Inhaled Anesthetics

This handout contains a written transcription of the narration in the online presentation (video). Please review the online presentation for additional material including interactive multimedia content, audio, and practice quizzes.

Case Study

You're about to anesthetize Jason, a 57-year-old with a history of ischemic heart disease. During the preoperative interview, Jason says he took his a.m. dose of metoprolol and notes that he takes lion's mane (a nootropic mushroom), as his memory has been failing him as of late. While formulating your anesthetic plan, you think back to this morning's conference where you learned that the pharmacy is investigating ways to reduce anesthetic drug costs. You think about incorporating nitrous oxide to reduce the amount of volatile agent, but is this a suitable technique for a patient with ischemic heart disease? What about Jason's memory problem? How might your anesthetic technique affect Jason's cognitive function after surgery? What does the current literature say about these topics? What else is new in this domain? Let's embark on a journey to discover the latest evidence that informs practice as well as take a few minutes to review the basic pharmacology of the inhalation agents.

Economics

In the year 2010, the cost of healthcare represented 18% of the gross domestic product. If the current trend persists, it's estimated that this cost will balloon to 40% of the GDP by the year 2050. To put the current situation into perspective, annual health care spending in the United States will nearly double from 2.6 trillion dollars in 2010 to 4.3 trillion dollars in 2020.

In an effort to temper the rise in healthcare expenditures, the American Medical Association advocates "value-based decision making" across all aspects of healthcare delivery. How can we as anesthesia providers affect good stewardship? One way to significantly reduce the economic impact is through the thoughtful selection and utilization of anesthetic drugs. Given that inhalation anesthetics account for nearly 20% of total anesthesia costs, this is one area where a few small tweaks in clinical practice can achieve meaningful and lasting results. In a cost-conscious environment, any reduction in drug costs that doesn't erode patient safety is worthy of consideration.

Dion's equation can be used to illustrate the cost of inhalation anesthetics:

> *Cost per MAC hour = [(Concentration vol%) x (FGF L/m) x (Time min) (Molecular weight) (Acquisition cost per mL)] / [(Anesthetic density g/mL) x (2412 which is molar volume of gas at 21°C)]*

As you can see, some variables are constant for a given agent, and so we can't manipulate them to lower the cost of utilization. Acquisition cost is primarily dependent on a hospital's negotiation power and acceptance of generic in lieu of branded drugs. While the vaporizer setting is determined by the patient's needs, the fresh gas flow rate remains under direct control of the anesthesia provider. The economic impact of the fresh gas flow rate cannot be over emphasized, where a lower flow rate conserves anesthetic through rebreathing and a higher flow rate contributes to waste by pushing more agent through the scavenger. It should be noted that a lower flow rate prolongs the time constant inside the breathing circuit, which can make rapid anesthetic titration more challenging, although this is less of an issue with agents of lower solubility.

A range of pharmacoeconomic studies reveal that an hour of volatile anesthesia delivery costs between $0.20 and $6.45 at a flow rate of 0.5 L/min and between $2.45 and $77.90 at a flow rate of 6 L/min. Drug selection also plays a role this context, because sevoflurane requires a minimum FGF of 1 L/min for under 2 MAC hours and 2 L/min after

that. To put this in perspective, sevoflurane at a fresh gas flow of 2 L/min costs nearly 20 times that of isoflurane at a flow rate of 0.5 L/min. In summary, the greatest cost savings for a given agent will always occur when using the lowest allowable flow rate for each agent.

Some consequences of drug selection manifest beyond interoperative care. A recent study examined the hypothesis that the choice of inhaled agent prolongs the duration of hospitalization. Beginning with a sophisticated, retrospective methodology, the authors studied adults undergoing inpatient noncardiac surgery who received either desflurane, sevoflurane, or isoflurane. Next, they conducted a prospective study where patients received sevoflurane or isoflurane.

The retrospective component of the study suggested that avoidance of isoflurane significantly reduced the duration of hospitalization. What came next is interesting; the prospective study component revealed no difference in hospital length of stay between isoflurane and sevoflurane. The authors concluded that inhaled anesthetic selection should not be based solely on the anticipated duration of hospitalization. Although there was no economic advantage in this institution, we must also be careful not to generalize these findings, as drug selection may be more likely to impact length of stay in settings with faster turnovers, such as ambulatory surgery centers. As an aside, the investigation we just described illustrates an important evidence-based practice teaching point. Studies that include both a retrospective and prospective component within the same body of work provide us with an opportunity to see how a research methodology can greatly influence a study's findings.

