Volatile Anesthetics
Is a New Player Emerging in Critical Care Sedation?

Angela Jerath[1], Matteo Parotto[1], Marcin Wasowicz[1], and Niall D. Ferguson[2]

[1]Department of Anesthesia and Pain Medicine, Toronto General Hospital, Toronto, Ontario, Canada; and [2]Interdepartmental Division of Critical Care Medicine, University of Toronto, University Health Network, Toronto, Ontario, Canada

Abstract

Volatile anesthetic agent use in the intensive care unit, aided by technological advances, has become more accessible to critical care physicians. With increasing concern over adverse patient consequences associated with our current sedation practice, there is growing interest to find non–benzodiazepine-based alternative sedatives. Research has demonstrated that volatile-based sedation may provide superior awakening and extubation times in comparison with current intravenous sedation agents (propofol and benzodiazepines). Volatile agents may possess important end-organ protective properties mediated via cytoprotective and antiinflammatory mechanisms. However, like all sedatives, volatile agents are capable of deeply sedating patients, which can have respiratory depressant effects and reduce patient mobility. This review seeks to critically appraise current volatile use in critical care medicine including current research, technical consideration of their use, contraindications, areas of controversy, and proposed future research topics.

Keywords: sedation; volatile agents; critical care medicine; mechanical ventilation; extubation

Volatile agents have been used for more than 150 years to provide general anesthesia (1). Expansion of their role as sedatives with potentially other therapeutic properties for critical care patients has gained increasing interest over the last 30 years. Current sedation practice predominantly relies on benzodiazepines (midazolam, lorazepam, diazepam), propofol, and ketamine, which are commonly combined with opioids to provide analgesia and cosedation (2). The sedative and hypnotic properties of benzodiazepines and propofol are mediated by promoting central type-A γ-aminobutyric acid receptor activity, although propofol has wider effects on glycine, nicotinic, and muscarinic receptors (2, 3). Ketamine possesses hypnotic and analgesic effects by directly blocking *N*-methyl-D-aspartate receptors and hyperpolarization-activated cyclic nucleotide channels but also has wider action on cholinergic, opioid, and aminergic systems (4). Benzodiazepines are widely available, inexpensive, and familiar to critical care health professionals. However, there is growing concern surrounding the consequences of oversedation from high doses of these agents with slow metabolism and clearance, which can impact awakening times, duration of mechanical ventilation, hemodynamic stability, and perhaps even mortality (2, 5, 6). Prolonged and heavy use of benzodiazepines may also promote drug tolerance, withdrawal, delirium, and long-term neuropsychiatric disorders (depression, anxiety, and post-traumatic stress disorders) (2, 7–9). Propofol may induce propofol infusion syndrome and is associated with greater cost, hemodynamic instability, and hypertriglyceridemia during prolonged use in comparison to benzodiazepines (2, 10). Greater awareness of these effects has led to suggestions to use alternative nonbenzodiazepine strategies (Grade +2B) within the revised PAD (pain, agitation, delirium) guidelines published by the Society of Critical Care Medicine in 2013 (2). Dexmedetomidine is a newer agent that provides analgesia with "lighter" sedation promoting greater patient interaction. Limitations of

(Received in original form December 17, 2015; accepted in final form March 18, 2016)

Supported by a Merit Award, Department of Anesthesia, University of Toronto (A.J.) and the Academic Medical Organization, Ontario, Canada (A.J.).

Author Contributions: A.J. and M.P. made substantial contributions to the conception of the work. A.J., M.P., and N.D.F. made substantial contributions to drafting the work and revising it critically for important intellectual content. A.J., M.P., M.W., and N.D.F. provided the final approval of the version to be submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Correspondence and requests for reprints should be addressed to Angela Jerath, M.B. B.S., B.Sc., Department of Anesthesia, University of Toronto and University Health Network, Toronto General Hospital, 200 Elizabeth Street, Toronto, ON, M5G 2C4 Canada. E-mail: angela.jerath@uhn.on.ca

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 193, Iss 11, pp 1202–1212, Jun 1, 2016

Originally Published in Press as DOI: 10.1164/rccm.201512-2435CP on March 22, 2016
Internet address: www.atsjournals.org

dexmedetomidine include high cost, common adverse effects of bradycardia and hypotension, inability to potentially provide deeper sedation as a single agent when clinically indicated, and limited license of use (11, 12). Given these issues, what is the role of volatile agents for sedation of patients in the intensive care unit (ICU)? This review provides an ICU perspective covering sedative and other potential therapeutic properties of volatiles, drug limitations, and consideration of future areas of research.

