



Anesthetics and anesthesia techniques: Impacts on perioperative management and postoperative outcomes

BRIAN M. PARKER, MD

Inhaled and intravenous anesthetic agents have diverse effects on the nervous, cardiovascular, and respiratory systems, as do local anesthetics administered neuraxially. New evidence suggests that they also alter the inflammatory response. This article provides an overview of how anesthetic agents and their method of administration differentially affect perioperative management and long-term postoperative outcomes.

■ QUALITIES OF GENERAL ANESTHESIA

General anesthesia involves the use of inhaled or intravenous anesthetic agents and has four broad objectives or components:

- Unconsciousness (also referred to as hypnosis)
- Analgesia (insensitivity to pain)
- Attenuation of sympathetic nervous system responses to the noxious stimuli of surgery
- Skeletal muscle relaxation.

■ INHALED ANESTHETIC AGENTS

Inhaled anesthetics, also known as volatile agents, include desflurane, enflurane, halothane, isoflurane, and sevoflurane. These fluorinated hydrocarbons are simple molecules with the ability to exert potent physiologic effects at very low concentrations. They are general anesthetics and are often used in conjunction with intravenous agents as well as with skeletal muscle relaxants.

The inhaled anesthetics act by making cells more porous to chloride ions via interactions with protein channels in the lipid membrane. It is unknown whether increased ionic movement occurs because

the drugs are incorporated within the lipid membranes, making them more fluid and causing conformational change of the ion channels, or whether the drugs interact with receptors in or near the protein channels, changing the channel conformation.

Effects on the central nervous system

Within the central nervous system, inhaled anesthetics interrupt transmission of excitatory and inhibitory pathways, causing amnesia and hypnosis. The cerebral cortex is affected, as are the more primitive areas of the brain, including the hippocampus, thalamus, and brainstem reticular formation. At high concentrations, the drugs penetrate the spinal cord and inhibit transmission at synapses, causing muscular paralysis and altering descending input from the brain.

Cardiovascular effects

The cardiovascular effects of inhaled anesthetics are direct and can be significant, with impacts on the following:

Contractility and diastolic function. All inhaled anesthetics alter the heart's ability to regulate calcium intracellularly, resulting in depressed contractility and diastolic dysfunction.

Heart rate. Some inhaled agents, like halothane, when used in high concentrations, cause profound bradycardia. High levels of desflurane, on the other hand, sometimes cause tachycardia, which is often seen in young, healthy patients.

Blood pressure. All the inhaled agents reduce arterial blood pressure, either through lowering systemic vascular resistance, contractility, and cardiac output, or by reducing left ventricular afterload.

Ischemia. Ischemia is of concern during general anesthesia, and many patients develop silent ischemia postoperatively. The strongest predictor of ischemia during surgery, however, is preexisting ischemia, a factor often more important than the surgical procedure itself or the anesthetic used.

Arrhythmias. Inhaled agents reduce sinoatrial

From the Department of General Anesthesiology, Cleveland Clinic Foundation, Cleveland, OH.

Address: Brian M. Parker, MD, Department of General Anesthesiology, Cleveland Clinic Foundation, 9500 Euclid Avenue, E31, Cleveland, OH 44195; parkerb1@ccf.org.

Disclosure: Dr. Parker reported that he has no financial relationships that pose a potential conflict of interest with this article.

node discharge, which can result in bradycardia and atrioventricular conduction abnormalities. Often, elderly patients without a documented history of cardiac disease but who report occasional “fluttering in the chest” or “strange rhythms” develop arrhythmias during anesthesia, which disappear as the agents wear off.

These drugs can have proarrhythmic or antiarrhythmic effects after myocardial ischemia and infarction: some induce arrhythmia but others may be protective. They also can prolong QT intervals, putting patients who have prolonged-QT syndrome at risk for torsade de pointes.

Several procedures, including many gynecologic and otolaryngologic surgeries, require local anesthetics and epinephrine to reduce blood loss. Combining inhaled anesthetics with epinephrine increases the risk of inducing ventricular tachycardia.