Pharmacokinetics

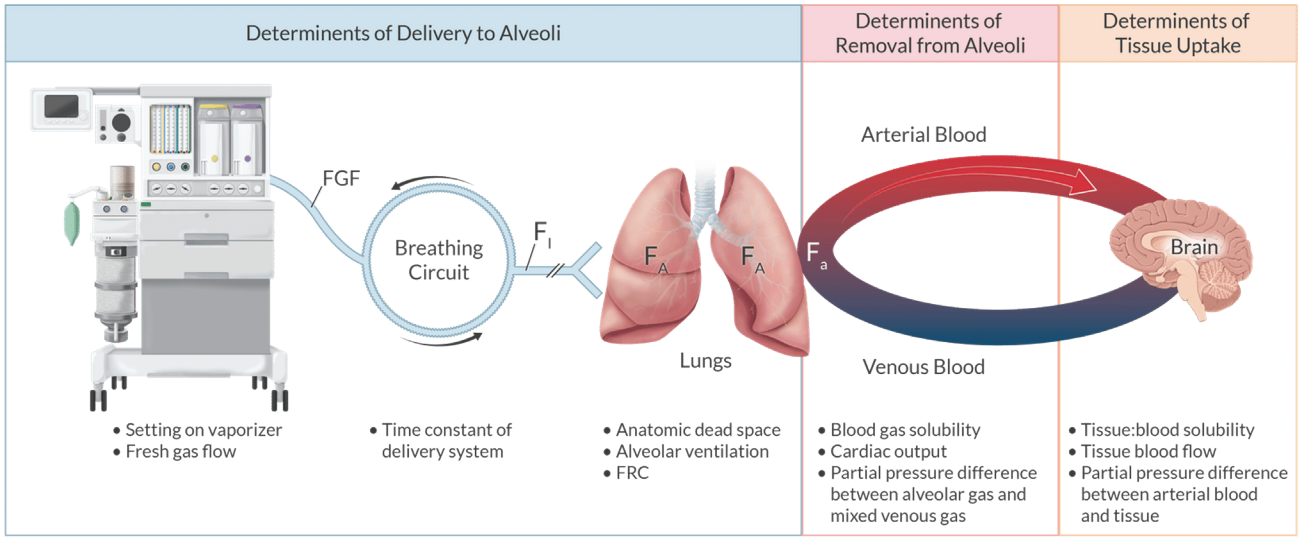
When administering an inhalation anesthetic, our main objective is to produce a state of anesthesia by establishing a partial pressure of anesthetic agent inside the patient's brain and spinal cord. In this video, we're going to review the basics of uptake and distribution.

The fresh gas flow, as set at the flowmeters on the anesthesia machine, provides the delivery mechanism for inhaled anesthetics. Turning on the vaporizer adds anesthetic vapor into the FGF as a percentage of the ambient pressure. We call this the inspired fraction of anesthetic or, more simply, F_I. As the patient ventilates, the anesthetic travels along a concentration gradient from the vaporizer towards the alveoli. We call alveolar concentration of anesthesia F_A. F_A is a critical value, because we recognize the relationship between the anesthetic concentration in the alveoli, the blood, and ultimately the central nervous system. Therefore, we can use F_A as a surrogate measure of the partial pressure of anesthetic in the brain, and thus the depth of anesthesia.

F_A is a function of: 1.) the rate of anesthetic delivery from the anesthesia machine to the alveoli and 2.) the rate of anesthetic transfer from the alveoli to the blood (otherwise known as uptake). Determinants of alveolar delivery include the setting on the vaporizer, the time constant of the delivery system, anatomic dead space, alveolar ventilation, and the volume of the functional residual capacity. Uptake into the systemic circulation is a function of the agent's blood:gas solubility (signified as lambda in the equation), the patient's cardiac output, and the arterial-venous partial pressure difference at the alveo-capillary interface. The F_A/F_I curve illustrates the speed at which F_A will approximate F_I. The F_A/F_I curve for nitrous oxide is highest (it has the fastest wash in period), followed by (in descending order) desflurane, sevoflurane, and isoflurane. Each curve's plateau is akin to steady state, where the amount of agent washed into the alveoli is roughly equivalent to the agent removed from the alveoli via uptake. How can we reach this plateau faster? Factors that increase the rate of wash in for a given gas include a higher FGF, higher alveolar ventilation, lower functional residual capacity, lower time constant, and lower anatomic dead space. Additionally, we can reduce the rate of uptake by selecting an agent with a lower blood:gas solubility, a lower cardiac output, and a lower P_a-P_v difference. Conversely, the rate of rise of F_A/F_I is reduced by slowing washing or enhancing uptake.

