vasodilation that may occur on initiation of cutaneous rewarming can contribute to cardiovascular collapse. Peripheral vasodilation or improvement in tissue hypoperfusion can also allow accumulated metabolic byproducts to enter the circulation and exacerbate acidosis. Afterdrop refers to the phenomenon of continued core cooling even after rewarming has been initiated, due to continued loss of heat from the core to the cool periphery. In general, as rewarming progresses, clinical and laboratory parameters must be followed closely to avoid overcorrection, particularly in the case of pH or temperature-dependent phenomenon such as insulin sensitivity.

HYPOTHERMIA OUTCOME

Outcome after treatment of hypothermia is highly dependent on whether there has been coincidental trauma, cardiac arrest, significant hypoxia, or advanced age, all of which adversely affect prognosis.⁵⁴ On the other hand, resuscitation from hypothermia with intact cardiac activity (core temperature typically > 28°C) has low mortality. Of a series of 1028 children admitted to hospital with accidental hypothermia, 91.5% survived.⁷⁴ In a study of 572 adults with accidental hypothermia (core temperature ≤ 32°C), 83% of patients younger than 75 survived to hospital discharge.⁷⁵

Hyperthermia

PHYSIOLOGY OF HYPERHERMIA

Optimal physiologic and biochemical homeostasis requires regulation of body temperature within a narrow range, typically 36.7°C to 37.5°C. Heat is generated by metabolism,

which can vary several-fold from resting during sleep to heavy exercise. Internally generated heat is dissipated through the skin by conduction, radiation, convection, and evaporation of sweat. In an environment where ambient temperature is greater than skin temperature (typically around 33°C), heat is gained from the environment, allowing only sweating as a mechanism for maintenance of normal body temperature. Adaptation to hot environments (acclimatization) can occur over days or weeks. Mechanisms of acclimatization include increased blood volume and body water, lower body temperature, enhanced skin vasodilatation and sweating, and production of a more dilute sweat.⁷⁶

When core temperature increases, the normal adaptive response is cutaneous vasodilatation and initiation of sweating. There is redistribution of cardiac output to the skin, with concomitant reduction in splanchnic and renal blood flow,⁷⁷ which can lead to gut, liver, and kidney ischemia. Dehydration and the resulting hypovolemia attenuate the increase in skin blood flow and accentuate splanchnic vasoconstriction. With continued hyperthermia, a nitric oxide-mediated mechanism causes vasodilatation in the splanchnic bed, which can precipitate hypotension and shock,⁷⁸ and possibly gastrointestinal ischemia-reperfusion injury.⁷⁹

Heat-induced cell damage occurs at temperatures beyond a threshold that is species-specific. In humans, the critical temperature is between 41.6°C and 42°C sustained for 0.75 to 8 hours.⁸⁰ The major mechanism for body injury from high temperature is damage to macromolecules, including lipids, DNA, and proteins. Temperature increases can cause oxidative stress, protein unfolding, entanglement, and aggregation.^{79,81} Uncoupling of oxidative phosphorylation and a reduction in mitochondrial number lead to a decrease in adenosine triphosphate (ATP) levels. In parallel with physiologic adaptive mechanisms, there is a cellular stress response (CSR), which is triggered by accumulation of damaged macromolecules.^{79,81} The CSR consists of altered gene expression that initiates the production of a series of heat shock proteins (HSPs) that falls into seven categories.⁸¹ The major HSP group consists of what are referred to as “molecular chaperones.” These chaperone proteins recognize unfolded proteins and either refold them into their normal functional state or direct them into degradation pathways. Another group of HSPs is proteolytic, which clear irreversibly damaged proteins. A third group facilitates DNA and ribonucleic acid (RNA) damage. A fourth group consists of enzymes that facilitate re-establishment of metabolic pathways after heat stress. A fifth group includes regulatory proteins. The sixth category comprises proteins involved in sustaining cellular structures such as the cytoskeleton. The final category consists of proteins that facilitate transport, detoxification, and membrane-modulation.

CLINICAL SCENARIOS

Definitions. *Heat exhaustion* is a mild form of heat illness that is notable for inadequate cardiac output accompanied by elevated body temperature, dehydration, and hot, dry skin. Symptoms include fatigue, dizziness, nausea and vomiting, headache, and hypotension.⁸² Heat exhaustion occurs in hot environments, often precipitated by exercise. It can also

be precipitated by some medications such as diuretics and inadequate water intake, often in older adults.⁸² Body temperature in heat exhaustion is usually between 37°C and 40°C.⁸³ *Heat injury* is more severe than heat exhaustion and after some hours may include some organ and tissue damage.⁸² If patients with heat injury are not rapidly cooled the condition may worsen to *heat stroke*, which is life-threatening. Heat stroke is commonly classified as *exertional* or *classic*. Exertional heat stroke usually occurs in young healthy individuals who are exercising in hot environments, often presenting with collapse. Classic heat stroke usually occurs in very young or older individuals exposed to a hot environment without strenuous physical activity.^{79,82}

Manifestations of heat stroke include hot dry skin, weakness, anorexia, dizziness, syncope, nausea and vomiting, headache, and confusion. Neurologic manifestations in heat stroke include mental status changes, delirium, coma, and convulsions, but there is often a lucid interval during which the patient may have normal mental status despite severe temperature elevation.

Body temperature in heat stroke is generally in the range of 40°C to 44°C, although temperatures extending from mild elevation to above normal to 47°C have been reported.⁷⁹ Differentiating heat stroke from exercise-related heat exhaustion requires assessment of body temperature. Sensors placed on or close to sites on the exterior of the body (e.g., axillary, oral, tympanic, and skin) are not valid during or after intense exercise in the heat. The only adequate measurement sites in this setting are from sensors in the rectum or via radio telemetry from pre-ingested thermistor capsules.^{82,84,85}

Metabolic acidosis occurs in the majority of cases of severe heat stroke, especially in exertional heat stroke, often accompanied by respiratory alkalosis.^{82,86,87} Rhabdomyolysis, hyperkalemia, and disseminated intravascular coagulation are common. Renal failure commonly occurs in exertional heat stroke, but not classic heat stroke. Hyperglycemia and hypophosphatemia are common in classic heat stroke, whereas biochemical features in exertional heat stroke include hyperphosphatemia, hypocalcemia, and hypoglycemia.

The differential diagnosis of heat stroke includes status epilepticus, stroke, and drug use (including recreational drugs, antidepressants, antihistamines, and antiparkinsonian drugs).⁷⁹ Another life-threatening condition that can be confused with heat stroke is exercise-associated hyponatremia (EAH). This condition, which occurs during prolonged exercise, has manifestations similar to heat shock: lightheadedness, nausea, headache, vomiting, altered mental status, and collapse but often without hyperthermia. When these signs and symptoms occur during prolonged exercise it is essential to exclude EAH as its treatment requires correction of serum sodium.⁸⁸ When hyperthermia occurs in the perioperative environment, possible diagnoses include malignant hyperthermia (MH), neuroleptic malignant syndrome (NMS), thyroid storm, and serotonin syndrome. Assessment of MH is described in [Chapter 35](#). NMS is manifested by muscle rigidity, fever, mental disturbances such as delirium and abnormal metabolic changes in patients treated with classic triggering agents such as antipsychotic drugs (e.g., phenothiazines, butyrophenones, lithium), metoclopramide, antidepressants, and some

anticonvulsants.⁸⁹ In addition to fever, manifestations of serotonin syndrome include clonus, agitation, tremor, muscle rigidity, and hyperreflexia in patients taking serotonergic medication.

TREATMENT OF HYPERHERMIA

As in the treatment of hypothermia, supportive care to correct physiologic derangements and potential complications is as vital as rapid correction of the core temperature. Fluid management is a primary consideration in virtually any hyperthermic patient, with the degree of perturbation dependent on the heat source, duration of exposure, and amount of sweating. Electrolyte depletion from sweating may also be profound, and hypercalcemia, hyper- or hypokalemia, hypophosphatemia, or hyper/hypoglycemia may require correction in hyperthermic patients.⁸²

The underlying cause of hyperthermia determines therapeutic options, and also impacts the effectiveness of selected cooling methods. Cooling in any hyperthermic patient should be expeditious to limit further organ damage, but ongoing excessive metabolic heat generation must also be addressed for cooling to be effective.

Fever induced by immunologic reaction may be responsive to antipyretics or antiinflammatory medications, and discontinuation of a fever-inducing medication or toxin is an obvious first step. Seizures or shivering can contribute significantly to hyperthermia, and a number of therapeutic options exist.⁶⁴ In these conditions, pharmacologic treatments may be combined with cooling, depending on the degree of hyperthermia. Treatment of MH is described in [Chapter 35](#). NMS is treated by discontinuation of suspected triggering drugs and supportive care. Pharmacotherapy may include dantrolene, bromocriptine, and amantadine.⁸⁹ Treatment of serotonin syndrome also includes discontinuation of triggering agents, supportive care, and administration of a 5-HT_{2A} antagonist such as cyproheptadine,⁹⁰ and possibly benzodiazepines. For heat stroke there is no recommended pharmacologic treatment (due to concerns for hepatic toxicity). Nonsteroidal antiinflammatory drugs (NSAIDs) and aspirin are ineffective, and acetaminophen is contraindicated (see earlier).^{79,82} Dantrolene is ineffective in heat stroke.⁹¹

Heat exhaustion usually responds to simple methods of cooling such as moving to an air-conditioned space, removal of excessive clothing, and application of cloths soaked in cool water. Hyperthermia in heat stroke is managed by institution of cooling as quickly as possible, combined with supportive treatment. The target to which cooling should be pursued is not well-supported by evidence, but many studies have used a target of less than 39°C rectal temperature.⁹² Ice water immersion and evaporative cooling are among the most effective noninvasive cooling methods, but they are not always logistically feasible, including in clinical settings where there are concerns for infection or significantly compromised integrity of the skin (e.g., dressings, burns, line sites). Ice packs (with a skin barrier to avoid direct contact and risk of tissue injury) can be applied to central areas with good blood flow, such as the groin, axillae, neck, and torso. All of these methods require ongoing refreshment of the cold source to maintain an effective temperature gradient, and attention to the skin

at the site of application to avoid cold injury to tissue is critical. Adhesive cold-water circulating devices are contained, provide continuous refreshment of the temperature gradient, and may be equipped with thresholds and alarms to provide some margin of safety from cold injury. But, as in the case of cutaneous warming, adhesive pads require large areas of intact skin with good blood flow for effective use. These transcutaneous cooling methods all depend on cutaneous vasodilation for effective heat transfer from the core. But with cutaneous cooling, local vasoconstriction and shivering can be induced if temperatures are sufficiently low. Inhibition of shivering or vasoconstrictive responses, as previously discussed, may be used to offset these effects.

Effective but increasingly invasive cooling methods include bladder, gastric, or colonic irrigation with cold saline, intravascular cooling catheters, and administration of cold intravenous fluids.^{82,93} Immersion in ice water is safe and effective in young individuals suffering from exertional heat stroke; however, in classic heat stroke it is poorly tolerated and may be associated with increased morbidity and mortality.⁷⁹ As in the case of hypothermia treatment, the effectiveness of cold intravenous fluids is limited by concerns for overexpansion of intravascular volume, although the temperature gradient that can be achieved is larger than that for warmed fluids for treatment of hypothermia; cold fluids can be near 4°C, as opposed to warm fluids, which must be near 37°C to avoid local hyperthermia. For patients requiring ECLS (or ECMO), some degree of cooling can be achieved passively due to blood volume flowing through external circuit components. It is noteworthy that while it is common for extracorporeal support circuits to be equipped with heat exchangers to warm the blood, some lack the ability to provide monitored active cooling (as opposed to cardiopulmonary bypass circuits, in which cooling capability is a standard feature). If cooling is a therapeutic goal, this should be considered at the time of circuit choice if there are multiple options available.

After cooling and successful resolution of hyperthermia, clinicians must continue to be vigilant for (1) hypothermia due to aggressive cooling or a dysregulated thermoregulatory response; (2) recurrent hyperthermia; and (3) the development and secondary effects of organ injury that occurred when body temperature was elevated.⁸² Short- and/or long-term lung, kidney, liver, cardiovascular, and neurologic injuries have all been described after heat stroke.