Myocardial protection. In addition to adverse cardiovascular effects, inhaled anesthetics can exert myocardial protective effects as well. All of the inhaled agents are weak coronary vasodilators. Isoflurane and other inhaled agents, despite what was once believed, do not cause coronary steal syndrome.¹ Instead, they appear to be cardioprotective against both reversible and irreversible ischemic insults, via several mechanisms:

- Reduced myocardial oxygen demand, owing to these agents' depressive effects
- Reduced release of reactive oxygen species after ischemia or an infarct has occurred
- Anesthetic preconditioning, in which cells are conditioned to tolerate ischemia through the reduced release of reactive oxygen species and through direct effects in the mitochondria of myocytes.

Pulmonary effects

Bronchodilation. Inhaled anesthetics are potent bronchodilators and theoretically help patients with chronic obstructive pulmonary disease or asthma. Bronchodilation occurs as a result of smooth muscle relaxation caused by depressed contractility, as also occurs in cardiac muscle. These agents also directly affect bronchial epithelium and indirectly inhibit local neural pathways within the lungs and spinal cord, resulting in reduced bronchoconstriction.

In reality, however, the manipulation of the airway required to administer general anesthesia can result in bronchospasm in patients with severe reactive airway disease, even if they are premedicated with steroids and inhalers, and inhaled anesthetics may actually

serve to stop the attack of bronchospasm.

Reduced functional residual capacity. At the same time, inhaled anesthetics also reduce functional residual capacity, increasing airway resistance. Patients with reactive airway disease have increased morbidity and mortality from anesthesia, which may be partially explained by this reduced functional residual capacity and the harm caused by mechanical ventilation.

Reduced clearance of mucus and foreign bodies. Inhaled anesthetics reduce ciliary movement, hampering the clearing of mucus and foreign bodies from the lungs.

Reduced surfactant production. Inhaled anesthetics impair the ability of type II alveolar cells to produce phosphatidylcholine, the main component of pulmonary surfactant.

Effects in spontaneously breathing patients. In patients who are spontaneously breathing, inhaled anesthetics can reduce both tidal volume and minute ventilation and cause tachypnea, resulting in increased “work of breathing.”

■ INTRAVENOUS ANESTHETIC AGENTS

Intravenous anesthetics are typically used to induce anesthesia, while inhaled agents are used to maintain general anesthesia afterwards. The exception is for children, in whom induction can be achieved with the inhaled agents halothane or sevoflurane alone.

Profiles of three representative agents

Three common intravenous anesthetics are propofol (an alkylphenol), thiopental (a barbiturate), and etomidate (an imidazole). Despite having different chemical structures, they all interact with GABA receptors in the brain and potentiate chloride movement, which may explain their ability to cause amnesia and hypnosis for short periods after administration.

Propofol is the most widely used anesthetic worldwide. It has both hypnotic and mild analgesic properties. It is antiemetic at low doses and has been also used for this purpose in patients undergoing chemotherapy.

Propofol causes mild cardiovascular changes: continuous infusion reduces both myocardial blood flow and oxygen demand. It decreases systemic blood pressure through vasodilation and direct myocardial depression, reduces cardiac output, stroke volume, and systemic vascular resistance, and causes minimal conduction changes.

Like the inhaled agents, propofol has bronchodilatory effects.

Thiopental and other barbiturates cause sedation,

loss of consciousness, hypnosis, and significant cardiac and respiratory depression. They have no analgesic properties.

Barbiturates cause blood to pool in veins as a result of venous dilation; they also reduce cardiac output through negative inotropy, increased capacitance, and decreased central sympathetic tone. Barbiturates also increase heart rate via baroreceptor actions. These drugs must be used cautiously in patients with cardiac disease who may not be adequately prepared with beta-blockers.

Etomidate causes minimal cardiac depression, so it is commonly used in cardiology for cardioversions and other procedures. It also causes minimal respiratory depression; patients may continue to breathe despite being completely unconscious unless a muscle relaxant is also given.

Etomidate has no analgesic properties. For invasive procedures, a narcotic or a beta-blocker is needed to attenuate the sympathetic nervous system responses.

■ LOCAL ANESTHETICS

Local anesthetics come in two classes: esters (eg, chloroprocaine, cocaine, tetracaine) and amides (eg, bupivacaine, lidocaine, ropivacaine). They vary in their half-lives and how they are used, and are widely administered for field blocks, peripheral nerve blocks, and neuraxial blocks (both spinal and epidural).