After inhalation anesthetic enters the blood, it is distributed to nearly all the tissues in the body. For each tissue type, uptake is dependent on tissue blood flow, solubility of the anesthetic in the tissue, and the arterial blood to tissue partial pressure gradient. Conceptually, we can divide all of the tissues into 4 compartments: the vessel

rich group, muscle, fat, and the vessel poor group. The vessel rich group consists of the heart, brain, kidneys, liver, and endocrine glands. It's only 10% of the body mass, yet it receives 75% of the cardiac output. Because the VRG receives a disproportionately large amount of the cardiac output relative to body mass, these organs receive most of the anesthetic agent during induction and are the first to equilibrate with F_A. After the VRG becomes saturated with anesthetic, the muscle group is responsible for the majority of continued tissue uptake. The muscle group is slower to saturate, because it receives a disproportionately lower amount of cardiac output and has a much larger capacity. The fat group is also soaking up anesthetic agent but at a slower rate. Once the muscle group is saturated, fat is responsible for any additional uptake. Because the halogenated agents are lipid soluble, the fat group functions as a high capacity sink capable of storing large amounts of agent. The vessel poor group consists of tendons, ligaments, cartilage, and bone. It doesn't receive enough blood flow to meaningfully contribute to anesthetic uptake.



Up to this point, we reviewed how to get inhalation anesthetic into the body, and now we'll discuss how to get it out. Elimination via the lungs is the primary way in which we can remove agent from the body. By turning off the vaporizer (or decreasing it below F_A), we reverse the concentration gradient from the body towards the breathing circuit. It should be noted that tissue redistribution still occurs during this time. Hepatic biotransformation is the secondary method of elimination. You can use the rule of 2's to remember how much each agent is degraded in the liver: desflurane equals 0.02%, isoflurane equals 0.2%, and sevoflurane equals 2 – 5%.

Pharmacodynamics: Respiratory

Airway reflexes are increased by desflurane and isoflurane and reduced by sevoflurane. Alveolar ventilation decreases as a function of a decreased tidal volume. The respiratory rate increases to provide partial compensation. The net result is that the CO_2 response curve shifts to the right ($PaCO_2$ rises for a given amount of alveolar ventilation). Even 0.1 MAC can impair the ventilatory response to hypoxia. Sevoflurane produces bronchodilation, and although isoflurane is a pungent gas, it too relaxes the airway smooth muscle. Desflurane is a pulmonary irritant and may precipitate bronchospasm in susceptible patients.

Pharmacodynamics: Cardiovascular

The halogenated anesthetics depress MAP in a dose-dependent fashion. The primary mechanism is a reduction in systemic vascular resistance from vasodilation. There is a small decrease in baseline contractility, however the myocardium remains preload responsive. Baroreceptor function is also affected. Halogenated anesthetics affect cardiac conduction by decreasing SA node automaticity, decreasing conduction velocity through the AV node, His-Purkinje system, and the ventricular conduction pathways. An increased duration of myocardial repolarization increases the