HYPHERHERMIA OUTCOME

After cooling, sequelae can include ongoing encephalopathy, seizures, liver failure, renal failure, and adult respiratory distress syndrome (ARDS). Recurrent fever is common during recovery, does not respond to aspirin or NSAIDs, and may further exacerbate brain injury. Acetaminophen is sometimes prescribed but has been associated with liver failure and is contraindicated.^{79,82}

Mortality in exertional heat stroke is reported as 3% to 5%.⁷⁹ As many as 60% of patients with classic heat stroke die before reaching the hospital, thus it is difficult to determine the true mortality. Of those who are admitted to an ICU, in-hospital mortality is 10% to 65%, however there is also 10% to 28% mortality at one and two years after treatment. Persistent neurologic manifestations including

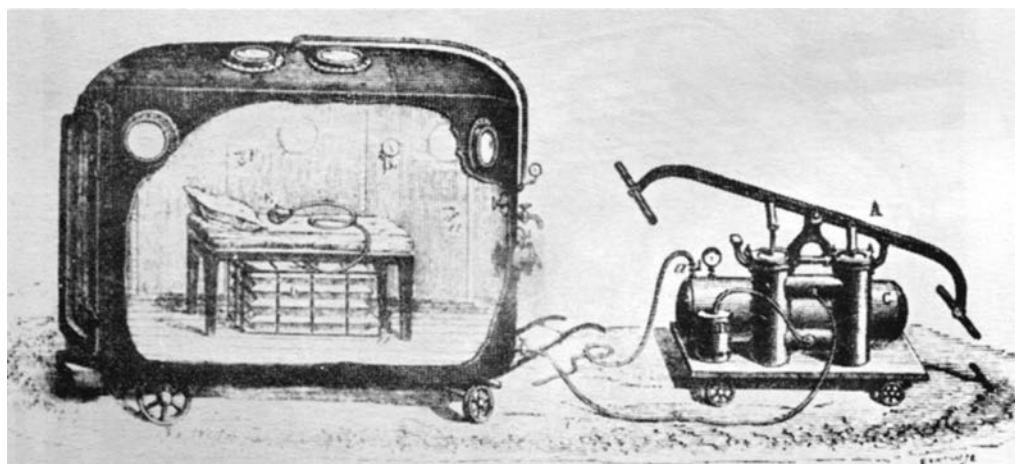


Fig. 75.4 Mobile hyperbaric operating room described by Fontaine in 1879–1895. Nitrous oxide storage tanks can be seen under the operating table. Compressed to 1.25 to 1.33 atmospheres absolute with air, a nitrous oxide–oxygen mixture was provided to the patient. Breathing air in this chamber would have provided an inspired partial pressure of oxygen (PO_2) equivalent to 26% to 28% O_2 at 1 ATA. (From Fontaine J-A: Emploi chirurgical de l'air comprimé. L'Union Médicale: journal des intérêts scientifiques et pratiques moraux et professionnels du corps médical Paris. 28 [Ser 3]:445–448, 1879. Reprinted with permission of the New York Academy of Sciences.)

ataxia, dysarthria, and problems with coordination occur in a high percentage of patients and are associated with imaging abnormalities such as cerebellar atrophy.^{79,82,87,94}

Effects of Increased Gas Pressure

HISTORY

Compressed air technology was developed in the 19th century, which led to men working in compressed air environments for bridge and tunnel construction. Surface-supplied compressed air, and later self-contained compressed air breathing apparatus (scuba), allowed divers involved in the collection of sponges, pearls, and ship salvage to spend significant periods of time breathing air under pressure. New occupational diseases due to in situ formation of bubbles from inert gas supersaturation and pulmonary barotrauma were described: respectively, DCS and arterial gas embolism (AGE). The technology was in an attempt to treat a variety of diseases without any plausible rationale. This included tuberculosis, heart failure, emphysema, bronchitis, asthma, croup, whooping cough, anemia, anorexia, dyspepsia, leukemia, menorrhagia, neuralgic pain, and depression. An exception was the use by Fontaine in 1879 of a mobile hyperbaric chamber for anesthesia and surgery.⁹⁵ Compressed to 1.25 to 1.33 atmospheres absolute (ATA), a nitrous oxide– O_2 mixture was provided to the patient (Fig. 75.4). Breathing air in Fontaine's chamber would have provided an inspired partial pressure of O_2 (PO_2) equivalent to 26% to 28% O_2 at 1 ATA. This was probably the first use of an elevated PO_2 during anesthesia and certainly the first administration of hyperbaric nitrous oxide.

Use of O_2 at high pressure for the treatment of DCS had been proposed⁹⁶ and later reported for the treatment of DCS,⁹⁷ but remained an isolated medical curiosity until the early 1960s. A few indications, such as support of oxygenation in hyaline membrane disease of the newborn⁹⁸ and during open heart surgery,^{99,100} were not useful. For other indications, such as CO poisoning, AGE, and DCS, HBOT proved to be effective, as evidenced by substantial clinical

experience and randomized controlled studies. Indications are reviewed regularly by the Undersea and Hyperbaric Medical Society (headquarters in Durham, NC). This medical organization publishes an extensive bibliography with a list of indications for hyperbaric oxygenation that is updated every 3 to 4 years.¹⁰¹ Laboratory and clinical data support the use of HBOT for a select number of acute and chronic illnesses (Box 75.1), and anesthesiologists are often called on to provide care of patients in this unusual environment.

INCREASED BAROMETRIC PRESSURE EFFECTS

Some effects of altered ambient pressure are summarized in Fig. 75.5.

An increase in environmental pressure is accompanied by significant adiabatic heat production, whereas decompression generates cooling. This results in an increase in chamber temperature during compression, and cooling and precipitation of water droplets during decompression. These phenomena may limit the rate of compression in manned chambers in order to maintain temperature within a comfortable range.

During changes in ambient pressure, pockets of trapped gas will contract and expand on compression and decompression. Examples include gas in the middle ear and paranasal sinuses, intestinal gas, pneumothorax, and gas pockets within medical equipment, including monitoring and life-support systems. Changes in gas volume are inversely proportional to ambient pressure (Boyle's law):

$$PV = \text{constant}$$

such that at constant temperature, a doubling of environmental pressure (P) will cause the volume (V) of a gas-filled cavity to decrease by half. This effect also underlies one of the major beneficial effects of hyperbaric treatment of pathologic gas, as in AGE or DCS (see later).

A comparison of pressure units used clinically with those in common use in hyperbaric environments is shown in Table 75.2.

BOX 75.1 Selected Conditions for Which There Is Evidence of Hyperbaric Oxygen Treatment Effectiveness

Gas-bubble Disease

Air embolism*,^{180,187,302,303}

Decompression sickness*,^{180,187,304,305}

Poisoning

Carbon monoxide*,^{141,147-149,155,156,161,306}

Cyanide¹⁴¹

Carbon tetrachloride^{307,308}

Hydrogen sulfide¹⁴¹

Infections

Clostridial myonecrosis*,^{205,207,208}

Other soft tissue necrotizing infections*,^{205,207,309-311}

Refractory chronic osteomyelitis*,^{101,198,312}

Intracranial abscess*,^{313,314}

Mucormycosis*,^{311,315,316}

Acute Ischemia

Crush injury*,^{317,318}

Compromised skin flaps*,^{319,320}

Central retinal artery occlusion, central retinal vein occlusion*,^{215,216,321,322}

Chronic Ischemia

Radiation necrosis (soft tissue, radiation cystitis, and osteoradionecrosis)*,^{101,323-325}

Ischemic ulcers, including diabetic ulcers*,^{101,111,326-330}

Acute Hypoxia

Exceptional blood loss anemia (when transfusion delayed or unavailable)*,¹⁰¹

Support of oxygenation during therapeutic lung lavage*,^{209,210}

Thermal Injury

Burns*,³³¹⁻³³⁵

Envenomation

Brown recluse spider bite³³⁶⁻³³⁸

Miscellaneous

Idiopathic sudden sensorineural hearing loss*,²¹⁷

*Approved by the Undersea and Hyperbaric Medical Society as an appropriate indication for hyperbaric oxygen treatment.¹⁰¹

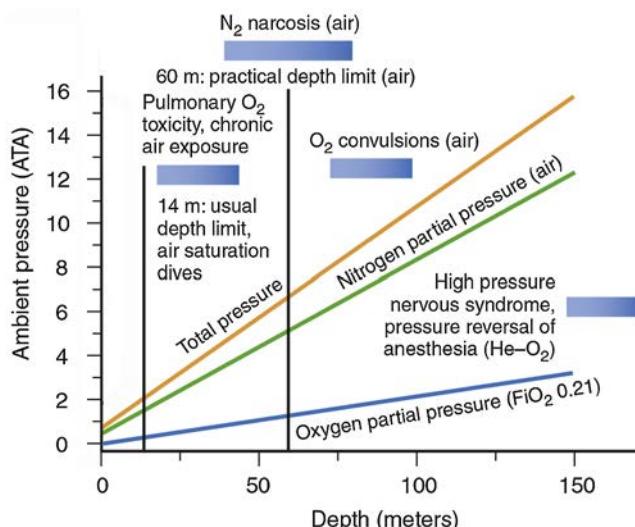


Fig. 75.5 Ambient pressure as a function of water depth. Ambient pressure increases linearly with depth, with pressure increasing by 1 ATM for each 10 m of depth. The oxygen partial pressure (PO_2) line is shown for a constant fraction of inspired oxygen concentration (FiO_2) of 21%. At increasing depth, inspired PO_2 eventually exceeds the pulmonary toxic limit (approximately 14 m in depth) and the central nervous system toxic limit (approximately 70 m in depth). The threshold for high-pressure nervous syndrome and pressure reversal of anesthesia (observed in nonnarcotic atmospheres, such as helium-oxygen) is 150 to 200 m depth. The shaded blue bars represent the depth or altitude ranges over which risk progresses from low (light shading) to high (dark shading). ATM, Atmosphere; He, helium; N_2 , nitrogen.

INCREASED PARTIAL PRESSURE OF OXYGEN

Breathing O_2 at increased ambient pressure will lead to elevation of alveolar O_2 tension (PAO_2), which can be calculated according to the alveolar gas equation for O_2 ^{102,103}:

$$PAO_2 = FiO_2(P_b - PH_2O) - PACO_2 \cdot \left(FiO_2 + \frac{1 - FiO_2}{R} \right)$$

where FiO_2 is the fractional inspired O_2 concentration; PH_2O is saturated water vapor pressure at body temperature (typically 47 mm Hg); $PACO_2$ is alveolar partial pressure of CO_2 (PCO_2), assumed to equal arterial PCO_2 ($PaCO_2$); and R is respiratory exchange ratio (usually ≈ 0.8 at rest). Arterial PO_2 (PaO_2) at any given ambient pressure or FiO_2 can be estimated from arterial blood gases measured breathing air at atmospheric pressure by assuming that the arterial/alveolar (a/A) PO_2 ratio remains constant.^{104,105}

TABLE 75.2 Units of Pressure

Atmospheres Absolute (ATA)	Absolute Pressure (mm Hg)	Gauge Pressure (mm Hg)	Feet of Sea Water (fsw)	Meters of Sea Water (msw)
1	760	0	0	0
2	1520	760	33	10
3	2280	1520	66	20
6	4560	3800	165	50

Whereas at 1 ATA the fraction of O₂ in arterial blood that is carried dissolved in the plasma is minimal, at an elevated PaO₂ in the range of 1000 to 2000 mm Hg, significant quantities of O₂ may exist in dissolved form (Table 75.3).

Increased PaO₂ has at least four pharmacologic effects:

1. Increased blood O₂ content
2. Vasoconstriction¹⁰⁶
3. Antibacterial action, particularly against anaerobic bacteria¹⁰⁷
4. Inhibition of endothelial neutrophil adhesion in injured tissue^{108,109}

The increased arterial O₂ content underlies the rationale for administering HBOT for the treatment of ischemic conditions, for example, wounds that fail to heal due to insufficient blood supply. Elevated PaO₂ leads to an increase in tissue PO₂, which can be estimated using transcutaneous PO₂ electrodes.^{110,111} The second effect, vasoconstriction, is an explanation for the effectiveness of HBOT in the treatment of traumatic edema (e.g., crush injury). The mechanism of HBOT-induced vasoconstriction appears to be inactivation of nitric oxide as a result of increased production of superoxide¹¹² and possibly decreased release of nitric oxide from circulating S-nitrosohemoglobin.^{106,112,113}

These two effects, increased O₂ content and vasoconstriction, lead to hemodynamic changes,^{106,114} shown in Table 75.3. There is also a slight increase in mean arterial pressure. Studies of HBOT effects on myocardial contractility using denervated hearts¹¹⁵ or autonomically blocked animals¹¹⁶ have indicated no intrinsic effect. In intact animals or humans, heart rate and cardiac output are decreased and systemic vascular resistance is increased.^{106,114,117} In both anesthetized dogs and awake humans, pulmonary vascular resistance is decreased.^{106,118} At 2 ATA, 100% O₂ in conscious dogs has no effect on coronary flow,¹¹⁷ whereas at 3 ATA, both coronary flow and myocardial O₂ consumption are decreased.¹¹⁶ Cerebral blood flow is decreased by O₂ administration over a range of pressures,^{112,117} whereas at 2 ATA, hepatic, renal, and mesenteric flows are unchanged.¹¹⁷ HBOT also has microcirculatory and cellular effects in various disease states (see later).