Pharmacokinetics and Pharmacodynamic Properties of Volatile Agents

Modern-day volatile agents consist of sevoflurane, desflurane, and isoflurane. These small fluorinated hydrocarbons possess subtle structural differences that impact their physicochemical properties, onset speed, potency, dosing, metabolism, and clearance (13). Their mechanisms of action are described in Figure 1 (14). Volatiles have a rapid onset of action, with no significant concerns of drug tolerance or tachyphylaxis (15). Rapid offset is aided by drug clearance via simple pulmonary exhalation with low levels of hepatic metabolism (sevoflurane 5%, isoflurane 0.2%, desflurane 0.02%) and production of no significant active metabolites (13). This contrasts with benzodiazepines, propofol, and dexmedetomidine, which rely on adequate hepatic and renal synthetic function for metabolism and clearance. Systemic accumulation of these intravenous agents, particularly among elderly and ICU patients who often display hepatic and renal dysfunction, leads to reduced clearance and "drug hangover" that can slow patient awakening and extubation (2). Desflurane undergoes the least biotransformation and displays the fastest onset/offset, followed by sevoflurane and isoflurane. However, desflurane is not commonly used in the ICU, given its higher cost and need for specialist equipment, because its boiling point is close to room temperature. Despite the faster onset and elimination times, it is important to note that, like intravenous agents, volatile anesthetics are capable of causing deep sedation levels that can lead to respiratory depression and reduced patient activity during the sedation period. Thus, whatever the type of drug, even if it has faster onset and elimination times, all recommended guidelines for sedation-analgesia management should be used along with fast-acting agents (2). This includes use of validated sedation and pain scales, prescription of a sedation target, implementation of bedside nurse-driven sedation algorithms, as well as checking safety criteria for daily awakening test to avoid inappropriate deep or prolonged sedation.

Volatiles are available in liquid formulations that require vaporization before inhalation. Sedation for ICU patients is often achievable at doses approximately one-third of those required for general anesthesia (0.2–0.3 minimum alveolar concentration), although higher doses may be required, particularly in those patients requiring deeper sedation levels when clinically indicated (16). Their administration involves routine bedside gas monitoring, which provides capnography and unique ability to accurately monitor breath-by-breath volatile concentrations delivered to and exhaled by the patient (Table 1). The expired end-tidal concentration provides an excellent real-time method to monitor the cerebral concentration, which aids dose titration and minimizes risk of drug overdosing.

Technical Considerations for Use of Volatile Agents in Critical Care

Volatiles have been reserved in the ICU to manage medically intractable status asthmaticus, status epilepticus, and complex sedation scenarios in patients with high sedation requirements, such as burns, chronic pain, multiple surgeries, and history of drug abuse (15–18). It is recognized that this class of agents has powerful dose-dependent hypnotic, bronchodilator, and

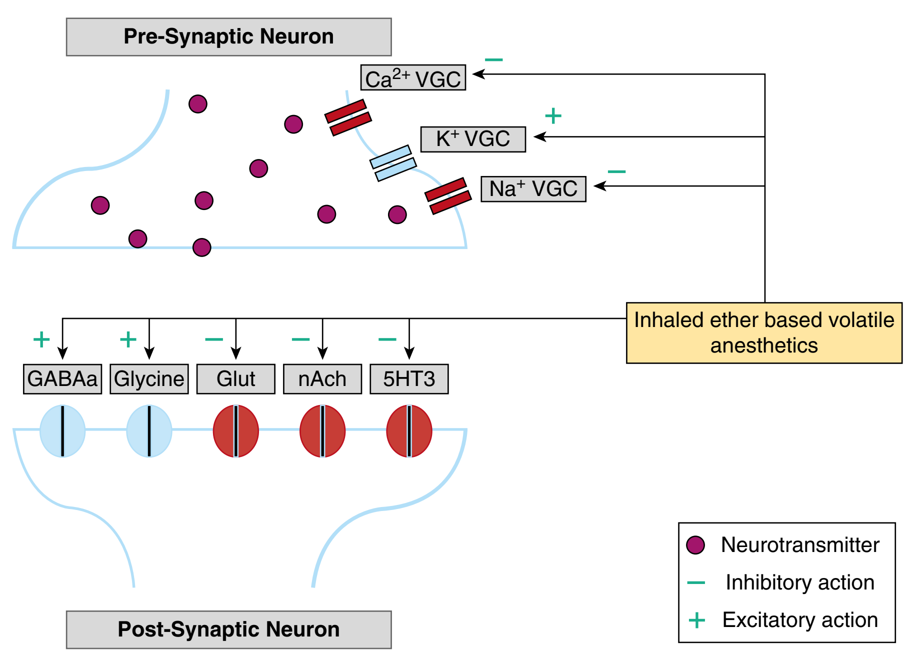

Figure 1. Modern theory of volatile activity involves complex interaction with multiple proteins on the pre- and postsynaptic nerve membrane as well as nonneural tissue. Volatiles reduce presynaptic excitation and neurotransmitter release through inhibition of sodium (Na^+) and several isoforms of calcium (Ca^{2+}) voltage-gated channels (VGCs) and promote repolarization through activation of potassium (K^+) channels. Volatiles reduce neurotransmitter activity in the postsynaptic membrane by enhancing inhibitory ion channel activity mediated by γ-aminobutyric acid (GABAa) and glycine receptors as well as inhibiting excitatory ion channels mediated by nicotinic acetylcholine (nAch), serotonin type 3 (5HT3), glutamate (glut), *N*-methyl-D-aspartate, and α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid receptors. Volatiles are also likely to possess widespread effects on G-protein–coupled receptors and intracellular signaling pathways on nerve and other cell types. This diagram provides a simplistic overview of volatile action on the synaptic junction; further details can be obtained from Campagna and colleagues (14).