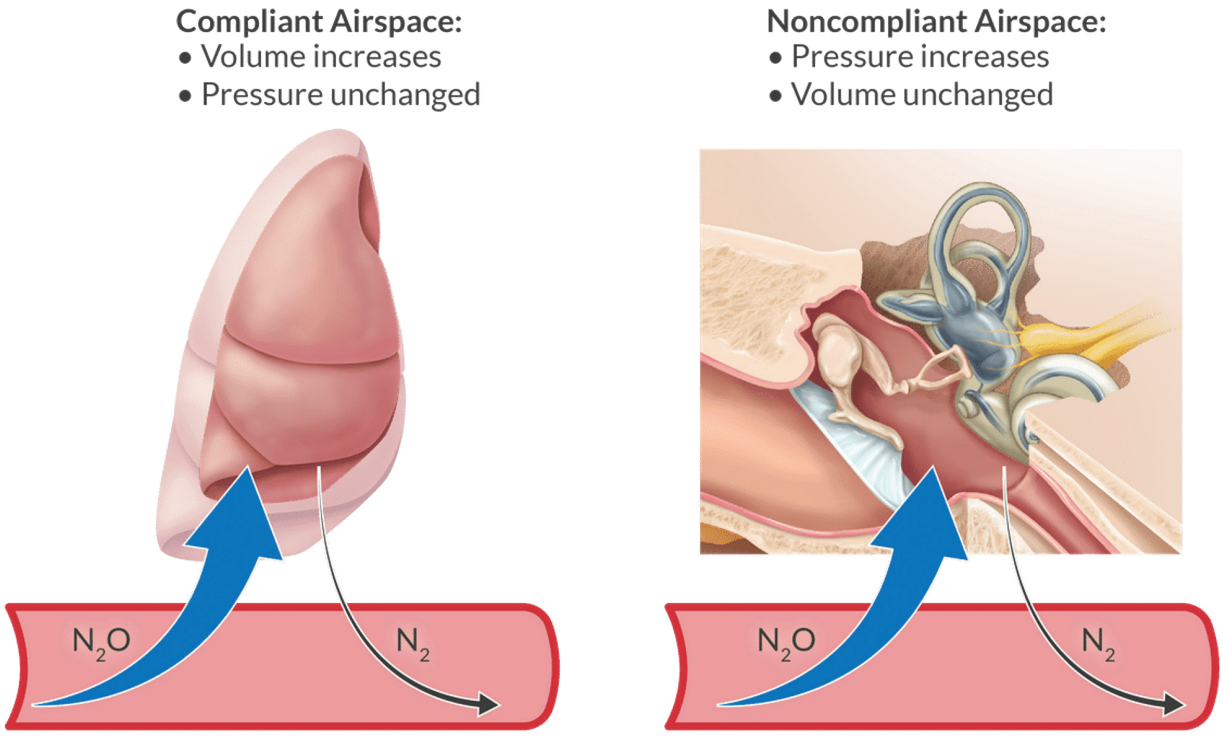
action potential duration as well as the QT interval. Rapid increases in desflurane, and to a lesser degree, isoflurane cause tachycardia. While isoflurane dilates the coronary arteries, the clinical concern about coronary artery steel is unjustified.

Pharmacodynamics: Neuro

Halogenated agents decouple the relationship between $CMRO_2$ and cerebral blood flow. Said another way, cerebral blood flow increases despite the fact that cerebral oxygen consumption is reduced. Volatile anesthetics reduce $CMRO_2$, but only to the extent that they reduce electrical activity. Once the brain is isoelectric, volatile agents cannot reduce $CMRO_2$ any further; 1.5 – 2.0 MAC is required to produce an isoelectric state. Volatile anesthetics disrupt autoregulation in a dose-dependent fashion. Cerebral blood flow becomes increasingly dependent on blood pressure as the concentration of the volatile agent is increased. Sevoflurane in high concentrations (2.0 MAC) can produce seizure activity. This is exacerbated by hypocapnia and is more common with pediatric inhalation induction. The volatile anesthetics produce muscle relaxation by acting in the ventral horn of the spinal cord. This potentiates the effects of neuromuscular blockers. Evoke potentials are impaired as evidenced by a decreased amplitude and increased latency.

Pharmacodynamics: Nitrous Oxide

Nitrous oxide stimulates the sympathetic nervous system, but it may produce myocardial depression when co-administered with an opioid. It is ~ 34 times more soluble than nitrogen. This means that for every 1 molecule of nitrogen that leaves a closed space, 34 molecules of nitrous oxide enter to take its place. This explains why nitrous oxide can increase middle ear pressure, expand an intraocular gas bubble, or increase the volume of the cuff of an endotracheal tube or LMA. Nitrous oxide supports combustion. It's associated with peripheral neuropathy following prolonged exposure, megaloblastic anemia, and may cause postoperative nausea and vomiting when the concentration exceeds 50%.