ELEVATION OF INERT GAS PARTIAL PRESSURE

Elevation of the partial pressure of the inert gas (usually nitrogen) present in a breathing mixture is associated with a narcotic effect, predictable by the Meyer-Overton hypothesis. Based on its solubility in olive-oil, nitrogen has 0.03 to 0.05 times the narcotic potency of nitrous oxide. At 3 to 4 ATA (breathing air), most people experience mild euphoria. At 6 ATA, there may be memory loss and poor judgment. At 10 ATA, some individuals lapse into unconsciousness. Nitrogen narcosis has been compared with alcoholic intoxication, with each increase in ambient pressure of 1.5 ATA breathing air resulting in an effect that is said to be similar to drinking one martini. Argon and to a lesser degree hydrogen are also narcotic, whereas helium has minimal if any narcotic effect. In animals exposed to high partial pressures of nitrogen, there is evidence of activation of GABA_A receptors of dopaminergic neurons in the nigrostriatal pathway, leading to a decrease in dopamine release.¹¹⁹

ELEVATION OF ABSOLUTE PRESSURE

High-Pressure Nervous Syndrome

High pressure induces a constellation of symptoms consisting of tremor, ataxia, nausea, and vomiting that is known as the high-pressure nervous syndrome (HPNS).¹²⁰ It occurs at an ambient pressure greater than 15 to 20 ATA and was first described during the compression phase of deep dives with a helium-O₂ atmosphere. HPNS is attenuated by slow compression and addition of a narcotic gas (e.g., nitrogen) to the breathing mix.¹²¹ Its pathogenesis may be related to an increase in striatal dopamine.¹²²

Pressure Reversal of Anesthesia

Studies in animals have demonstrated that high pressure has the tendency to reverse general anesthesia. Elevations in ambient pressure in the absence of a narcotic inert breathing gas will tend to decrease the effectiveness of both inhaled and intravenous anesthetics. At 50 ATA, a 20% increase in the 50% effective dose (ED₅₀) occurs in mice with a variety of inhaled anesthetics. At 50 and 100 ATA, the effective dose of barbiturates increases by 30% to 60%.¹²³ The ED₅₀ for diazepam in rats is markedly reduced at 90 ATA in a helium-O₂ atmosphere.¹²⁴ At 31 ATA, the effective concentration for half-maximal effect (EC₅₀) of propofol for loss of righting reflex in tadpoles is increased by 19%, and at 61 ATA, by 38%.¹²⁵ Using the same technique, the EC₅₀ for dexmedetomidine at 31 ATA is nearly double the value at 1 ATA, and it is increased 2.5-fold at 61 ATA.¹²⁶ At 80 ATA, the MAC of desflurane as assessed by response to a noxious stimulus is increased by 19%.¹²⁷ The mechanisms of pressure reversal are not fully understood, but may be secondary to physical chemical effects of pressure on membranes¹²⁸ or may be related to alterations in neurotransmitter release.¹²² However, within the range of pressures used for HBOT (up to 3 to 6 ATA), the effects of pressure on sedative or anesthetic drugs are not clinically significant.

EFFECTS OF HYPERBARIC EXPOSURE ON DRUG DISPOSITION

A few studies have examined the disposition of drugs and drug effects at increased environmental pressures. Studies in awake dogs at pressures up to 6 ATA and ambient PO₂ up to 2.8 ATA have shown that liver plasma flow decreased when either ambient pressure or PO₂ was increased. There was an apparent increase in plasma volume at 1.3 ATA and a return toward 1 ATA values at higher pressures. In the same studies plasma volume was inconsistently affected by ambient pressure, but reduced by increases in PO₂.¹²⁹

There is no major pharmacokinetic or pharmacodynamic effect of hyperbaric exposure for most drugs up to 6 ATA. Pharmacokinetic studies of a few drugs have shown that up to 6 ATA pressure and 2.8 ATA PO₂, the pharmacokinetics of meperidine,¹³⁰ pentobarbital,¹³¹ theophylline,¹³² and salicylate¹³³ are unaffected.

Use of benzodiazepines, chlorpromazine, and lithium carbonate has been reported for the treatment of agitation, auditory and visual illusions, and paranoia in a previously normal subject participating in an experimental dive to 650 m (66 ATA).¹³⁴ The symptoms, poorly controlled with

TABLE 75.3 Mean Blood Acid-Base and Cardiovascular Responses to Hyperbaric Oxygenation in 14 Normal Subjects

Atmo-spheric Pressure (ATA)	Inspired Gas	ARTERIAL					MIXED VENOUS					Mean Pulmonary Artery Pressure (mm Hg)	Pulmonary Artery Wedge Pressure (mm Hg)	Systemic Vascular Resistance (dyne.sec.cm ⁻⁵)	Pulmonary Vascular Resistance (dyne.sec.cm ⁻⁵)		
		PO ₂ (mm Hg)	PCO ₂ (mm Hg)	O ₂ Saturation (%)	Dissolved O ₂ (mL/dL)	Total O ₂ * (mL/dL)	PO ₂ (mm Hg)	pH	PCO ₂ (mm Hg)	HbO ₂ Saturation (%)	Cardiac Output (L.min ⁻¹)						
1	Air	94	7.40	37	95.7	0.3	18.4	43	7.39	42	75.5	6.5	86	13	9	1061	64
3	100% O ₂	1542	7.42	36	99.1	4.6	22.7	399	7.37	43	97.7	5.8	95	12	9	1286	41

*Assuming Hb=13 g/dL.

ATA, Atmospheres absolute; O₂, oxygen; PCO₂, partial pressure of carbon dioxide; PO₂, partial pressure of oxygen.

Data from McMahon TJ, Moon RE, Luschinger BP, Luschinger BP, et al. Nitric oxide in the human respiratory cycle. *Nat Med*. 2002;8:711–717.

diazepam 120 mg/day and temazepam 60 mg/day, ultimately responded to chlorpromazine 300 mg/day. Lithium carbonate administered in conventional doses appeared to display normal pharmacokinetics. Although the effect of chlorpromazine appeared clinically to be appropriate, the authors were uncertain as to whether the failure of benzodiazepines to elicit a desired therapeutic response was due to the patient's condition or to a pressure-reversal phenomenon.

In summary, clinical experience and the published literature indicate that for a variety of drugs administered under hyperbaric conditions at the pressures used for clinical treatment (up to 6 ATA), conventional parenteral drug dosing schedules are safe.

Hyperbaric Oxygen Therapy

RATIONALE FOR HYPERBARIC TREATMENT OF SELECTED ACUTE CLINICAL ENTITIES

Carbon Monoxide Poisoning

Hemoglobin (Hb) binds CO with an affinity much higher (by a factor of about 200) than that for O₂. This binding of CO with Hb to form carboxyhemoglobin (HbCO) has two major effects. First, the proportion of Hb that is occupied by CO molecules is unavailable for O₂ transport, resulting in a functional anemia. Second, the avidity with which the remaining Hb binds O₂ is increased (shift to the left of the Hb-O₂ dissociation curve).¹³⁵ The result of this is a decreased ability to unload O₂ from blood to tissue at the capillary level and therefore, a reduction in tissue PO₂. Previously it was believed that these effects were totally responsible for the toxicity of CO. However, evidence has since been presented to show that the binding of CO to intracellular pigments (e.g., cytochrome a, cytochrome a₃, myoglobin) and oxidative stress may contribute significantly to the toxicity of CO.¹³⁶⁻¹⁴⁴ CO exposure also triggers intravascular platelet-neutrophil aggregation and neutrophil activation.¹⁴⁴ These mechanisms result in toxicity to multiple organ systems, including brain and heart.^{141,145} Immune-mediated effects have also been described.¹⁴⁶

Clinical effects include headache, nausea, vomiting, dizziness/ataxia, myocardial ischemia, loss of consciousness, and, during pregnancy, fetal distress. Persistent or delayed neurologic sequelae can occur, often after a clear window of lucidity.^{147,148} Increased risk factors for persistent sequelae include older age (≥ 36 years) and longer CO exposure.¹⁴⁹

The diagnosis of CO poisoning is made by a history of exposure (internal combustion engine exhaust, fire, improperly adjusted gas or oil heating, charcoal or gas grills, or exposure to paint stripper containing methylene chloride, which is metabolized by the liver to CO). Confirmation of the diagnosis is made by finding an elevated HbCO level in either arterial or venous blood. HbCO concentration is stable for several days in anticoagulated blood samples. Therefore, if HbCO determination is not available at a referring facility, the diagnosis can be confirmed using a blood sample obtained at the time of initial evaluation and transported with the patient. Fetal hemoglobin (HbF) can produce a falsely elevated reading for HbCO on certain

four-wavelength laboratory co-oximeters.¹⁵⁰ In the first few weeks of life, blood from normal infants may therefore falsely indicate 7% to 8% HbCO.

Actual HbCO levels measured on arrival in the emergency room correlate poorly with clinical status and should not be used as the sole criterion to determine the need for treatment. Because of the lower intracellular PO₂, elimination of CO from intracellular binding sites occurs more slowly. Significant mental obtundation, vomiting, and headache may remain even in patients with a normal HbCO level.

Brain imaging may reveal a variety of abnormalities in patients with CO poisoning, including hypodensities in the globus pallidus and subcortical white matter, cerebral cortical lesions, cerebral edema, hippocampal lesions, and loss of gray matter/white matter differentiation, and white matter hyperintensities.¹⁵¹⁻¹⁵³ Except to exclude other pathologic processes, brain imaging is not useful for determining who should receive HBOT, but it may provide prognostic information. Lesions in both globus pallidus and white matter are associated with poor long-term outcome.^{151,154}

O₂ is the primary treatment modality for CO poisoning. High PaO₂ hastens the removal of CO from blood, as indicated by a reduced half-life of HbCO. Fig. 75.6 shows the HbCO half-time in a series of CO-poisoned patients during normobaric O₂ administration; HBOT reduces the half-time even further, to around 20 minutes at 2.5 ATA.¹⁵⁵ Additionally, the increased dissolved O₂ in plasma may support tissue oxygenation pending removal of CO from Hb and other proteins important for O₂ transport. Mounting evidence indicates that for poisoning in which neurologic symptoms occur, HBOT may decrease both early and late morbidity.¹⁵⁶ Although the results of one randomized prospective trial of hyperbaric versus normobaric oxygen revealed no apparent benefit of HBOT,¹⁵⁷ in four other trials HBOT resulted in improved outcome compared with treatment at 1 ATA (Fig. 75.7).^{147,148,158,159} HBOT has been observed to reduce mortality in CO poisoning.¹⁶⁰

Commonly used guidelines for the application of HBOT in CO poisoning include the following:¹⁶¹

Neurologic impairment (including dizziness, loss of consciousness), even if the patient seems normal at the time of medical evaluation

Cardiac abnormalities (ischemia, arrhythmias, ventricular failure)

Metabolic acidosis (consider also concomitant cyanide poisoning)

HbCO level that has been greater than 25%

Fetuses are particularly susceptible to CO toxicity. Pregnant women who fulfill the criteria just listed or in whom there is fetal distress should be treated with HBOT. Case reports,¹⁶²⁻¹⁶⁴ published series,^{165,166} and a critical review¹⁶⁷ support the concept that inadequately treated CO poisoning is a serious risk to the mother and fetus, and the benefits of HBOT outweigh the theoretical risks to the fetus from HBOT. Potential adverse effects of currently implemented HBOT protocols have not been confirmed in clinical practice.

Gas Embolism and Decompression Sickness

Introduction of gas into the arterial circulation (AGE) has traditionally been associated with scuba divers and attributed to pulmonary barotrauma during ascent from a dive

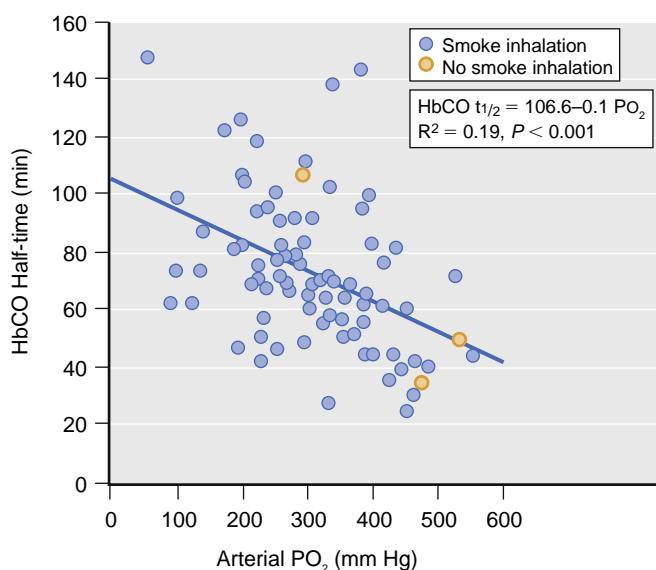


Fig. 75.6 Elimination half time of carboxyhemoglobin in 93 carbon monoxide-poisoned patients. Although there is scatter in the data, it is apparent that carbon monoxide dissociates from hemoglobin faster at higher partial pressure of oxygen (PO₂). (Re-drawn from Weaver LK, Howe S, Hopkins R, Chan KJ. Carboxyhemoglobin half-life in carbon monoxide-poisoned patients treated with 100% oxygen at atmospheric pressure. *Chest*. 2000;117[3]:801–808.)