Table 1. Potential Advantages, Disadvantages, and Settings for the Use of Volatile Anesthetics for Critical Care Patients

Advantages	Disadvantages	Potential Clinical Settings
Pharmacokinetic and pharmacodynamic properties		**Short-term (<24 h) postoperative sedation** Volatiles have been shown to provide shorter time to extubation and faster recovery of higher executive function when compared with intravenous sedatives.
Rapid onset/offset of action	Dose-dependent cerebral vasodilation, rise in intracranial pressure	
No significant tolerance/tachyphylaxis or withdrawal	Dose-dependent hypotension	
Drug clearance via pulmonary exhalation	Risk of malignant hyperthermia in genetically predisposed patients	
Low levels of hepatic metabolism, no active metabolites	Rise in serum fluoride levels but currently no evidence of nephrotoxicity	
Bronchodilation		**Longer-term (>24 h) sedation** Volatiles have shown faster time to extubation after discontinuation of sedation with opioid-sparing effects when compared with intravenous sedatives among general medical-surgical ICU patients.
Anticonvulsant effect		
No alteration to renal or hepatic laboratory markers		
Drug delivery and specialized equipment		
Easy to titrate to clinical endpoint	Specialized volatile delivery systems such as the AnaConDa and MIRUS devices	**Complex and failure of sedation** Scenarios using intravenous sedatives (e.g., burns, chronic pain, drug abuse, and status asthmaticus and epilepticus) are well managed using inhalational techniques.
Real-time bedside breath-by-breath monitoring of inspired and expired gas concentration	Gas scavenging and end-tidal gas monitoring required	
Expired (end-tidal) gas concentration provides good correlate of cerebral concentration	Recommended minimum tidal volume with AnaConDa is 350 ml and MIRUS is 300 ml	
	Use of volatiles in the ICU is off-label and specialized medical licensing is recommended	
	Optimal drug delivery may become impractical in patients with high-volume bronchial secretions	
End-organ effects		
Potential therapeutic end-organ protective properties on heart, lung, bowel, liver, kidney, and brain	Potential neurotoxicity on the developing brain and elderly patients	

Definition of abbreviation: ICU = intensive care unit.

anticonvulsant properties. Wider ICU uptake has been limited due to technical challenges of needing large anesthesia machines, scavenging systems to minimize atmospheric pollution, and limited familiarity with this class of drugs among intensivists. Over the past 20 years, the availability of specialized ventilators and miniature vaporizers, such as the Anesthesia Conserving Device (AnaConDa; Sedana Medical, Uppsala, Sweden) or the more recently investigated MIRUS system (Pall Medical, Dreieich, Germany), have simplified bedside volatile administration (16). However, use of these systems is subject to local availability, and "off-label" volatiles use in the ICU requires specialist medical licensing and government health approval. AnaConDa is more commonly available and is placed between the endotracheal tube and Y-piece of the ventilator circuit (Figure 2; *see* Figure E1A in the online supplement). Sevoflurane or isoflurane is infused into the device for vaporization before inhalation. Desflurane cannot be used with this device, given this agent's low boiling point. AnaConDa has a built-in carbon layer that allows for more than 80% recycling of the expired agent, which facilitates low infusion rates of 1 to 5 ml/h of volatile agent (16). As recommended by the manufacturer, this device is replaced every 24 hours. The AnaConDa must be used with a separate bedside gas analyzer and gas scavenging system. The MIRUS is a newer bedside vaporizing device that has several advantages over the AnaConDa. These include the ability to titrate volatile drug to a desired end-tidal concentration, integrated gas analysis, ability to monitor respiratory parameters (tidal volume, gas flow, ventilator pressures, positive end-expiratory pressure), and the ability to administer desflurane (Figure 2, Figure E1B). Currently, the MIRUS device is available in Europe, and AnaConDa is available in 20 countries predominantly located in Europe, Canada, and Australia (excluding United States).