Cardiovascular effects

Many “complications” of neuraxial anesthesia (as well as of general anesthesia) are actually expected physiologic responses to particular drugs. For example, administering a local anesthetic neuraxially results in sympathectomy, which may slow the heart rate, reduce systemic vascular resistance, and lower arterial blood pressure. These responses are predictable for patients with or without cardiac disease.

Preblock hydration (ie, with up to 2,000 mL intravenous fluids, such as a colloid or crystalloid) does not prevent hypotension or otherwise adequately protect patients with cardiovascular disease who are about to undergo a neuraxial block.² In such patients, intravascular volume loading only transiently increases stroke volume and cardiac output because the fluid redistributes quickly. In these cases, pharmacologic cardiovascular protection is needed.

Respiratory effects

Local anesthetics administered neuraxially result in an unchanged tidal volume, while vital capacity decreases slightly.

Administering an unintentionally high spinal

anesthetic can result in respiratory arrest. There is a misconception that this occurs because of phrenic nerve dysfunction or respiratory muscle paralysis. However, this is not possible because of the small volume of drug being administered and the large anatomic distance from the brainstem. Respiratory arrest is actually caused by brain hypoperfusion: when fluids and drugs to increase blood pressure are administered, the patient's apnea resolves.³

Gastrointestinal effects

Nausea and vomiting develop after neuraxial administration of local anesthetics in many patients, probably as a result of hypotension caused by the sympathetic blockade and the resultant reduced arterial blood pressure as well as the unopposed parasympathetic response of increased peristalsis.

Hepatic blood flow is reduced as a result of spinal anesthesia, which can be dangerous for patients with liver disease. Many physicians hope to avoid problems by using a neuraxial block instead of a general anesthetic, but any neuraxial block reduces both hepatic blood flow and hepatic oxygen uptake.

Epidural vs spinal administration

Compared with spinal anesthesia, epidural anesthesia involves administration of larger volumes of local anesthetics over longer periods of time (such as for lower extremity revascularization procedures). Despite perceptions to the contrary, the onset of reduced arterial blood pressure is *not* more gradual or of less magnitude with epidural anesthesia as opposed to spinal anesthesia.

■ LOCAL VS GENERAL ANESTHESIA: EFFECT ON POSTOPERATIVE CLINICAL OUTCOMES

In the perioperative period, outcomes are influenced by anesthetics, the techniques used to deliver them, and patients' preexisting medical conditions. Although the long-term effects of anesthetics on outcomes have not been well studied, some data are beginning to emerge.

Local anesthesia improves cardiovascular outcomes

Three published studies have examined the outcomes of patients who received either epidural anesthesia and analgesia or general anesthesia without a regional block.

Christopherson et al⁴ reported a study of 100 patients scheduled to undergo lower extremity revascularization procedures who were randomized to epidural anesthesia followed by epidural analgesia or to general anesthesia followed by intravenous

patient-controlled analgesia. The postoperative revascularization rate was significantly higher in patients who received general anesthesia (20%) than in those who had epidural anesthesia (4%). No differences were found between the groups in postoperative myocardial infarctions or deaths. The institutional review board stopped the study early, citing a clear relative benefit of epidural anesthesia.

In another randomized trial, Tuman et al³ compared postoperative epidural analgesia or on-demand narcotic analgesia in 80 patients who underwent lower extremity revascularization under general anesthesia. In the patients randomized to epidural analgesia, epidurals were placed intraoperatively. The group that received epidural analgesia had fewer thrombotic events as well as fewer cardiovascular, infectious, and overall postoperative complications. Length of stay in the intensive care unit was also reduced in the epidural analgesia group.

Yeager et al⁵ randomized 53 high-risk patients who were about to undergo major noncardiac surgery to receive either epidural anesthesia and postoperative analgesia or standard anesthetic and analgesic techniques without an epidural. Patients who received epidural anesthesia and analgesia had a reduced postoperative complication rate, a lower incidence of cardiovascular failure, fewer major infectious complications, and fewer deaths. Hospitalization-associated costs were also 40% lower in the group that received epidurals.