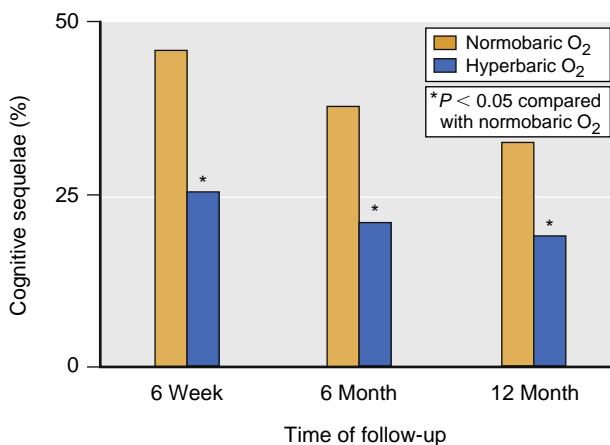


Fig. 75.7 Cognitive sequelae in a randomized prospective trial of hyperbaric oxygen (O₂) in carbon monoxide poisoning. Cognitive sequelae were defined as any T score for a neuropsychological subtest more than 2 standard deviations (SD) below the mean of demographically corrected standard T scores, or if two or more T scores for subtests were more than 1 SD below the mean. If the patient reported difficulties with memory, attention, or concentration, then cognitive sequelae were defined as a T score on any neuropsychological subtest more than 1 SD below the mean of demographically corrected standardized T scores. (Drawn from data reported by Weaver LK, Hopkins RO, Chan KJ, et al. Hyperbaric oxygen for acute carbon monoxide poisoning. *N Engl J Med*. 2002;347[14]:1057–1067.)

while breathing compressed gas. However, it may also occur iatrogenically in several clinical circumstances, such as during cardiopulmonary bypass or as a result of inadvertent injection of air during a diagnostic arteriogram or hemodialysis. Additionally, large amounts of gas may enter the venous system, for example during neurosurgical procedures with the patient in the sitting position, accidental disconnection of hemodialysis access equipment, major back surgery, total hip replacement, cesarean section,

laparoscopy, intrauterine laser surgery, arthroscopy (from air escaping from a faulty air-powered instrument), and hydrogen peroxide irrigation or oral ingestion (due to elaboration of gaseous oxygen from tissue and blood catalase). Venous gas embolism (VGE) can also occur when a central venous catheter is opened to air. Severe VGE has also occurred during orogenital sex after blowing air intravaginally.¹⁶⁸ VGE has been reported in patients with ARDS who are being ventilated with positive end-expiratory pressure (PEEP).¹⁶⁹ VGE in sufficient quantity may overwhelm the ability of the pulmonary vasculature to filter the gas, allowing bubbles to pass into the arterial circulation. Even small amounts of venous gas (e.g., VGE caused by decompression from diving) have recently been implicated in neurologic syndromes in scuba divers because of transatrial passage through a patent foramen ovale.^{170,171}

The effects of gas embolism can be partly due to vessel obstruction by bubbles, but bubble-endothelial interaction causes increased capillary permeability and extravasation of fluid,^{172–174} resulting in hemoconcentration. Impaired endothelial function also occurs.¹⁷⁵ Another effect has been demonstrated in a model of AGE in anesthetized rabbits^{176,177}: small doses of intracarotid air may pass through the cerebral microcirculation yet produce vasoplegia, delayed reduction of cerebral blood flow, and neurophysiologic impairment. This reduction in blood flow is abolished when there is neutropenia; thus it has been concluded that leukocytes are a major component of the pathophysiology.¹⁷⁸ This phenomenon of delayed reduction of cerebral blood flow may be responsible for the clinical observation of initial neurologic improvement after AGE, followed by delayed deterioration.¹⁷⁹

A related syndrome that results from pathologic effects of tissue and blood gas bubbles is DCS, seen in aviators and compressed gas divers. The gas bubbles in these situations occur because of a decrease in ambient pressure at a rate sufficient to induce local inert gas supersaturation, resulting in formation of bubbles *in situ* from tissue stores. Manifestations of AGE classically consist of impaired consciousness, hemiparesis, or seizures, but may be of a less severe nature. DCS most commonly presents as any combination of joint pain, paresthesias, motor weakness, bladder or bowel sphincter dysfunction, vertigo, tinnitus, and hearing loss.^{180,181}

Treatment principles for both forms of gas bubble disease, AGE and DCS, are the same in most instances. First aid includes therapy with O₂.¹⁸² High PO₂ results in an increased rate of resolution of gas bubbles because of the resulting higher partial pressure gradient for diffusion of inert gas from the interior of the bubble into the surrounding tissue or blood. Fluid resuscitation will replenish intravascular volume, relieve hemoconcentration, and facilitate microcirculatory flow,¹⁸³ principles that have been confirmed by both animal¹⁸⁴ and human observations.¹⁷³ However, excessive fluid administration can worsen pulmonary gas exchange in cardiorespiratory DCS (pulmonary edema from VGE), and aggressive fluid therapy is not indicated for isolated AGE.¹⁸³ Although capillary leak resulting from cerebral AGE can raise intracranial pressure, studies in anesthetized pigs have shown that hyperventilation is ineffective in reversing its effects.¹⁸⁵

HBOT is the definitive treatment for AGE and DCS.¹⁸⁰ The increased pressure causes a diminution in gas volume and thus further hastens resolution. The usefulness of HBOT for diving-related or aerospace-related gas embolism associated with rapid decompression is well documented.¹⁸⁶⁻¹⁸⁸ HBOT may effect neurologic improvement even after many hours and sometimes days between the embolic event and treatment,¹⁸⁹⁻¹⁹¹ although some evidence suggests that severe abnormalities are less likely to resolve if not treated promptly.¹⁹² Treatment of AGE is usually performed at ambient pressures from 2.8 to 6 ATA (see the section "Hyperbaric Treatment Schedules").

The decision to administer recompression treatment should be based entirely on clinical evaluation.¹⁸⁰ The only appropriate role for brain or spinal imaging (e.g., computed tomography [CT], magnetic resonance imaging [MRI]) is to exclude other pathologic processes such as hemorrhage, and only if there is a high degree of suspicion that bubbles are not the cause of a patient's symptoms. Some authors have suggested that patients with AGE should only be treated with HBOT if CT of the brain reveals air.¹⁹³ However, brain and spinal cord imaging of patients with AGE or DCS is insensitive,^{191,192,194,195} and the abnormalities on either CT or MRI are usually not specific. Neither the presence nor absence of intravascular gas predicts response to hyperbaric treatment.^{191,192} Nuclear imaging of the brain using single photon emission tomography (SPECT) or positron emission tomography (PET)¹⁹⁶ does not provide clinically useful information in the management of patients with bubble-induced neurologic injury. If either AGE or DCS is suspected, HBOT should be initiated as soon as possible unless there is high suspicion of another condition that may require different treatment.

Acute Infections

Anaerobic bacteria are especially sensitive to increased tissue PO₂. High O₂ tensions inhibit clostridial α -toxin production.¹⁹⁷ Other mechanisms include reversal of hypoxia-induced neutrophil function,¹⁹⁸⁻²⁰⁰ enhanced macrophage interleukin-10 expression,²⁰¹ and antiinflammatory effects.²⁰²⁻²⁰⁴ Evidence in favor of the use of HBOT in clostridial and non-clostridial infections is provided by clinical series and database analyses.²⁰⁵⁻²⁰⁸

Support of Arterial Oxygenation in Therapeutic Lung Lavage

HBOT is a safe and effective method of supporting arterial oxygenation during therapeutic lung lavage, during which oxygenation has to be maintained by the contralateral (non-lavaged) lung.^{209,210} In the authors' experience of over 100 procedures, using this technique to treat arterial oxygenation has been uniformly successful with no complications specific to HBOT. A reversible simulation of pulmonary gas exchange during the lavage procedure can be provided by temporarily ventilating the lung to be lavaged with 5% to 6% O₂/balance nitrogen, which reduces PAO₂ in that lung to approximately the level of mixed venous PO₂ and confining O₂ exchange to the contralateral lung. Hypoxemia within 5 minutes is predictive of hypoxemia during the actual lavage.

Maintenance of Oxygen Transport in Severe Anemia

The ability of HBOT to increase arterial O₂ content in plasma to clinically useful levels may allow support of tissue O₂ delivery even without Hb. HBOT can therefore be used for temporary support of severely anemic patients pending availability of definitive therapy in the form of cross-matched blood.

Crush Injury

HBOT increases tissue oxygen tensions, reduces edema, and, consequently, increases blood flow through injured soft tissue and may mitigate ischemia-reperfusion injury.²¹¹⁻²¹⁴

Central Retinal Artery Occlusion and Central Retinal Vein Occlusion

Central retinal artery occlusion (CRAO) and central retinal vein occlusion (CRVO) are uncommon but devastating conditions resulting in sudden painless vision loss, which is usually permanent and with poor outlook for recovery of vision. Intermittent HBOT can maintain viability of the retina via diffusion of oxygen from the choroidal vessels pending recanalization of the occluded vessel. Urgent HBOT should be considered for patients presenting within 24 hours of symptom onset.^{215,216}

Idiopathic Sudden Sensorineural Hearing Loss

Sudden sensorineural hearing loss is defined as hearing loss of at least 30 dB identified at 3 or more consecutive frequencies that occur over a period of less than 72 hours. The pathophysiology is unknown but local hypoxia has been speculated as a possible cause. Empirical HBOT has been shown to offer benefit, with greater success when it is administered soon after symptom onset.^{217,218}

THERAPEUTIC SYSTEMS

The traditional method of administering hyperbaric therapy is with a multiplace chamber, which accommodates two or more persons (Fig. 75.8). Size may vary from a small, portable 2-person chamber used for transporting patients in the field to one 20 feet or more in diameter, in which up to 12 or more patients may be comfortably treated, in addition to tenders (attendants). Multiplace chambers are compressed with air while the patient breathes O₂ with a head tent (Fig. 75.9), face mask, or endotracheal tube. Because of immediate access to the patient by accompanying nursing personnel or physicians, monitoring and resuscitative procedures are straightforward. However, multiplace chambers take up a significant amount of space and are expensive.

Monoplace chambers are large enough to accommodate only one patient (Fig. 75.10), or a tender with a small child. The chamber wall in most types is manufactured of Plexiglas, facilitating close visual observation of the patient. The chamber is usually compressed with 100% O₂. The advantage of monoplace chambers is their relatively low cost and ease of installation. Chamber operation can often be implemented by connecting the O₂ inlet to the hospital supply. Operation is relatively simple, but the patient inside is not directly accessible. Monitoring is somewhat more remote, and emergency airway management is not possible.

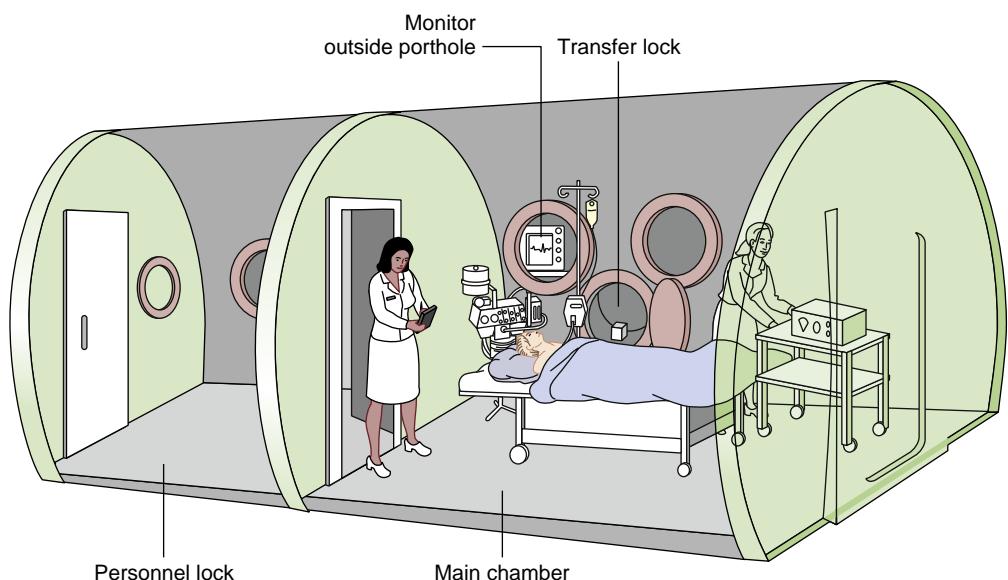


Fig. 75.8 Multiplace hyperbaric chamber large enough for one or more patients and tenders. The chamber atmosphere is compressed air. The patient receives 100% oxygen by mask, head tent, or endotracheal tube. Monitors are usually kept outside the chamber because of electrical safety considerations. Monitoring is possible through a porthole. A personnel lock and a transfer lock allow physicians, nurses, or other personnel, in addition to medications, food, and blood samples, to be moved into and out of the chamber without repeated compression and decompression of the patient.

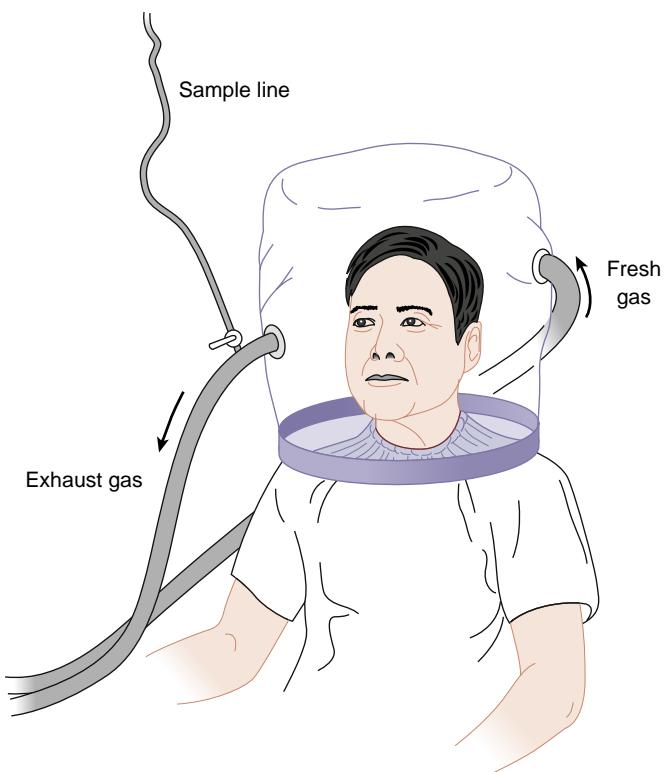


Fig. 75.9 Head tent circuit for use in a multiplace chamber. Fresh gas (100% O₂) flows at a constant rate (>30 L/min) through the head tent. Exhaust gas may be either vented outside the chamber or recirculated through a carbon dioxide scrubber. The sample line attached to the exhaust hose allows monitoring of the patient's breathing gas.