Theories of Unconsciousness

The mechanism of anesthetic-induced unconsciousness is a fundamental question in both anesthesiology and neuroscience, with links to the still hazy understanding of consciousness itself. The following is a summation of a great deal of literature examining the "bottom-up" and "top-down" theories of anesthetic action. The "bottom-up" theory suggests that inhalation anesthetics produce unconsciousness by affecting the cerebral structures that regulate the sleep-wake cycle, such as the brainstem, hypothalamus, and other subcortical nuclei. Therefore, we can say that the bottom-up theory suggests that anesthetic agents primarily affect "level" of consciousness, which we can define as the state of wakefulness or arousal.

By contrast, the "top-down" theory is evidenced by a growing body of literature illuminating how general anesthetics disrupt higher-order cognitive function in the cortical and thalamocortical pathways. It's possible that the observed changes in cortical function are not simply signatures of lower-order anesthetic actions, but rather the genesis of anesthetic-induced unconsciousness may begin in the higher-order pathways. Said another way, the "top-down" theory suggests that anesthetic agents suppress "content" of consciousness, which we can define as awareness of sensory stimuli. Of course, the "top-down" and "bottom-up" theories don't' have to be mutually exclusive. Rather, anesthetic agents could theoretically affect level and content of consciousness simultaneously. This topic becomes even more interesting as we use it as a lens to examine conditions such as the vegetative state, where patients appear awake but unable to willfully respond to sensory stimuli

The most recent research using functional magnetic resonance imaging (FMRI) highlights the importance of the cortical and thalamocortical pathways in the "top-down" theory, with the frontal-parietal network playing a key role. Indeed, unconsciousness produced by sevoflurane appears to be influenced by the drug's ability to disrupt information transfer in this area. Why is this important? While FMRI isn't likely to arrive in your operating room anytime soon, a deeper understanding of anesthetic action may provide a basis for newer generations of anesthetic depth monitors.

Anesthetic Risks at Extremes of Age: Young Child

For over a decade, the literature has been bombarded with case reports, retrospective studies, reviews, and expert opinions about the cognitive risks of general anesthesia in the developing brain. The fear is that general anesthesia promotes apoptosis (or programed cell death) in the young brain that may manifest as learning and/or behavioral problems later in life. Which drugs increase this risk? To date, animal data suggests that GABA agonists and NMDA antagonists are problematic. While opioids and dexmedetomidine are believed to be safe, the problem, of course, is that these agents are not complete anesthetics.

The long-term adverse neurodevelopmental effects that have been observed after prolonged or repeated anesthesia administration are difficult to interpret because of many confounders, most importantly the medical indication for anesthesia in the first place. That is to say, otherwise young healthy children do not undergo lengthy, or repeated procedures under general anesthesia, so one must question whether it's the drugs themselves or a complex interplay of additional factors that conspire to produce cognitive issues later in life.

Let's examine the current state of the science to gain a better understanding of this complex and rather frightening situation. The General Anesthesia vs Spinal Anesthesia (GAS) study and the Pediatric Anesthesia and Neurodevelopment Assessment (PANDA) study, both using strong methodological approaches including formal neurodevelopmental testing, revealed that a brief, single exposure to general anesthesia was not associated with poor neurodevelopmental outcomes. (13,14). The Mayo Anesthesia Safety in Kids (MASK) study comparing unexposed children, those with a single anesthetic exposure, and those with multiple exposure is currently underway with its results anticipated in the near term.

On December 14, 2016, the FDA issued the following warning: *"The U.S. Food and Drug Administration (FDA) is warning that repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains."* Naturally, this

warning was met with questions and concern from all stakeholders including parents, family members, perioperative care providers, as well as hospital administrators and insurance carriers. The problem is that, in many cases, there's simply no alternative to general anesthesia, although spinal anesthesia is a reasonable option for those children undergoing lower abdominal or lower extremity procedures. As we await more information from ongoing trials and encourage new trials to be initiated (such as outcomes studies specifically focused on fetal exposure) we should proceed with caution. Additionally, it's important to engage in compassionate conversation with the parents of young children who require anesthesia to get through a necessary operation.

Anesthetic Risks at Extremes of Age: Older Adult

Bedford, in 1955, was the first to formally recognize cognitive dysfunction following general anesthesia in aged adults, terming it, "adverse cerebral effects of anaesthesia on old people." Today, we call cognitive impairment in the aftermath of anesthetic drug exposure postoperative cognitive dysfunction (POCD).