Local anesthesia reduces blood loss

Compared with general anesthesia, epidural anesthesia is associated with less blood loss in patients undergoing total hip replacement or urologic procedures such as transurethral resection of the prostate or radical retropubic prostatectomy. Reduced blood loss probably results from the fact that sympathetic blockade reduces arterial blood pressure, redistributing blood flow from the surgical site.⁶ Central venous pressure is also reduced, as epidurals are performed without the positive pressure ventilation inherent in general anesthetic procedures.⁷

Local anesthesia reduces thromboembolic risk

Surgery enhances coagulation, and epidural and spinal anesthesia can help avoid this phenomenon. Local anesthetics directly inhibit platelets as well as reduce platelet-fibrinogen actions.⁸ In addition, sympathetic blockade increases lower extremity blood flow.⁹

In a meta-analysis of 13 randomized trials comparing local and general anesthesia in patients undergoing hip fracture repair, Sorenson and Pace¹⁰ demonstrated a 31% reduction in the incidence of deep venous thrombosis and pulmonary embolism in

patients receiving spinal or epidural anesthesia.

Similarly, Sharrock et al¹¹ retrospectively examined more than 15,000 patient records from one institution before and after the hospital transitioned from general anesthesia to epidural anesthesia for patients undergoing total hip and total knee arthroplasty. They found that the incidence of pulmonary embolism declined from 0.4% before the shift to epidural anesthesia to 0.1% after the shift.

■ DEPTH OF ANESTHESIA CORRELATES WITH POSTOPERATIVE OUTCOME

Recent inquiries into the relationship between anesthesia and postoperative outcomes have begun to focus on an issue specific to general anesthesia—the patient's intraoperative level of unconsciousness or their “depth” of anesthesia.

Two methods of measuring anesthesia depth

Until recently, depth of anesthesia was estimated only by observing patient physiologic responses (heart rate, blood pressure) to surgical stimuli and respiratory patterns as well as ocular position and pupillary diameter. Now, two currently available methods of measuring the depth of anesthesia use processed electroencephalic (EEG) information and convert the data into a unitless scale ranging from zero (no EEG activity) to 100 (fully conscious).

The bispectral index monitor gathers EEG data from the frontal cortex only but assumes uniform global data.

The patient state index monitor gathers EEG data from the front, back, and top of the head.

Data supporting a correlation with outcomes

The first studies suggesting a correlation between depth of anesthesia and patient outcomes were reported in abstract form. Weldon et al¹² used the bispectral index monitor to evaluate 907 patients while they underwent major noncardiac surgery of at least 2 hours' duration. They found that deeper maintenance anesthetic levels were associated with higher 1-year postoperative death rates in patients aged 40 years or older. Similarly, in a study of more than 5,000 patients, Lennmarken et al¹³ found that the risk of death within 1 year after surgery increased nearly 20% for every hour that a patient had a bispectral index monitor score of less than 45 (indicating deep hypnotic time) during the surgery, although the total duration of surgery or anesthesia did not affect mortality. Other risk factors for death included male gender, lower body mass index, and higher American Society of Anesthesiologists Physical Status score

(indicating poorer health) at the time of surgery.

More recently, Monk et al¹⁴ evaluated more than 1,000 patients who underwent noncardiac surgery and found that increased cumulative deep hypnotic time (bispectral index monitor score < 45) was a significant independent predictor of death within 1 year of surgery.

■ IS INFLAMMATION THE KEY TO POSTOPERATIVE RESPONSE?

Studies indicating that the depth of anesthesia is proportional to mortality raise the question of why this is so. We are increasingly recognizing the importance of inflammation in this process.

We now understand that inflammation is a driving force in many disease states, including atherosclerosis. In response to injury—such as a surgical procedure—tissue responds with vasodilation, increased vascular permeability, chemotactic peptides, and white blood cells. This starts the inflammatory cascade, mediated by plasma proteases, lipid mediators, peptides, amines, cytokines, and the leukocytes themselves.

Of particular interest are cytokines, which include the interleukins and tumor necrosis factor. Cytokines are released into the circulation from the site of injury during surgery, and are also elevated in patients with cancer or atherosclerosis.

An inflammatory role for anesthetics?