The addition of the AnaConDa or MIRUS device to the breathing circuit will increase dead space by approximately 100 ml. Recent work from Chabanne and colleagues demonstrated an increased work of breathing when the AnaConDa device is placed in the breathing circuit without volatile sedation in adult patients with no history of chronic pulmonary disease (19). However, these altered respiratory parameters were normalized when low doses of sevoflurane were used with the AnaConDa device, which may be partially due to the bronchodilator effects of these agents and reduction in respiratory drive. Ventilator weaning of patients with low doses of volatile agents is feasible, but removal of the AnaConDa device from the breathing circuit when no sedation is required may be advisable to improve patient comfort and respiratory parameters.

Because of historical data linking high atmospheric volatile levels with infertility and spontaneous abortions, gas scavenging of expired volatiles has become routine in the operating room to ensure occupational atmospheric levels are maintained below recommended national safety standards of less than 2 parts per million in North America and less than 50 parts per million

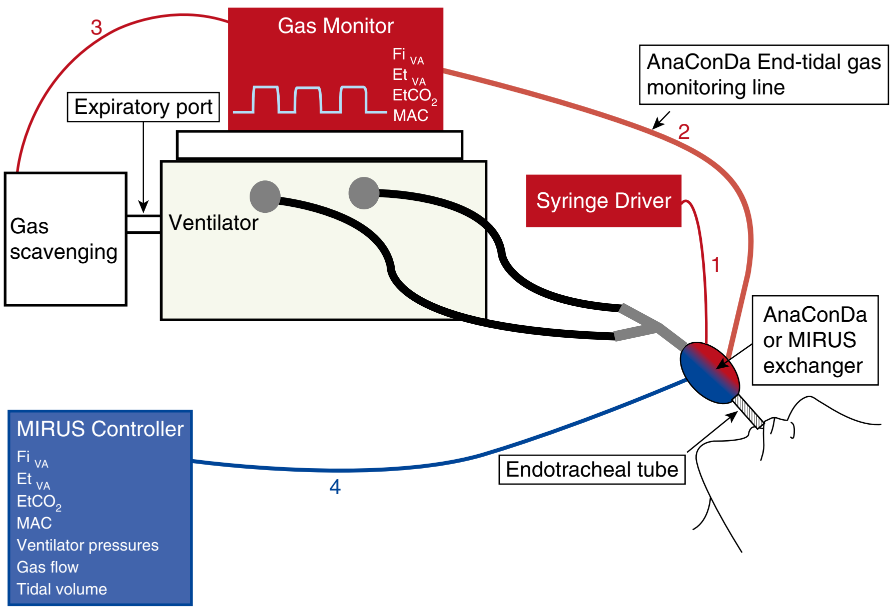

Figure 2. Bedside equipment setup for administering volatile agents. AnaConDa or MIRUS exchanger is placed between the endotracheal tube and Y-piece of the ventilator breathing circuit. These devices contain a reflector, which recycles expired volatile agent and humidifier/antibacterial filter. Use of these devices does not require any additional humidification and increases dead space of the breathing circuit by approximately 100 ml. Expired volatile agent is scavenged at the ventilator expiratory port. Equipment setup for AnaConDa is marked in *red* and MIRUS system in *blue*. The AnaConDa has a combined reflector and filter unit that is replaced every 24 hours. Liquid volatile agent is infused (*1*) into the AnaConDa with the aid of a syringe driver. A monitoring line (*2*) connects AnaConDa to a bedside gas monitor that measures minimum alveolar concentration (MAC), inspired and expired ($EtCO_2$) carbon dioxide, inspired (Fi_{VA}) and end-tidal (Et_{VA}) volatile agent concentration. An additional line (*3*) can be used to connect the gas monitor to the scavenging system. The MIRUS exchanger has separate reflector and filter units, which can be changed independently and allows the reflector to be used for up to 7 days. This reflector is also capable of measuring respiratory parameters (tidal volume, gas flow, and ventilator pressures). The MIRUS controller is an integrated end-tidal volatile agent feedback unit, which performs wash-in of the volatile agent to a desired minimum alveolar concentration, automatically adjusts volatile delivery with any change in ventilation settings, and monitors volatile and carbon dioxide gas concentrations (*4*).

in the United Kingdom (20, 21). Similarly, atmospheric pollution is minimized by combining standard room air exchanges with capturing expired waste gases using passive or active scavenging systems in conjunction with AnaConDa to ensure workplace safety. Passive gas adsorption uses charcoal canisters (Contrafluran, Novasorb) attached to the ventilator expiratory port (16). Excellent safety profiles have been demonstrated using active scavenging systems, which siphon waste gases to the main central hospital waste gas outlet system or use suction-assisted adsorption systems (22–24). Atmospheric pollution can be further reduced by connecting the gas analyzer's output using a Y-connector to the passive charcoal adsorber or active system. Room air recycling varies among institutions, between the operating room and critical care unit, and thus it would be advisable to check air recycling within the ICU rooms and also monitor volatile atmospheric levels using infrared spectrophotometric monitors or dosimeters (22, 24). To minimize drug spillage and inhalation of volatile agents, filling of the AnaConDa syringe should be performed by trained personnel.