Development of a pneumothorax during treatment, particularly a tension pneumothorax, can be fatal because pleural decompression with a needle or chest tube cannot be performed before decompression; however, this complication is extremely rare. A minor disadvantage of these



Fig. 75.10 Monoplace chamber. This type of chamber has room for one patient or a tender with a small child. The patient is moved into and out of the chamber on a wheeled gurney. The chamber atmosphere is usually 100% oxygen. The chamber is constructed of transparent Plexiglas to allow observation. Through-hull penetrators in the door on the left can be seen and allow monitoring, intravenous fluid administration, and control of a ventilator inside the chamber. (Photograph courtesy Dr. Lindell Weaver.)

chambers is that the ambient pressure limit is 3 ATA, and for practical reasons (psychological aversion to confinement) treatment times are limited. Moreover, intermittent periods of air breathing, to decrease the risk of O₂ toxicity during some types of treatment schedules (see later), requires installation of an additional gas delivery system. Nevertheless, monoplace technology now permits intravenous fluid administration from outside the chamber, invasive intravascular monitoring, mechanical ventilation, and utilization of pleural drainage systems incorporating regulated suction.^{219,220}

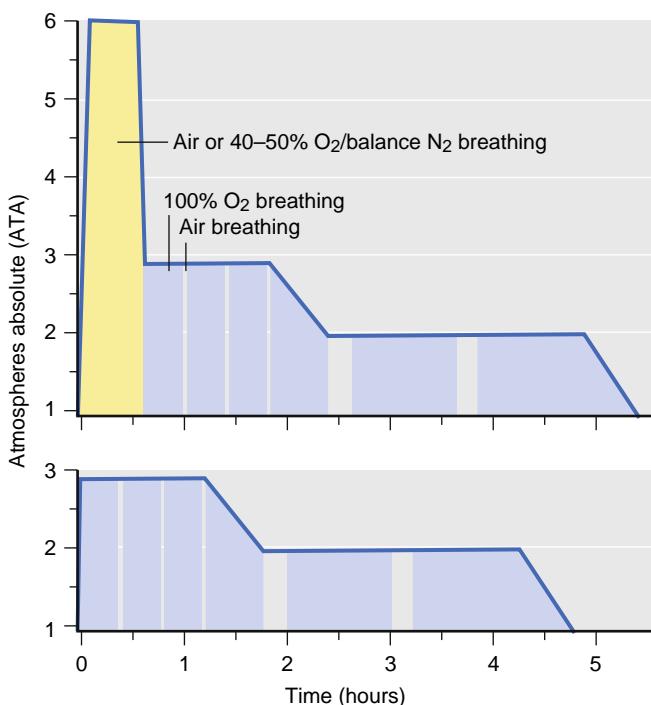


Fig. 75.11 US Navy treatment tables. (A) US Navy Table 6A. This schedule is occasionally used for the treatment of arterial gas embolism. During the 30-minute period at 6 atmospheres absolute, air or 40% to 50% oxygen (O_2) can be administered. (B) US Navy Table 6. This table was originally designed for the treatment of decompression sickness but is now the most commonly used table for gas embolism as well. The shaded areas represent $100\% O_2$ breathing; the white areas represent air breathing periods. Further details can be found in the US Navy Diving Manual. (From Navy Department. *US Navy Diving Manual, Revision 7, Vol. 1: Diving Medicine and Recompression Chamber Operations*. NAVSEA 0910-LP-115-1921. Washington, DC: Naval Sea Systems Command; 2016.)

HYPERBARIC TREATMENT SCHEDULES

Ideally, a patient who has therapeutic indication for HBOT would be exposed for an unlimited time until the condition resolves. Unfortunately, several factors limit the dose and duration of HBOT:

- O_2 toxicity
- Decompression obligation for nursing staff (or other tenders) accompanying patient
- Adequacy of monitoring
- Patient isolation and boredom in a confined environment

Treatment schedules are compromises between O_2 partial pressure and exposure time on one hand and O_2 toxicity and other practical limiting factors on the other. The original schedules (or “tables”) were developed by the various navies of the world to treat DCS and gas embolism in divers (Fig. 75.11).

U.S. Navy Table 6 (see Fig. 75.11) prescribes an initial exposure to 2.8 ATA (equivalent to 60 feet of sea water [fsw], or 18 m of sea water [msw]), followed by slow decompression to 1.9 ATA (30 fsw). Periods of O_2 breathing are interspersed with 5- or 15-minute periods of air breathing to decrease O_2 toxicity (see later). This schedule remains the mainstay of treatment for DCS in multiplace chambers

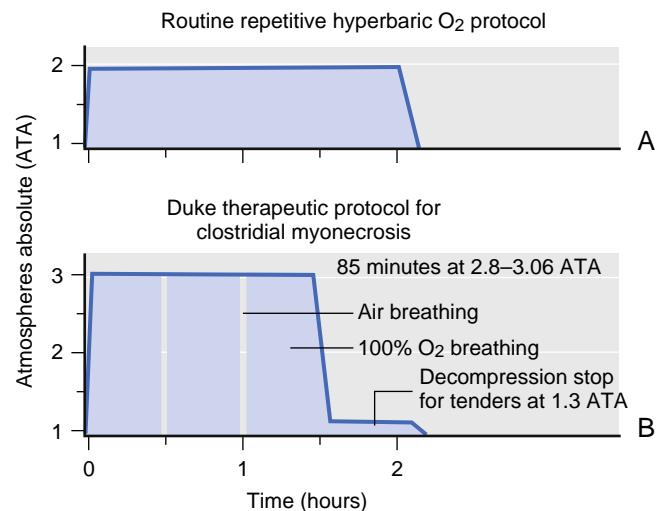


Fig. 75.12 Examples of clinical hyperbaric oxygen (O_2) treatment schedules. (A) The patient breathes $100\% O_2$ for 2 hours at an ambient pressure of 2 ATA. Generally, this schedule is used for repetitive treatment of chronic conditions (e.g., osteoradionecrosis). (B) Therapeutic schedule often used for treatment of clostridial myonecrosis. The patient and tender spend 85 minutes at 2.8 to 3.06 ATA (3 ATA shown). The patient breathes $100\% O_2$, except for two 5-minute air breaks to reduce pulmonary and central nervous system O_2 toxicity. A decompression stop is made at 1.3 ATA, according to the US Navy standard air decompression table. The stop is designed to facilitate safe decompression of the tender, who breathes air at 3 ATA. ATA, Atmosphere absolute.

throughout the world. Incomplete relief of signs or symptoms can be treated with repeated applications of U.S. Navy Table 6 or a shorter treatment on a once- or twice-daily basis.

“Saturation” treatment consists of an extended exposure to elevated pressure (e.g., 2.8 ATA) for an unspecified period of time (often 1 to 2 days) until manifestations have stabilized. Periodic O_2 breathing is given according to a recommended schedule as tolerated. Because saturation treatment results in a much larger degree of nitrogen uptake in both the patient and the tender, decompression must occur much more slowly, usually over 24 to 36 hours.²²¹ Although this therapy avoids the theoretical disadvantage of intermittent treatment—failure of resolution of gas bubbles—it is also considerably more labor intensive. Because hyperbaric chambers used for saturation treatments require additional hardware (e.g., CO_2 scrubbing capability) and personnel, their application outside military and commercial diving has been limited.

Examples of schedules used for treatment of patients with wound healing problems and with clostridial myonecrosis or other life-threatening anaerobic infections are shown in Fig. 75.12. The schedule for clostridial myonecrosis consists of 85 minutes at 3 ATA followed by a 33-minute decompression stop for the tenders at 1.3 ATA. This treatment schedule has been designed to maximize PaO_2 (and hence tissue bactericidal activity resulting from O_2) without an undue risk of hyperoxic seizures.

Treatment schedules for CO poisoning have varied. However, the proven efficacy of the schedule reported by Weaver (60 minutes at 3 ATA, 60 minutes at 2 ATA in addition to air breaks and compression-decompression time) supports the use of 3 ATA for at least the first treatment.¹⁴⁸

Administration of HBOT to patients with chronic diseases (e.g., radionecrosis) is usually performed using shorter tables at lower ambient pressure, most commonly 1 to 2 hours at 2.0 to 2.5 ATA (see Fig. 75.9) once or twice daily. At this lower ambient pressure, the risk of O₂ toxicity is minimal and treatments are well tolerated by most patients.

SIDE EFFECTS OF HYPERBARIC OXYGEN THERAPY

Oxygen Toxicity

A wide body of evidence supports the notion that O₂ toxicity is caused by excessive production of oxygen free radicals (e.g., superoxide, hydroxyl radicals, and singlet oxygen). At high O₂ partial pressures, scavenging mechanisms can be overcome by increased rates of free radical production.²²² With the use of supplemental O₂ at 1 ATA, the manifestations of O₂ toxicity are almost exclusively confined to the lung; however, during hyperbaric O₂ exposure, other organs can be affected as well.

O₂ toxicity during HBOT can affect mainly the lung, the central nervous system (CNS), and the eye. Pulmonary toxicity in the conscious patient is heralded by symptoms of tracheobronchial irritation, namely, cough and burning chest pain. Prolonged exposure may result in a decrease in vital capacity, and if O₂ administration continues, ARDS. In the rare instances in which prolonged HBOT is indicated, the rate of development of pulmonary O₂ toxicity can be slowed by intermittent air-breathing periods ("air breaks") (Fig. 75.13).

O₂ toxicity is related to the PO₂ of the inspired gas. At 1 ATA, 100% O₂ is as toxic as 16.7% O₂ at 6 ATA or 2% O₂ at 50 ATA. One method of quantification of O₂ exposure is the

unit pulmonary toxic dose, or UPTD.²²³ In this system, the number of UPTD units is calculated by the formula:

$$U = t \cdot \sqrt[m]{0.5 / (P - 0.5)}$$

where U is the unit; t is the exposure time in minutes; P is the inspired PO₂ in ATA; and m is a slope constant that has an empirical value of 1.2. After 1425 UPTD units of O₂ exposure, an average 10% decrease in vital capacity occurs. After 2190 UPTD units, an associated decrease of 20% occurs. Complete reversal of vital capacity decrements as large as 40% of control has been observed after extended O₂ exposure at 2 ATA.²²³

Reanalysis of a larger data set than the one used for the UPTD model, which included those data, resulted in a different prediction equation:

$$\% \Delta VC = -0.009 \cdot (P - 0.38) \cdot t$$

where P and t are the same as for the previous equation (3).²²⁴

Using previously published data, Arieli and colleagues²²⁵ developed the following equation:

$$\% \Delta VC = 0.0082 \cdot t^2 (PO_2 / 101.3)^{4.57}$$

where t is time in hours, and PO₂ is measured in kilopascals (kPa).