At any age, the study of drug effects on the older brain is complex and proves daunting for reasons related to ethical concerns, logistics, patient safety, and the many factors that independently, or in combination, serve to influence outcome. It is further complicated by the need to establish baseline function (i.e., prior to drug exposure) as we define POCD as new cognitive impairment arising after anesthetic exposure. This requires careful comparison of pre- and post-exposure assessments.

In patients undergoing cardiac surgery, systematic review of high-quality studies reveals that, at time of hospital discharge, the incidence of POCD is 30-65%, and after several months it is in the range of 20 – 40% (reference). In patient's undergoing non-cardiac surgery, Monk reported the following incidence of POCD occurring at the time of hospital discharge: 36.6% at 18 – 39 years of age, 30.4% at 40 – 59 years of age, and 41.4% at greater or equal to 60 years of age [17].

Just like in children, anesthesia exposure is not an isolated, independent event as it occurs when the need for a noxious intervention arises. Given the well-appreciated inflammatory response associated with surgery, the role of neuroinflammation is gaining traction as a possible mechanism of POCD [18]. Ongoing work suggests that neuroinflammation impairs central neurotrophic factors, impairs neuronal plasticity, and weakens the blood-brain barrier, allowing pro-inflammatory molecules to enter the CNS and perturb intra-neuronal communication. Sevoflurane and isoflurane are halogenated ethers that may induce apoptosis and elevate levels of beta-amyloid protein, increase the vulnerability in states of Alzheimer disease-like pathology, and impair neuronal signaling pathways [19]. It should be noted, however, that these observations emerge from animal models.

Who is at greatest risk of POCD? The literature and experience to date find that the etiology, chronology, and ultimate outcome of POCD remains foggy, though there is strong association and overlap with risk factors and neuropathology observed in central degenerative processes. Risk factors identified thus far include old age, female gender, repeated exposure to general anesthetics, a high concentration of isoflurane, cardiac surger`y, and a low CSF Aβ1–42 and Aβ40–42/tau ratio (*Anesthesia and cognitive disorders: a systematic review of the clinical evidence*).

Where does this leave us? What can be concluded is that major surgery and general anesthesia do not cause POCD that extends beyond six months. Rather, it appears that concurrent diseases and the patient's preoperative condition in terms of his or her cognitive trajectory are most predictive of long-term POCD. Should POCD occur, there are no specific treatments available at this time.

Occupational Exposure

It is interesting (and concerning) that, despite daily exposure to low concentrations of sevoflurane, neither its harmfulness nor its harmlessness has been systematically proven. The National Institute for Occupational Safety and Health recommends an exposure limit of 2 ppm for sevoflurane as calculated from the time-weighted average for the length of the procedure. Despite this, and other published values, it's only logical that sevoflurane exposure should be kept as low as possible.

In the most recent, and elegantly performed study of its kind, researchers examined the ambient sevoflurane concentration around the anesthesia workstation. The LumaSense Photoacoustic Gas Monitor was used to measure sevoflurane concentrations during elective surgery in 119 patients. The amount of sevoflurane inhaled by the providers was estimated using a standard formula that has been validated in previous studies. The research findings revealed measurable concentrations of sevoflurane at the anesthesia workstation regardless of induction type, airway management device, or type of operating room ventilation system (laminar or turbulent flow).

The authors concluded that: 1) the anesthesia provider is chronically exposed to trace concentrations of sevoflurane during surgery. 2.) Inhalation inductions, use of an LMA, and turbulent-flow air conditioning systems were associated with a higher sevoflurane exposure. Interestingly, about 30% of the LMAs leaked sevoflurane into the anesthesia provider's breathing zone. 3.) The authors urged that although measured sevoflurane concentrations were lower than expected, every effort should be taken to minimize occupational sevoflurane exposure.

Nitrous Oxide & Cardiovascular Disease

Despite over a century of clinical use, a great deal of controversy continues to surround the use of nitrous oxide, with some providers using the drug routinely and others who believe the drug should be abandoned. Among these concerns is that nitrous oxide inhibits methionine synthase. This elevates the blood concentration of homocysteine, setting the stage for endothelial dysfunction. A high homocysteine level is used by some researchers and clinicians as a marker for cardiovascular risk and cardiovascular disease.