It is possible that anesthetics themselves may augment the cytokine inflammatory response, and this response may be dose-related, such that a deeper level of anesthesia may trigger a greater response. Two types

of cytokines exist—some are proinflammatory while others are anti-inflammatory—and anesthetics may alter their balance, possibly resulting in more complications, more infections, and a greater risk of death.

After surgery, lymphocyte levels and activity are reduced, a phenomenon that can be caused by intraoperative hypothermia as well as by a direct effect of volatile anesthetics. This may also predispose patients to poorer postoperative outcomes.

In addition, in patients who undergo total intravenous general anesthesia (eg, propofol without an inhalation agent), cytokine levels and other inflammatory responses postoperatively are significantly lower than in patients who receive a general anesthetic with an inhalation agent.¹⁵

■ SUMMARY

Inhaled and intravenous anesthetic agents have diverse effects on the nervous, cardiovascular, and respiratory systems. Spinal and epidural anesthetics also produce significant physiologic changes.

Some evidence points to improved immediate postoperative outcomes (in terms of cardiovascular outcomes, blood loss, and venous thromboembolism) for certain types of surgical procedures with epidural and spinal techniques relative to general anesthesia. Evidence is just beginning to emerge, however, on the relation between specific anesthetics and anesthetic techniques and long-term clinical outcomes. A proposed relationship between anesthetics, inflammation, and long-term outcomes has attracted increasing research interest but has yet to be well defined.

■ REFERENCES

- Sahlman L, Milocco I, Appelgren L, William-Olsson G, Ricksten SE. Control of intraoperative hypertension with isoflurane in patients with coronary artery disease: effects on regional myocardial blood flow and metabolism. *Anesth Analg* 1989; 68:105–111.
- Liu SS, McDonald SB. Current issues in spinal anesthesia. *Anesthesiology* 2001; 94:888–906.
- Tuman KJ, McCarthy RJ, March RJ, DeLaria GA, Patel RV, Ivankovich AD. Effects of epidural anesthesia and analgesia on coagulation and outcome after major vascular surgery. *Anesth Analg* 1991; 73:696–704.
- Christopherson R, Beattie C, Frank SM, et al. Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery. Perioperative Ischemia Randomized Anesthesia Trial Study Group. *Anesthesiology* 1993; 79:422–434.
- Yeager MP, Glass DD, Neff RK, Brinck-Johnsen T. Epidural anesthesia and analgesia in high-risk surgical patients. *Anesthesiology* 1987; 66:729–736.
- Blake DW. The general versus regional anaesthesia debate: time to re-examine the goals. *Aust N Z J Surg* 1995; 65:51–56.
- Rodgers A, Walker N, Schug S, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. *BMJ* 2000; 321:1493.
- Borg T, Modig J. Potential anti-thrombotic effects of local anaesthetics due to their inhibition of platelet aggregation. *Acta Anaesthesiol Scand* 1985; 29:739–742.
- Perhoniemi V, Linko K. Effect of spinal versus epidural anaesthesia with 0.5% bupivacaine on lower limb blood flow. *Acta Anaesthesiol Scand* 1987; 31:117–121.
- Sorenson RM, Pace NL. Anesthetic techniques during surgical repair of femoral neck fractures. A meta-analysis. *Anesthesiology* 1992; 77:1095–1104.
- Sharrock NE, Cazan MG, Hargett MJ, Williams-Russo P, Wilson PD Jr. Changes in mortality after total hip and knee arthroplasty over a ten-year period. *Anesth Analg* 1995; 80:242–248.
- Weldon BC, Mahla ME, van der Aa MT, Monk TG. Advancing age and deeper intraoperative anesthetic levels are associated with higher first year death rates [abstract]. *Anesthesiology* 2002; 96:A1097.
- Lennmarken C, Lindholm M-L, Greenwald SD, Sandin R. Confirmation that low intraoperative BIS levels predict increased risk of post-operative mortality [abstract]. *Anesthesiology* 2003; 99:A303.
- Monk TG, Saini V, Weldon BC, Sigl JC. Anesthetic management and one-year mortality after noncardiac surgery. *Anesth Analg* 2005; 100:4–10.
- Schneemilch CE, Bank U. Release of pro- and anti-inflammatory cytokines during different anesthesia procedures. *Anaesthesiol Reanim* 2001; 26:4–10.