Although these algorithms may be useful as an approximate guide to safe O₂ exposures in populations, interindividual variability is such that they cannot be relied on to predict accurately the development of pulmonary O₂ toxicity for a specific patient.²²⁶ Furthermore, O₂ toxicity can be modified by humidity,²²⁷ circulating catecholamine and

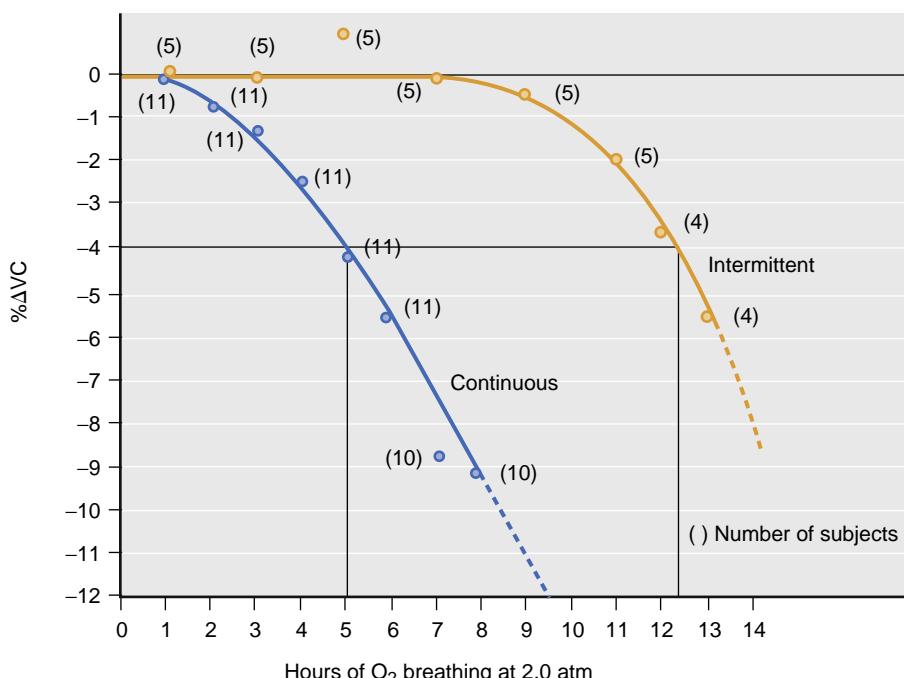


Fig. 75.13 Decrease in vital capacity (VC) as a function of time breathing 100% oxygen (O₂) at 2 ATA in humans. The figure illustrates the value of intermittent O₂ (20 minutes O₂, 5 minutes air) versus continuous O₂ administration in the prevention of pulmonary O₂ toxicity. The numbers in parentheses represent the number of subjects tested. (From Clark JM. Oxygen toxicity. In: Bennett PB, Elliott DH, eds. *The Physiology and Medicine of Diving*. Philadelphia, PA: WB Saunders; 1993:121–169. With permission.)

corticosteroid levels, leukocyte accumulation in the lungs (e.g., with pneumonia), and circulating endotoxin. A more useful guide to the development of pulmonary toxicity is the patient's symptoms, which include cough and inspiratory central burning chest pain. These symptoms do not occur during routine repetitive HBOT, but they may become evident during extensive O₂ periods at 2.8 ATA (e.g., when treating neurologic DCS). Asymptomatic persons usually have minimal or no change in vital capacity. Minor changes in forced expiratory volume in 1 second [FEV₁] reported during repetitive HBOT²²⁸ are of uncertain clinical importance.

Some antineoplastic agents, such as bleomycin²²⁹ and mitomycin C,^{230,231} appear to predispose to fatal pulmonary O₂ toxicity (ARDS and respiratory failure) from what should otherwise have been well-tolerated doses of supplemental O₂. The risk of pulmonary O₂ toxicity from HBOT in patients with previous exposure to such agents is unknown, although we have treated several such individuals with a remote history of bleomycin treatment with repetitive doses of HBOT at 2 ATA for 2 hours (initially once daily, then increased to twice daily).²³² Occasional mild pulmonary O₂ toxicity symptoms such as retrosternal chest tightness did occur, but none of these patients experienced severe O₂ toxicity. Propensity to pulmonary O₂ toxicity engendered by these drugs appears to diminish a few weeks after their discontinuation.

CNS O₂ toxicity manifests as nausea, vomiting, numbness, twitching, dizziness, olfactory, acoustic, or gustatory sensations, and in its most severe form, as non-focal tonic-clonic seizures.^{233,234} The probability of seizures increases with increasing PO₂ and time of exposure. In a study of 36 divers breathing 100% O₂ at 3.7 ATA, all experienced one or more of these symptoms within 100 minutes or less.^{233,234} In clinical practice, convulsions in patients undergoing HBOT are rare at ambient PO₂ up to 2.5 ATA (typically 0.008% to 0.035% of treatments²³⁵), and they often have another predisposing factor (hypoglycemia). The probability of a convulsion is also greater when administered for acute indications such as CO poisoning.²³⁶ Metabolic factors may reduce the seizure threshold, such as the administration of high-dose penicillin (e.g., for clostridial infection), sepsis, and hypoglycemia.

The treatment of hyperoxic seizures is immediate reduction of the inspired PO₂ until the seizure stops. Some physicians then routinely administer an anticonvulsant such as phenobarbital, phenytoin, or a benzodiazepine. It is recommended that the chamber should not be decompressed while the patient is actively convulsing because airway closure and failure to exhale during this period may cause pulmonary barotrauma. Hyperoxic seizures otherwise have no sequelae and rarely recur even if HBOT is continued. Thus, the occurrence of CNS O₂ toxicity should not preclude further HBOT. There is no evidence that hyperoxic seizures are more common in patients with preexisting seizure disorders.

An acute effect of HBOT on the eye is narrowing of the visual fields,²³⁷ which is generally only observed at a PO₂ of 3 ATA or greater, and thus rarely, if ever, during routine HBOT. A subacute or chronic ocular effect is a change in the refractive index of the lens that results in myopia.^{238,239} Such refractive index change occurs during the course of intermittent HBOT over several weeks and usually resolves

in a similar period of time. However, some patients may be left with residual myopia, particularly older patients.²⁴⁰

Concern has been raised about the risk of retrosternal fibroplasia in the unborn child of a woman who may require acute HBOT during pregnancy. Although many pregnant women have been treated with single exposures to HBOT (e.g., for CO poisoning), we are not aware of any subsequent occurrence of retrosternal fibroplasia in the child. Pregnancy is not a contraindication to HBOT for appropriate acute indications (e.g., CO poisoning^{163,165,167,241,242}), as the risk to the fetus of the underlying condition exceeds that of the treatment.

Inert Gas Uptake

Breathing air at high ambient pressure can result in nitrogen narcosis, a dose-dependent decrement in cerebral performance due to the anesthetic properties of nitrogen. This mostly occurs at ambient pressures exceeding 4 ATA, a treatment pressure that is used only for severe AGE or DCS. Nitrogen uptake can also theoretically result in DCS during or after decompression (see earlier). However, chamber decompression schedules are so conservative that this rarely occurs (most hyperbaric facilities use standard compressed air decompression tables such as those published by the US Navy).²²¹ Additional safety for the tender can be provided by 100% O₂ breathing for a period immediately before and during decompression. Rare episodes of DCS in hyperbaric tenders are usually of a minor nature, generally consisting of joint pain. Nitrogen narcosis and DCS could only occur in tenders in a multiplace hyperbaric chamber; patients breathe 100% O₂ and are therefore not susceptible.

Barotrauma

As the ambient pressure is altered, the pressure within gas-containing spaces in the body must equilibrate with the ambient pressure or undergo a change in volume. Volume change can easily occur in compliant compartments such as the gastrointestinal tract, but if the free flow of gas into and out of containing spaces surrounded by a rigid shell (e.g., the lung, paranasal sinuses, and middle ear) is obstructed, then tissue disruption and hemorrhage can occur. Indeed, the most common side effect of hyperbaric chamber use for patients is difficulty with middle ear pressure equilibration.^{243,244} This causes pain, bleeding into the middle ear cavity ("squeeze"), and rarely, tympanic membrane rupture. Difficulty equilibrating middle ear pressure could also result in labyrinthine window (round or oval window) rupture, which has been reported in divers²⁴⁵ but to the authors' knowledge not in patients undergoing HBOT. Patients who have previously had irradiation of the head and neck and acute respiratory tract infections are at particular risk. Squeeze may occasionally also affect the sinuses, resulting in acute pain. Despite the common occurrence of middle ear or sinus squeeze on compression, symptoms on decompression, as a result of the inability of gas to exit through the eustachian tubes or sinus ostia ("reverse squeeze"), are rare.

Pulmonary barotrauma is most likely during decompression. Areas of regional hypoventilation could lead to pulmonary over-pressurization and alveolar rupture, causing pneumothorax, pneumomediastinum, or AGE.^{246,247} However, pulmonary barotrauma during HBOT is extremely

rare, probably because of the slow decompression rates typically used. Although a pneumothorax should diminish in size and resorb more quickly after compression, continuing leakage of air from the lung could result in tension pneumothorax during decompression.²⁴⁶

Despite these potential adverse effects of HBOT, major complications are extremely rare.^{248,249}

PRACTICAL ASPECTS OF HYPERBARIC THERAPY

Middle Ear Pressure Equilibration

In awake patients, equilibration may be accomplished using several techniques, such as performing intermittent Valsalva maneuvers, swallowing while the nose is pinched, thrusting the jaw forward, or simply by swallowing intermittently during compression. Equilibration may be facilitated by application of a topical nasal vasoconstrictor (e.g., oxymetazoline 0.05%) that shrinks the nasopharyngeal mucosa and increases the patency of the eustachian tube. For patients who cannot equalize despite these measures or for obtunded or intubated patients, myringotomy or tympanostomy tubes may be required.

Pulmonary Pressure Equilibration

Pneumothorax detected before HBOT is usually treated by insertion of a chest tube and water seal or Heimlich-type valve (in this instance, before monoplace chamber treatment, a chest tube should *always* be inserted). Caution must be exercised when using certain commercially available pleural suction regulators, which can exert high negative pleural pressures during chamber compression.²⁵⁰ Such excessive suction can be relieved by an attendant inside a multiplace chamber by activating the manual pressure relief valve on the chest drainage unit. Patients with large bullous lesions in the lung are probably at increased risk of pulmonary barotrauma, and risk versus benefit of HBOT should be considered for such individuals before treatment.

Patient Monitoring

Despite the changes in the acoustic properties of compressed air, blood pressure measurement may be performed without difficulty with a standard sphygmomanometer and stethoscope. Aneroid pressure gauges are preferred to mercury to avoid contamination of the closed environment. Monitoring of the electrocardiogram (ECG) and of intravascular pressures requires that transducer cables be plumbed through the chamber wall to preamplifiers outside the chamber. Standard intensive care monitors can be used to provide simultaneous measurement of arterial and PA pressures and intermittent measurement of cardiac output by thermodilution. If pressure bags are used to drive continuous flow systems, they must be repressurized during compression and vented before or during decompression. Pulmonary artery catheter balloon ports should also be left open to the chamber during compression and decompression.

Defibrillation could generate a fire if sparking occurs or combustible materials are present in the vicinity of the paddles. Sparking and heat generation can be minimized by using a low-resistivity conductive gel between the electrodes and the skin²⁵¹ or preapplied conductive disposable

pads.²⁵² To avoid pressure-related malfunction of the device, the defibrillator can remain outside the chamber and connected to the patient via through-hull high-voltage wiring. Despite the fear of causing fire, defibrillation has been carried out in multiplace chambers numerous times without arcing, fire, or explosion.^{253,254} Defibrillation cannot be safely performed inside a monoplace chamber compressed with O₂.

Intravenous Fluid Administration

In multiplace chambers, the air volume within the drip chamber will shrink during the compression phase of the HBOT and expand during decompression (which could force air into the intravenous line). Most intravenous infusion pumps work well inside a hyperbaric chamber at pressure (although there are electrical safety issues—see later). Glass bottles are best excluded from the chamber because of the possibility of explosive rupture during decompression.

Administration of fluids to patients inside a pressurized monoplace chamber requires an infusion pump outside the chamber capable of handling the pressure differential (up to 3 ATA or 1500 mm Hg pressure gradient across the chamber wall). Check valves can prevent unintended backflow of blood from the patient in the event of disconnection of the pump. Rigid arterial pressure transducer tubing helps to prevent kinking while the patient is inside the chamber.

Blood Gas Assessment and Ventilator Management

Blood gas measurement on arterial samples obtained from a patient inside a hyperbaric chamber can be erroneous. There are two reasons. At 1 ATA, O₂ tensions that exceed the ambient pressure are supersaturated and thus O₂ will rapidly diffuse out of the blood, lowering its tension. An additional error (extrapolation error) results from the impossibility of accurate PO₂ electrode calibration at PO₂ values exceeding approximately 700 mm Hg. Blood gas tension measurement should therefore ideally be performed inside the hyperbaric chamber by using an appropriately calibrated analyzer. If such a capability is not available, rapid analysis at 1 ATA of decompressed samples can produce acceptably accurate values.²⁵⁵

Another approach is to estimate the hyperbaric PaO₂ based on measurements obtained at 1 ATA. Using a measured PaO₂ and a calculated alveolar PO₂ (PAO₂) the ratio of the two (PaO₂/PAO₂, or a/A ratio) is a constant.^{104,105} On this basis, 1 ATA arterial blood gas values and the following equations can be used to predict PaO₂ at pressure.