Cost analyses of the use of volatiles for ICU sedation have been performed by several European centers where the AnaConDa has been more commonly used and retails for 70 to 80€. In a series of 15 patients who received isoflurane for an average of 4 days, the cost of midazolam/sufentanil sedation (171 ± 101€) was comparable to isoflurane/sufentanil (122 ± 44€), which was inclusive of drug, device, and scavenging costs (25). A short-term postoperative sedation randomized controlled trial comparing desflurane to propofol sedation showed overall drug costs for volatiles was lower (95€ desflurane vs. 171€ propofol) and cost neutral with the addition of the AnaConDa device (26). Other centers using sevoflurane for short-term sedation have shown that volatile sedation is more expensive than intravenous propofol sedation (27). Currently, we lack a cost-effectiveness analysis that takes into account any beneficial clinical outcomes such as faster awakening, extubation times, and lengths of ICU stay.

What Are Potential Indications for Volatile Agents in ICUs?

Several randomized controlled trials have assessed volatiles in the ICU, but the majority of trials have assessed them as short-term postoperative sedatives (Table 2) (26–32). An early trial conducted by Kong and colleagues in 1989 compared isoflurane to midazolam in 60 adult medical-surgical ICU patients sedated for approximately 18 hours (28). Patients who received isoflurane showed faster median (range) extubation times at 60 minutes (30–135 min) compared with 195 minutes (50–1,080 min) in the midazolam group. These results are supported by other recent trials conducted predominantly in cardiac surgical patients (Table 2) (27–30). Several trials have also shown faster patient recovery of higher executive function as evidenced by obeying commands or writing home address (28). Rapid drug clearance via pulmonary exhalation is likely to explain faster emergence time in patients sedated with volatiles (16).

Beyond postoperative sedation, similar findings have been identified among general ICU patients sedated for longer periods (33–36). In 2004, Sackey and colleagues compared isoflurane to midazolam sedation in 40 medical-surgical patients sedated for up to 96 hours. Mean times to extubation and to follow verbal commands were 10 versus 250 minutes and 10 versus 130 minutes in the isoflurane and midazolam group, respectively (33). Recently, a three-arm randomized controlled trial compared

Table 2. Summary of the Main Findings from Several Key Randomized Controlled Trials Assessing Volatile-based Sedation

Study	Sample Size, ICU Setting	Duration of Sedation (*h*)	Sedation Agents	Main Study Findings
Short-term sedation trials (<24 h)				
Kong *et al.*, 1989 (28)	60, MSICU	18	Isoflurane vs. midazolam	Time to extubation (min): isoflurane 60 [30–135] vs. midazolam 195 [50–1,080]* Time to write home address (min): isoflurane 58 [20–270] vs. midazolam 275 [75–1,440]†
Meiser *et al.*, 2003 (26)	60, SICU	9.7–11.5	Desflurane vs. propofol	Time to BIS 75 (min): desflurane 4.5 (3–5.8) vs. propofol 7.7 (5.2–10.3)† Time to extubation (min): desflurane 7.7 (5.8–10) vs. propofol 13.5 (9.7–18.9)† Time to recalling birth date (min): desflurane 10.5 (7.7–15.5) vs. propofol 19.4 (13–31.8)† Psychometric tests: no difference in psychometric performance except faster recall of a five-word memory test in desflurane group Hemodynamics: no difference in heart rate or mean arterial pressure during sedation. Higher postextubation systolic pressure in desflurane group (152.3 ± 22 mm Hg) than in propofol group (138.3 ± 26.9 mm Hg)*
Röhm *et al.*, 2008 (27)	70, CICU	8.1–8.4	Sevoflurane vs. propofol	Time to extubation (min): sevoflurane 21.5 (8–46) vs. propofol 150.5 (69–299)* Ventilator time (h): sevoflurane 9 ± 4 vs. propofol 12.5 ± 5.8* ICU length of stay (h): sevoflurane 27.8 ± 14 vs. propofol 39.6 ± 35.5, $P = 0.062$ Hospital length of stay (d): sevoflurane 10.6 ± 3.3 vs. propofol 14 ± 7.7* No difference in shivering, nausea, vomiting, renal insufficiency, or patient mortality
Hellström *et al.*, 2012 (29)	100, CICU	2.8–3.1	Sevoflurane vs. propofol	Time to extubation (min): sevoflurane 10 [10–100] vs. propofol 25 [21–240]† ICU length of stay (h): sevoflurane 22 (5) vs. propofol 22 (4), $P = 0.364$ Hospital length of stay (d): sevoflurane 6 (2) vs. propofol 6 (2), $P = 0.866$ No difference in shivering, nausea, vomiting, or ICU Memory tool test
Steurer *et al.*, 2012 (31)	117, CICU	Not specified‡	Sevoflurane vs. propofol	Troponin T: lower in sevoflurane group on postoperative Day 1 (adjusted difference, –0.2; 95% CI, –0.4 to –0.02)* No statistically significant difference in risk-adjusted models of oxygenation index (Pa_{O_2}/FI_{O_2}) at 4 h and first postoperative day, postoperative respiratory complications, postoperative nausea and vomiting, or ICU or hospital length of stay
Jerath *et al.*, 2015 (30)	157, CICU	<12 h	Isoflurane/sevoflurane vs. propofol	Time to extubation (min): volatile 182 (140–255) vs. propofol 291 (210–420)† Hemodynamics: volatile group demonstrated higher postoperative cardiac output with vasoplegia requiring more common use of vasoconstrictor agents No difference in postextubation pain scores, opioid requirement, nausea, vomiting, shivering, or postoperative ICU or hospital length of stay
Longer-term sedation trials (>24 h)				
Spencer *et al.*, 1991 (36); Spencer and Willatts, 1992 (35)	60, MSICU	36	Isoflurane vs. midazolam	Spontaneous ventilation (h): isoflurane 0.25 [0.1–1.0] vs. midazolam 3 [0.17–42]† Time to extubation (h): isoflurane 0.9 [0.2–70] vs. midazolam 15 [1.3–223]† Write address (h): isoflurane 1 [0.2–71] vs. midazolam 21 [2–72]† Plasma fluoride (μmol/L): isoflurane peak mean concentration 20.01 (95% CI, 13.3–26.73) vs. midazolam peak concentration 6.76 (95% CI, 5.09–8.44) No correlation between plasma fluoride level and serum creatinine No difference in ICU discharge time or systolic blood pressure