The ENIGMA-I trial (Evaluation of Nitrous Oxide in the Gas Mixture for Anesthesia) examined the effect of nitrous oxide on death and major cardiovascular complications at one year after non-cardiac surgery. Criticisms of this investigation are that it was underpowered and suffered from several flaws in its methodology.

ENIGMA-II was born of the need to address this important clinical question while employing a sounder methodology. ENIGMA-II was a multi-national, multi-institutional study, involving nearly 6000 patients undergoing non-cardiac surgery. Each patient received a general anesthetic and was randomized to receive either 70% nitrous oxide or 70% nitrogen as part of the anesthetic plan. Inclusion criteria required that the patient be at least 45-years-old and considered at risk for cardiovascular complications. Again, the goal was to explore the risks and benefits of nitrous oxide in this patient population. In this properly powered and methodologically sound study, there was no difference in death rate, myocardial infarction, stroke, or disability between the groups at one year after surgery. ENIGMA II essentially alleviated previous concerns about the effect of nitrous oxide on the heart and vascular systems. In the same issue of the journal, there was an editorial accompanying the ENIGMA-II trial which read as follows: *"The assessment of long-term follow-up of the ENIGMA II trial was critical in ensuring that the question of nitrous oxide's safety was fully addressed. Based on the results, we can conclude that nitrous oxide is safe for the general population and in patients with cardiovascular disease undergoing non-cardiac surgery when the concentration of oxygen is held constant."*

Nitrous Oxide for Labor Analgesia

Nitrous oxide has a long history of obstetrical use dating as far back as the late 1800s. In recent years, we've witnessed a resurgence of nitrous oxide for labor analgesia, most commonly by a blender device. Examples include Nitronox and Entonox. The parturient self-administers an inhaled dose of nitrous oxide (most commonly a 50% concentration) approximately 30 seconds before each uterine contraction, though its timing and use likely vary based on institutional protocol.

Interestingly, the use of nitrous oxide for labor analgesia varies considerably worldwide. For example, a 2002 study detailed its use in 50 – 75% of women in England and 60% of women in Finland. By contrast, the United States has been rather slow to embrace nitrous oxide for labor analgesia, however a variety of factors have conspired to create interest and urge its use. Examples include concerns about minimizing the stress of labor pain for both mother and fetus, a desire to avoid epidural analgesia, as well as enhancing the marketability and desirability of a hospital's labor services.

While a great deal is known about nitrous oxide and the maternal/fetal dynamic (e.g., nitrous is rapidly transmitted via the placenta and is rapidly eliminated by the neonate after birth once breathing begins, etc.), there is much that we are currently unclear about (e.g., adverse effects on the mother and newborn, its ideal dosing and timing, etc.)

The most recent systematic review on the subject revealed the following. The studies in the available literature are generally of low methodological quality and involved small sample sizes. The most common side effects include nausea, vomiting, dizziness, and drowsiness. When used in the obstetric setting, the occupational exposure to nitrous oxide is unknown.

Apgar scores in newborns whose mothers received nitrous oxide did not differ significantly from mothers who received another form of labor pain management or from mothers who received no analgesic interventions. Follow-up of newborns was very short, almost always limited to discharge from the delivery room. While not as effective as epidural analgesia, nitrous oxide is inexpensive and noninvasive. For those women who do not like nitrous oxide for whatever reason, or find it inadequate for pain relief, the intervention can be easily discontinued and switched to an alternative form of analgesia.

Key Points

Here are some key points for your practice.

- A great deal of recent and ongoing work reveals concerns about the neurotoxicity of anesthetic drugs especially in the very young and the elderly patient populations.
- A variety of agents, especially our inhalational anesthetics, may induce cellular apoptosis, dysregulate intra- and extracellular calcium, and cause protein malformation, misdistribution, and accumulation.
- Likewise, neurotoxic effects in the older brain may accelerate, promote, or even initiate neurodegenerative processes, especially where plasticity or 'cognitive reserve' may be limited or nonexistent.
- There will likely be continued efforts to develop drugs that have no lasting or toxic effect, as we deepen our understanding of the molecular mechanisms of neurotoxicity. In the meantime, we should tread cautiously and always be mindful of the potential downstream consequences of our interventions.