The alveolar gas equation is required to calculate PAO₂:

$$\text{PAO}_2 = (\text{Pb} - \text{P}_{\text{H}_2\text{O}}) \cdot \text{FiO}_2 - \text{PACO}_2 \cdot \left(\text{FiO}_2 + \frac{1 - \text{FiO}_2}{\text{R}} \right)$$

where Pb and PH₂O are, respectively, ambient and saturated water vapor pressures, and R is the respiratory exchange ratio. If FiO₂ = 0.2, R = 0.8, and body temperature = 37°C, then this equation can be simplified to

$$\text{PaO}_2 = (\text{Pb} - 47) \cdot 0.2 - 1.2 \cdot \text{PCO}_2$$

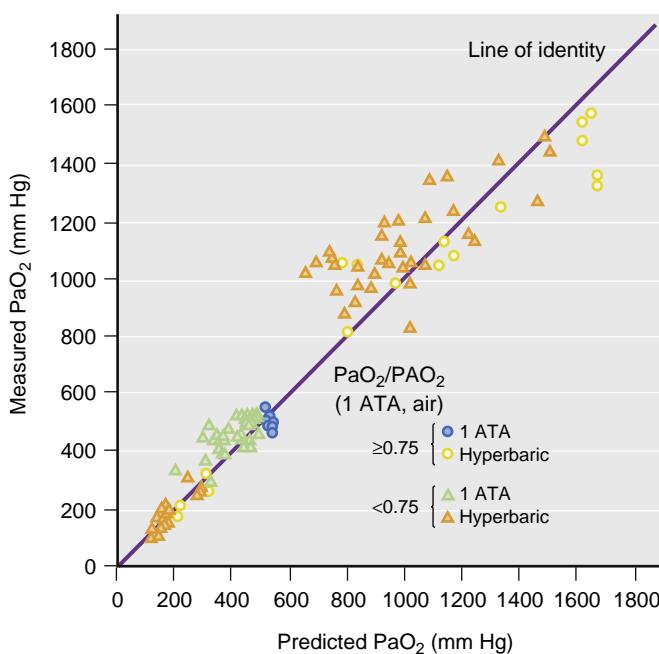


Fig. 75.14 Measured versus predicted arterial partial pressure of oxygen (PaO_2) at increased ambient pressure. Predicted PaO_2 is calculated from room air arterial blood gases, assuming that the arterial-alveolar PO_2 ratio ($\text{PaO}_2/\text{PAO}_2$, or a/A ratio) is a constant. Data are shown both for persons with normal lungs (a/A ratio ≥ 0.75) and for patients with gas exchange abnormalities (a/A ratio < 0.75). It is evident that PaO_2 predicted in this way is close to the actual measured PaO_2 . (From Moon RE, Camporesi EM, Shelton DL. Prediction of arterial PO_2 during hyperbaric treatment. In: Bove AA, Bachrach AJ, Greenbaum LJ Jr, eds. *Underwater and Hyperbaric Physiology IX. Proceedings of the Ninth International Symposium on Underwater and Hyperbaric Physiology*. Bethesda, MD: Undersea and Hyperbaric Medical Society; 1987:1127-1131.)

Having calculated PAO_2 and measured PaO_2 , the a/A ratio can then be obtained at 1 ATA. The predicted PaO_2 at increased ambient pressure while breathing 100% O_2 may then be obtained from this next equation:

$$\text{PaO}_2(\text{pred}) = \text{a}/\text{A} \cdot [(760 \cdot \text{ATA} - 47) - \text{PaCO}_2]$$

where ATA is the chamber pressure in atmospheres absolute. Although as yet there are no dose-response curves for HBOT, a reasonable aim is to achieve PaO_2 greater than or equal to 1000 mm Hg for routine chronic therapy and to as high a level as possible for treatment of acute necrotizing infections (Fig. 75.14).

A better monitor of tissue oxygenation may be mixed venous PO_2 (PvO_2), which, in the absence of left-to-right shunt, may be a reasonably accurate estimate of mean tissue PO_2 .²⁵⁶ Thus, a low value may indicate inadequate tissue oxygenation despite HBOT, as a result of insufficiently high cardiac output.

Normal values for pH and PCO_2 under resting clinical hyperbaric conditions are the same as they are at 1 ATA.¹⁰⁶ PCO_2 (and hence pH) do not change significantly in blood samples that are decompressed.

Mechanical ventilation in a hyperbaric environment presents a variety of challenges. The ideal requirements for ventilation include small size, no electrical requirement, absence of flammable lubricants, ability to operate on a

volume-cycled basis over a wide range of tidal volumes and respiratory rates, minimal modification requirement for installation, and ability to provide PEEP, as well as to ventilate in intermittent mandatory ventilation and assist/control modes.²⁵⁷ Additionally, the ideal gas source to actuate the ventilator should minimize the risk of combustion caused by buildup of static electricity.

As ambient pressure increases, gas density is proportionately raised, whereas relatively little change occurs in gas viscosity. Therefore, in regions of turbulent flow (i.e., in the large airways) airway resistance increases. Measurements of respiratory conductance (the reciprocal of resistance) during tidal breathing²⁵⁸ indicate that it varies with gas density according to the following formula:

$$G = G_0 \rho^\kappa$$

where G is lung conductance at gas density ρ , G_0 is the conductance at gas density 1.1 g/L (1 ATA), and κ is a constant that was found to have a mean value of -0.39. At 6 ATA, this equation predicts that lung conductance would decrease by 50%, which is equivalent to a doubling of pulmonary resistance. In addition, the higher gas density results in a less efficient distribution of ventilation, manifested by an increase in physiologic dead space.²⁵⁹ The effects of these two phenomena include higher airway pressures during mechanical ventilation and an increased ventilatory requirement. If ventilator settings are not adjusted to compensate for the higher dead space, a rise in PaCO_2 will occur.

Several types of ventilators have been used and tested in hyperbaric chambers. Pressure-cycled devices have been used with some success because their compactness admirably fulfills the requirement for small size. However, continual adjustment of rate and cycling pressure is necessary with changes in ambient pressure. Volume-cycled ventilators seem to work well, although at increased pressure some changes in rate may occur.

Two specific safety considerations exist. First, in any ventilator delivering enriched O_2 , a possible fire hazard can occur from O_2 buildup within the ventilator case or leakage of O_2 into the chamber. This hazard can often be offset by minor alterations (e.g., for a pneumatic ventilator, using air instead of O_2 to drive the bellows).²⁵⁷ The risk of ignition can be substantially mitigated by purging the device with an inert gas such as 100% nitrogen (see later). Air-filled endotracheal tube cuffs tend to lose volume during compression and reexpand during decompression. Appropriate cuff inflation volume can be maintained either by manually adjusting the air pressure within the cuff during compression and decompression or filling the cuff with water.

Other Medical Devices

Some electrical devices (e.g., pacemakers, automated internal cardioverter-defibrillators, intravenous infusion pumps) have been specifically tested at high ambient pressures; specific information can usually be obtained from the manufacturers. Ventricular assist devices may work satisfactorily, however the required rechargeable batteries (typically lithium) may be unsafe. To the authors' knowledge, at this time ECMO devices have not been tested or used during hyperbaric oxygen therapy.

Atmosphere Control

Chamber atmosphere safety includes management of levels of O₂, CO₂, and trace gases. In a multiplace chamber it is essential that the patient breathe as high a concentration of O₂ as possible (usually 98% or greater) while maintaining the chamber O₂ concentration close to 21% in order to minimize fire hazard. In some hyperbaric units, head tent O₂ concentration is routinely monitored. In others, the concentration is assumed to be high because of a high rate of O₂ flow through the head tent. Leakage of O₂ from head tents, masks, and ventilators tends to raise the chamber O₂ concentration. Typically, an upper limit of approximately 23% is used as a criterion for ventilating the chamber with air or small volumes of 100% nitrogen until the O₂ concentration decreases.

Significant elevations of inspired CO₂ concentration cause cerebral vasodilatation, increased cerebral blood flow and tissue PO₂, thus increasing the risk of CNS O₂ toxicity. Therefore, a typical standard for the upper limit for head tent CO₂ is 1% "surface equivalent" CO₂, equal to a partial pressure of 7.6 mm Hg. Using a nonscrubbing (open circuit) system, head tent O₂ flow rates of 40 to 60 L/min (measured at chamber pressure) are usually adequate to keep CO₂ levels at such a level. Chamber CO₂ is usually limited to less than 0.5% "surface equivalent" (3.8 mm Hg).

Trace gases that may enter the environment include CO and hydrocarbons from improperly functioning compressors or from automobile exhaust that may be near the compressor air intake. Volatile gases such as alcohol vapor from skin disinfectant solutions and mercury vapor from spillage of sphygmomanometer columns may also pollute the atmosphere. Trace gas concentrations that are innocuous at atmospheric pressure can be toxic under hyperbaric conditions because their pharmacologic or toxic effects are related to partial pressure. Mercury in any form should be excluded from hyperbaric chambers because spillage can cause acute toxicity in chamber occupants.

Considerations of battery use may have implications for chamber atmosphere control as well as fire hazards. All batteries release small quantities of hydrogen, although not usually in amounts that would be hazardous. Lithium-sulfur dioxide batteries carry a theoretic risk of sulfur dioxide discharge. Similarly, an objection exists to the use of mercury cells (now banned in the United States). Alkaline cells are considered safe, although temporary failure has been observed at extremely high ambient pressures (40-60 ATA).

Fire Hazards

Although fires in hyperbaric chambers are rare, they are usually lethal. The effects of fire at elevated ambient pressure are so devastating and so fast that fire extinguisher systems may not be effective.²⁶⁰ The very real risk of fire in hyperbaric chambers has been illustrated by recent accidents in which chamber fires were started by a hand warmer, a sparking toy, and other sources of ignition carried into the chamber in the patient's clothing. Minimization of these risks involves the following:

Controlling chamber O₂ concentrations (irrelevant in a monoplace chamber)

Minimizing the use of combustible materials within the chamber

Eliminating sources of heat and spark

Having a chamber fire-extinguisher system

The geometric increase in burning rate with increases in O₂ concentrations mandates careful monitoring of chamber O₂, as already noted. At increased ambient pressure, burning occurs more rapidly, even when O₂ concentration is 21%. Cotton garments are recommended because of their reduced risk of static electricity. Elimination of hair grease and humidification of the O₂ within the head tent can reduce the risk of hair ignition. Hydrocarbon lubricants (e.g., for stretcher wheels) can spontaneously ignite on contact with aluminum in the presence of high O₂ tensions and should therefore be replaced with nonflammable fluorocarbon lubricants.

Sources of sparks from electrically powered equipment should be minimized. Cigarette lighters, matches, and other sources of ignition should be excluded from the chamber. Plugging and unplugging electrical cables during hyperbaric treatments is a source of sparking that can be eliminated by taping all electrical plugs onto receptacles before compression. In multiplace chambers, the flammability of electrically powered devices (e.g., intravenous controllers) can be reduced by purging with 100% nitrogen through ports drilled in the covering, at a rate sufficient to keep O₂ concentration at a level that does not support combustion (typically at a flow rate of two to three times the internal volume per minute). Electrical systems used in monoplace chambers must comply with specific codes, which stipulate the types of switches, grounding, and insulation that can be used.²¹⁹

Volatile anesthetics can be combustible at 1 ATA in high concentrations. However, isoflurane and sevoflurane Dräger vaporizers have been tested up to 3 ATA using 100% O₂, with no evidence of spontaneous combustion at room temperature. Given the experience with halothane under hyperbaric conditions,²⁶¹ without any reported fires, and the resistance to combustion in 100% O₂ at 1 ATA, in the absence of a source of ignition it is unlikely that any of the modern fluorinated anesthetics pose a fire safety hazard in the hyperbaric environment.

Evaluation of a Patient for Safety of Hyperbaric Oxygen Treatment

In addition to ensuring that HBOT is indicated for the disease process in question, it is important to assess the patient in terms of general effectiveness and safety of HBOT. The following issues are pertinent:

Whether a sufficient elevation in PaO₂ can be obtained

Whether the patient can equilibrate middle ear pressure

Optimization of reversible obstructive lung disease and the presence of pulmonary bullae or blebs

Whether the patient is susceptible to claustrophobia

The calculation of predicted PaO₂ in the hyperbaric chamber was described previously. For example, a patient who has sufficient lung disease or injury such that PaO₂ during treatment would not exceed 1000 mm Hg would probably obtain marginal benefit from HBOT unless the reason for HBOT is gas bubble disease.

The ability to vent the middle ears may be assessed before treatment by observing directly the tympanic membrane with an otoscope while the patient holds his or her nose or performs a Valsalva maneuver. Movement of the eardrums indicates a patent eustachian tube and the ability

to equilibrate middle ear pressure. If otic barotrauma is difficult to avoid (e.g., with mental obtundation or the presence of an endotracheal tube) or because of a condition that may render the patient susceptible to inner ear injury (e.g., stapedectomy), myringotomy or tube placement can be performed prior to HBOT. The presence of pulmonary bullae or blebs represents a relative contraindication to HBOT because of the possibility of barotrauma, although a large clinical experience suggests that the risk is extremely low.

For patients requiring more than 20 to 30 HBOT sessions, periodic checks of visual acuity may be useful to detect hyperbaric myopia.

Because most hyperbaric chamber systems are small and cramped, patients who cannot tolerate enclosed spaces may require anxiolytic therapy to facilitate toleration of the HBOT.

Delivery of Anesthesia at Increased Ambient Pressure

A review of the problems of anesthesia under HBOT was published as a report to a committee of the American Society of Anesthesiologists.²⁶² This report explored various issues, including the potential for nitrous oxide to be used as a sole anesthetic.

Anesthesia while breathing spontaneously in a 100% O₂ atmosphere at 3 ATA was reported in the 1950s for radiation therapy.²⁶³ Patients were intubated after administration of pentobarbital 250 to 750 mg and meperidine 100 mg; some patients also received chlorpromazine 50 mg. Intubation was performed after succinylcholine and topical anesthesia of the airway. Patients breathed spontaneously.

Anesthesia may be required during the hyperbaric exposure. Ross and associates²⁶⁴ discussed the challenges of anesthesia up to 35 ATA, to provide care for injured divers while in a saturation diving system (e.g., in North Sea oil fields). These investigators suggested using intravenous instead of inhaled general anesthesia because of the problems of pollution of the chamber environment. Regional anesthesia was recommended whenever possible. The authors noted that muscle relaxants should be titrated to effect because some degree of pressure reversal at around 10 ATA has been reported.