(Continued)

Table 2. (*Continued*)

Study	Sample Size, ICU Setting	Duration of Sedation (*h*)	Sedation Agents	Main Study Findings
Sackey *et al.*, 2004 (33)	40, MSICU	32–52	Isoflurane vs. midazolam	Time to extubation (min): isoflurane 10 ± 5 vs. midazolam 250 ± 270[†] Time to obey verbal command (min): isoflurane 10 ± 8 vs. midazolam 110 ± 130* Time within target sedation (%): isoflurane 54 vs. midazolam 59 Opiate requirement (mg/h): isoflurane 2.7 ± 2 vs. midazolam 4.2 ± 3.8 No difference in patient mortality
Mesnil *et al.*, 2011 (34)	60, MSICU	50–57	Sevoflurane vs. propofol vs. midazolam	Time to extubation (min): sevoflurane 33.6 ± 13.1 vs. propofol 326.1 ± 360.2 vs. midazolam 599.6 ± 587[†] 24-h postextubation morphine use (mg): sevoflurane 20 (4.5–30) vs. propofol 40 (30–60) vs. midazolam 76 (55–111)[†] No. hypnotic dose changes/day (n): sevoflurane 1.5 (0–2.5) vs. propofol 5 (4–8.5) vs. midazolam 3.5 (2–5)[†] Vasoactive drug use (%): sevoflurane 35 vs. propofol 48 vs. midazolam 42[†] No difference in renal or liver function

Definition of abbreviations: BIS = bispectral index; CI = confidence interval; CICU = cardiac surgical intensive care unit; ICU = intensive care unit; MSICU = medical surgical intensive care unit; SICU = surgical intensive care unit.
Data presented as median [range], median (interquartile range), or mean ± SD. Further results are awaited from a trial by Soukup and colleagues (32).
*$P < 0.05$.
[†]$P < 0.001$.
[‡]Duration of sedation not clearly specified but expected to be at least 4 hours and likely <24 hours given this is a postcardiac surgical population.

sevoflurane to propofol and midazolam in 60 adult ICU patients using a sedation-analgesia algorithm for up to 96 hours (34). Extubation occurred at 33 minutes after discontinuing sedation for sevoflurane, compared with 326 minutes for propofol and 599 minutes for midazolam. Volatile agents may possess mild analgesic properties, with both studies demonstrated that volatile sedation significantly reduced morphine consumption by 35 to 74%. These opioid-sparing effects may be attributable to volatile mediated *N*-methyl-D-aspartate receptor blockade or simply a more stable sedation profile (34). A larger adequately powered randomized controlled trial is now required to further assess these outcomes.

All sedatives have dose-dependent hemodynamic effects. The effect of volatile sedation on cardiovascular stability has produced mixed results, with several trials in medical-surgical patients showing lower need for vasoactive drug support in comparison to intravenous agents, but higher vasoactive support has been seen in studies in neuro ICU patients (34, 37, 38). Current data have also demonstrated no significant difference in other adverse effects of volatiles, such as postextubation shivering, hepatotoxicity, or nausea and vomiting (30). To date, these outcomes have not resulted in faster ICU or hospital discharge beyond one single-center study (27). This may be due to other factors independent of sedation, such as close monitoring of complex patients, ongoing hemodynamic management, and availability of general ward beds. Recently, Bellgardt and colleagues showed reduced in-hospital mortality (adjusted odds ratio, 0.35; 95% confidence interval, 0.18–0.68; $P = 0.002$) and 1-year mortality (adjusted odds ratio, 0.41; 95% confidence interval, 0.21–0.81; $P = 0.01$) in a retrospective study of 200 surgical patients sedated with isoflurane compared with midazolam/propofol for more than 96 hours (39). Reasons for lower mortality in the isoflurane group may include potential antiinflammatory, end-organ protective properties and avoidance of oversedation. However, in this nonrandomized study, selection bias possibly with exclusion of hemodynamically unstable patients or those exhibiting significant airway disease (hypercarbia, severe acute respiratory distress syndrome) may have played a role in explaining these very large treatment effects.

Nonsedative Properties of Volatile Anesthetics

Potential therapeutic end-organ protective properties of volatile anesthetics have attracted the attention of researchers and clinicians. Among these, the most extensive laboratory research has been conducted in pharmacological conditioning of the heart. This is a phenomenon whereby transient exposure to an anesthetic agent protects the heart from the harmful consequences of myocardial ischemia and reperfusion injury, with cellular and molecular mechanisms that appear to mimic those of ischemic pre- and postconditioning (40).

Volatile anesthetics were shown to protect the heart both *in vitro* and *in vivo* when applied shortly before a period of prolonged coronary artery occlusion (41). This phenomenon is called anesthetic preconditioning and also appears to be present if volatiles are applied up to 72 hours before a prolonged ischemic event (“delayed” preconditioning) (40). A potentially more clinically relevant phenomenon is that of postconditioning. Volatiles decrease infarct size when administered immediately after the ischemic event at the onset of reperfusion (40). These properties may play a role in several clinically relevant scenarios in the ICU. One interesting application may be during cardiopulmonary resuscitation. In a recent rat study, Knapp and colleagues showed animals who received sevoflurane for 5 minutes before, during, or after resuscitation in a model of ventricular fibrillation had improved contractility 24 hours after restoration of spontaneous circulation with a higher ejection fraction (42). Similarly, Meybohm and colleagues demonstrated sevoflurane postconditioning reduced apoptosis, proinflammatory cytokine expression, myocardial damage, and dysfunction after cardiopulmonary resuscitation in the early postresuscitation period in a study on pigs (43). Other experimental work has shown ischemic postconditioning after 15 minutes of untreated cardiac arrest provided neuroprotection and improved 48-hour survival (44).

Many human studies have been conducted in cardiac surgical populations aiming to show reduced myocardial damage as assessed by levels of cardiac biomarkers (troponin, creatinine kinase-MB, brain natriuretic peptide) (31, 45, 46). Human translation of the above findings has produced mixed results in measurement of serum troponin levels, with no strong evidence supporting improved long-term patient survival (31, 45, 47, 48). Reasons underlying these equivocal findings include the need for potentially higher volatile doses that may lead to hemodynamic instability in complex patients and inability to mirror the controlled environments of healthy animal experiments.

The beneficial effects of volatile anesthetics on ischemia reperfusion and other types of injuries have been shown in experimental and clinical studies assessing other organ systems such as lung, liver, bowel, kidney, and brain (49–53). Volatiles have shown to confer protection and antiinflammatory effects in various clinical studies and animal models of lung injury, including inhaled endotoxin, ventilator-induced lung injury, sepsis, and hemorrhagic shock (52, 54). Fortis and colleagues recently reported that sevoflurane suppressed pulmonary inflammation in a two-hit experimental model of lung injury (acid instillation and ventilator-induced lung injury) exerting a lung-protective effect, which is likely mediated by pulmonary type-A γ-aminobutyric acid receptors (55). Recently, Englert and colleagues showed that in a murine two-hit model of endotoxin-induced inflammation followed by ventilator-induced lung injury, isoflurane exposure before mechanical ventilation ameliorated the lung injury by improving both lung mechanics and vascular leakage without changing inflammatory responses (56). Larger clinical studies are required to assess whether these antiinflammatory effects translate into a significant improvement in pulmonary oxygenation (31, 34).

Inhalational anesthetics have also been shown to modulate a number of cell death and survival signaling pathways in experimental *in vitro* and *in vivo* models of brain ischemia, which may have a beneficial impact (53, 57). Li and colleagues demonstrated that isoflurane pre- and postconditioning produced reduced cortical neuronal death and ischemia reperfusion injury in rat models of middle cerebral artery occlusion (58, 59). Given the important implications of perioperative stroke after neurosurgical and cardiovascular procedures as well as stroke beyond surgical settings on patients' outcomes, the potential of inhalational anesthetic administration to provide neuroprotection and mitigate neurological sequelae would be of great relevance. However, thus far few clinical studies have been performed in this area, and they were mostly limited to perioperative settings with a focus on indirect markers of neuroprotection rather than changes in cognitive function and neuronal damage (53). A retrospective study looked at the incidence of cognitive dysfunction 6 months after on-pump coronary artery bypass graft surgery and showed no difference between sevoflurane and propofol anesthesia (60). Further details on clinical data on volatiles and neuroprotection, as well as concerns around their potential for neurotoxicity in the developing brain and in the elderly, are explored later.