Since the 1960s anesthesia has been performed at increased ambient pressure using a variety of agents for carotid endarterectomy,²⁶⁵ cesarean section,²⁶⁶ therapeutic lung lavage for patients with alveolar proteinosis (Fig. 75.15),^{209,210} emergency surgery in a saturation dive,²⁶⁷ open heart surgery,²⁶⁸ and enhancement of the effectiveness of irradiation of carcinoma.²⁶⁹

Inhaled Anesthesia. Inhaled anesthesia of any type can pollute the enclosed chamber atmosphere with anesthetic gases, which may exert pharmacologic effects on medical personnel inside the chamber, particularly at high ambient pressures. Russell and associates²⁷⁰ reported nitrous oxide concentrations in chamber air of 2500 ppm; ventilation of the chamber with air at a high rate (3500 L/min of air) was required to reduce the concentration to 25 to 75 ppm.

NITROUS OXIDE. The increased ambient pressure in a hyperbaric chamber allows nitrous oxide to be used at partial pressures exceeding its MAC.²⁷⁰⁻²⁷² Although in both studies induction of anesthesia by nitrous oxide was



Fig. 75.15 General anesthesia administered in a multiplace hyperbaric chamber for support of arterial oxygenation during therapeutic lung lavage. Lung lavage is performed by flooding one lung with normal saline via a double-lumen endotracheal tube. Protein washout is performed by cyclic filling and emptying with 400 L to 500 mL saline volumes until the effluent clears.³⁴¹ After a period of 60 minutes the contralateral lung is lavaged using the same technique. Depicted is a patient under general anesthesia with propofol/opioid receiving manual chest percussion during the emptying phase. (From Duke University Medical Center.)

rapid (<60 seconds), it was accompanied by tachypnea, tachycardia, hypertension, diaphoresis, muscle rigidity, catatonic jerking of the extremities, eye opening, and opisthotonus. After 2 to 4 hours of anesthesia, most subjects emerged rapidly from the anesthetic; however, the majority subsequently experienced nausea and vomiting, which was often severe.

A potential problem associated with nitrous oxide anesthesia at high ambient pressures is the possibility that tissues could become supersaturated during decompression, thus allowing nitrous oxide bubbles to form during decompression. This complication was not observed by Russell and associates,²⁷⁰ who used an empiric staged decompression schedule with a decompression stop for 30 minutes at 1.3 ATA while the patients breathed 100% O₂. Bubble formation can occur without decompression if the patient breathes one gas while surrounded by an atmosphere of another gas that is more diffusible. For example, breathing air while in a helium-O₂ environment at 5 to 7 ATA can lead to urticaria and vestibular dysfunction.²⁷³ The reason is rapid diffusion of helium into tissues that causes local inert gas pressure to exceed ambient pressure (isobaric gas counterdiffusion). This phenomenon can occur even at normal atmospheric pressure if a person breathes nitrous oxide-O₂ while surrounded by helium.²⁷⁴ Therefore, it is imperative that nitrous oxide never be administered in a helium-O₂ atmosphere.

Another risk of hyperbaric nitrous oxide is the dilutional effect of large volumes of dissolved gas entering the lungs during decompression, causing dilutional hypoxia. This situation can be prevented by administration of an O₂-enriched breathing mix for several minutes before decompression.

In patients who have recently engaged in scuba diving or have suffered DCS, nitrous oxide should be avoided, even

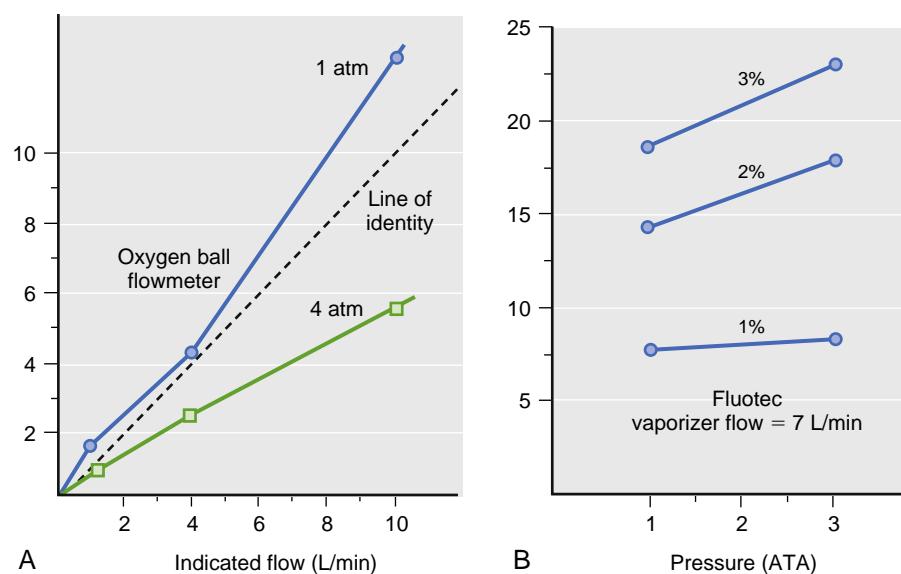


Fig. 75.16 Performance of an anesthetic vaporizer system at increased ambient pressure. (A) Flow characteristics of a rotameter system are shown. At 4 ATA, the actual delivered flow is less than 60% of the flow indicated by the rotameter. (B) Fluotec vaporizer output in partial pressure of halothane as a function of ambient pressure. Only small increases in delivered partial pressure are evident at 3 ATA, at the 2% and 3% settings. (From Committee on Hyperbaric Oxygenation. *Fundamentals of Hyperbaric Medicine*. Publication No. 1298. Washington, DC: National Academy Press; 1966.). ATA, Atmospheres absolute.

at 1 ATA, because its administration may result in tissue or blood bubble growth and recrudescence of pain or neurologic symptoms. Neurologic symptoms can occur after nitrous oxide anesthesia and apparent spontaneous resolution of DCS.²⁷⁵

HALOGENATED ANESTHETICS. The effect of a volatile anesthetic on a patient is proportional not to the alveolar concentration but to the partial pressure of the anesthetic. For example, the effect of 1% halothane at 1 ATA (with a partial pressure of 7.6 mm Hg) is equivalent to a 0.5% concentration at 2 ATA (with the same partial pressure). The anesthetic concentration of an anesthetic-specific calibrated vaporizer varies with ambient pressure, but in a manner such that delivered partial pressure remains constant (see Fig. 75.12). Because of the effect of increased gas density on this flow ratio, in practice the delivered partial pressure depends somewhat on ambient pressure. A slightly increased partial pressure of halothane delivered by a Fluotec vaporizer at 3 ATA has been observed (Fig. 75.16).²⁶² Our testing of a sevoflurane vaporizer revealed delivery of a constant partial pressure of anesthetic up to the maximum tested ambient pressure: 3 ATA.

Rotameter flowmeters calibrated at 1 ATA will indicate falsely high values at increased ambient pressure because of the increased gas density. McDowell²⁷⁶ reported the following relationship for rotameter flow:

$$\text{Flow}_{\text{actual}} = \text{Flow}_{\text{read}} \cdot \sqrt{\frac{\rho_1}{\rho_p}}$$

where $\text{Flow}_{\text{actual}}$ and $\text{Flow}_{\text{read}}$ are the actual and scale reading flows, and ρ_1 and ρ_p are the gas densities at 1 ATA and P ATA, respectively. This inaccuracy in rotameter performance up to 4 ATA has been confirmed by others (see Fig. 75.16).²⁶²

Intravenous Anesthesia. Intravenous anesthetics behave similarly and are unlikely to be affected within the usual clinical range of ambient pressure (see Chapter 23). There is no evident alteration in the pharmacokinetics of either meperidine¹³⁰ or pentobarbital¹³¹ at ambient pressures up to 6 ATA. For therapeutic lung lavage, we have provided general anesthesia at ambient pressures up to 3 ATA by using conventional doses of ketamine and benzodiazepines or propofol and narcotics with nondepolarizing muscle relaxants.

Regional Anesthesia. Regional anesthesia is likely to be both safe and effective in a hyperbaric environment by avoiding the requirement for mechanical ventilation. A bowel resection was performed at an ambient pressure of 6.75 ATA in a helium-O₂ environment by using local injection of lidocaine supplemented with parenteral meperidine.²⁶⁷ Extreme care should be taken to ensure sterile technique because of the propensity for enhanced bacterial growth in the warm, humidified environment of a hyperbaric chamber, particularly during saturation chamber exposures.

FUTURE DIRECTIONS IN HYPERBARIC OXYGEN THERAPY

Preoperative Hyperbaric Oxygenation

Preconditioning is described as the application of an insult to activate endogenous protective mechanisms to lessen the morphologic and functional sequelae of a subsequent insult. Ischemic preconditioning is the application of a brief period of ischemia, which activates endogenous protective mechanisms to reduce the damage from subsequent ischemic insults. Ischemic preconditioning was first described in canine myocardium and subsequently was shown to also exist in the brain. Since then, intense research in the field of pharmacology has ensued to identify other agents that

lead to preconditioning, such as volatile anesthetic agents, lipopolysaccharide exposure, heat, CNS seizures, hypoxia, and hyperoxia, and more recently hyperbaric hyperoxia.²⁷⁷

Several clinical trials have provided evidence that HBOT before cardiac or surgical procedures can improve outcome. Sharifi and associates described the use of HBOT to inhibit restenosis after percutaneous coronary intervention in acute myocardial infarction.²⁷⁸ In 2005, Alex and associates observed that repetitive pretreatment with three sessions of HBOT at 2.4 ATA before on-pump coronary artery bypass graft (CABG) surgery reduced neuropsychometric dysfunction and modulated favorably the inflammatory response after cardiopulmonary bypass.²⁷⁹ Yogaratnam and associates reported that preconditioning with a single session of HBOT at 2.5 ATA before on-pump CABG surgery improved left ventricular stroke work post-CABG surgery while reducing intraoperative blood loss, ICU length of stay, and postoperative complications.²⁸⁰ Li and associates demonstrated in patients undergoing on-pump and off-pump CABG that HBOT preconditioning decreased the release of cerebral and myocardial biochemical markers. Patients in the on-pump group pretreated with hyperbaric oxygen had a reduced length of ICU stay and decreased use of inotropic drugs.²⁸¹

The mechanism by which HBOT can be protective is not currently known but does not involve support of metabolism by increased tissue oxygen stores, since tissue and blood oxygenation are dissipated within minutes after hyperbaric exposure. The etiology of cerebral injuries is probably multifactorial, including cerebral microemboli, global cerebral hypoperfusion, inflammation, cerebral temperature modulation, and genetic susceptibility.^{277,282} The mechanism of protection therefore may include HBOT-induced oxidative stress due to increased reactive oxygen species (ROS) generation, which could induce ischemic tolerance similar to ischemia-reperfusion. Alternatively, HBOT preconditioning may reduce ischemia-reperfusion damage by reducing tissue leucocyte recruitment and activation, reduction of tissue edema, protection from cellular necrosis, reduction of tissue apoptosis, and improving tissue outcome and preservation.²⁸³⁻²⁸⁵ Another possible mechanism is upregulation of antioxidant enzymes such as superoxide dismutase,²⁸⁶ and possibly also heme oxygenase-1, as shown in a model of liver ischemia.²⁸⁷

Published data are highly suggestive of a beneficial effect of HBOT when administered before or after selected procedures.^{277,288} The role of HBOT in this setting will be determined by larger clinical trials.

Stroke

Several studies of middle cerebral artery occlusion in rats have demonstrated beneficial effects of hyperbaric oxygen.²⁸⁹⁻²⁹³ In an unselected case series of patients with acute stroke treated within 5 hours of symptom onset, some patients improved with HBOT where arterial PO₂ was 1100 to 1300 mm Hg.²⁹⁴ Since then there have been several clinical studies, with mixed results,²⁹⁵ perhaps because of the failure to start HBOT in a timely fashion²⁹⁶ or use of subtherapeutic PO₂. Interestingly, a recent double blind study reported improved outcome when HBOT was administered after the acute stroke, suggesting some effect on neuroplasticity.²⁹⁷

Acute Traumatic Brain Injury

Hyperoxia may have several protective mechanisms of action in severe traumatic brain injury (TBI), including improved oxidative metabolism and mitochondrial function, and reductions in intracranial hypertension, apoptosis, neuroinflammation, and free radical mediated damage. Support for efficacy of HBOT is provided by small clinical trials and mechanistic observations.²⁹⁸⁻³⁰¹ This has led to an NIH-supported multi-center trial of HBOT in acute TBI (Hyperbaric Oxygen Brain Injury Treatment Trial [HOBIT], [ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT02407028).

Summary

Environmental exposures can cause specific types of clinical conditions that require targeted therapy. Experience with compressed air and diving has led to new treatments using hyperbaric oxygen. Increasingly widespread use of HBOT to treat critically ill patients has created a demand for individuals skilled in using this technology. Planning and design of monitoring capabilities will enable optimal control of hemodynamics and oxygenation. Patient safety in this environment can be achieved with careful attention to detail that includes patient selection and monitoring, and chamber procedures. Optimized treatment schedules will evolve from studies of mechanism of action and further clinical trials. Advances in prevention and treatment of O₂ toxicity may allow more prolonged therapy than can currently be safely administered, and a more aggressive approach to ischemic and infectious syndromes.

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