Preclinical research reported evidence of renoprotective properties of isoflurane and sevoflurane (61, 62). Clinical data remain limited, with perioperative studies in cardiac surgery showing improved markers of glomerular filtration rate but no evidence of decreased postoperative acute kidney injury (50, 63). Further studies are needed to verify to what extent the experimental evidence of organ protection from volatiles could be translated to humans. A more comprehensive understanding of the intracellular mechanisms would also better inform potential clinical applications and permit tailored and optimized administration protocols under different clinical scenarios (57).

What Are the Limitations of Using Volatile Agents within the ICU?

Volatile agents and suxamethonium are well known triggers for patients genetically predisposed to malignant hyperthermia. This condition is hallmarked by sudden-onset hemodynamic instability, hypercarbia, hyperthermia, muscle rigidity, and extremely high serum creatine kinase. Suspicion of this syndrome requires early intervention with immediate change of the ventilator circuit, dantrolene infusion, artificial cooling with specialist follow up, and genetic and muscle biopsy testing. A case of malignant hyperthermia has been identified during sevoflurane therapy in a patient with pneumonia (64). However, this condition remains rare (1/50,000–100,000) in comparison to propofol infusion syndrome, which affects up to 1% of ICU patients (10). Diagnosis of malignant hyperthermia within ICU settings is highly complex, with many of the above features easily mimicked by the more common critical care problems of sepsis and acute respiratory distress syndrome. Undoubtedly, wider use of volatiles beyond the operating room will require staff education, malignant hyperthermia protocol adoption, and dantrolene availability to manage this rare medical emergency.

Several types of patients may be unsuitable for inhalational sedation secondary to equipment limitations. The ideal weight-based tidal volume with the AnaConDa is unknown, but a minimum tidal volume of 350 ml for pediatric patients is recommended to overcome device dead space and avoid rebreathing of carbon dioxide. This will not be feasible in smaller patients who require lung-protective (6 ml/kg) or even ultra-protective (<4 ml/kg) ventilation protocols and those who need one-lung ventilation strategies. This device may also become impractical in patients with high-volume bronchial secretions, which may occlude and prevent optimal drug delivery.

Current Controversies and the Future Role of Volatile Agents in the ICU

Volatiles pose an attractive, novel approach for expanding our current sedation options, with unique pharmacological properties that may potentially improve patient care and outcomes. However, to date the number of studies and included patients is low, particularly in the setting of general ICUs with longer duration of use. Several key clinical questions of this promising new technology remain to be explored and are outlined below.

True impact of volatiles on delirium has not been directly studied using the currently recommended measurement tools of Confusion Assessment Method for the ICU or the Intensive Care Delirium Screening Checklist. Several sedation trials have performed other cognitive and psychological assessment by measuring the level of postextubation agitation and applying 14-point ICU Memory tool, which assesses delusion, negative feelings, and factual ICU memories (29, 34, 65). These studies compared isoflurane, sevoflurane, and desflurane to either midazolam or propofol and demonstrated a predominantly non–statistically significant trend in the reduction of these events in patients who received volatile sedation. Investigation of the development of long-term neuroaffective disorders was assessed by Sackey and colleagues in a trial of 40 patients who received isoflurane or midazolam sedation (65). Anxiety and depression were assessed using the well-validated Hospital Anxiety and Depression Scale, and post-traumatic stress disorder was assessed using the Impact of Event Scale at 6 months post ICU discharge. This study showed no difference in the psychological morbidity between these two groups.

Fluoride ions are constituents of all volatile agents. Methoxyflurane is an older-generation volatile agent, no longer in use, that shows high lipid solubility and undergoes 50 to 70% biotransformation to form fluoride. Historical work conducted by Cousins and Mazze during the 1970s identified that fluoride levels beyond 50 μmol/L can impair the renal tubular concentrating ability leading to high-output renal failure (66). This safety threshold has continued to be used despite modern-day anesthetic drugs displaying markedly different pharmacokinetic profiles. The elimination half-life of serum fluoride ions is 21.4 to 24.8 hours. Sevoflurane, isoflurane, and desflurane have 7, 5, and 6 fluoride ions, respectively, but undergo low levels of metabolism to produce inorganic fluoride. Serum fluoride levels do rise during both short anesthetic and longer ICU duration of use, with sevoflurane displaying higher levels than isoflurane given its greater metabolism and fluoride content (33, 67, 68). However, no significant association between renal dysfunction and fluoride levels has been identified despite several patients displaying levels beyond 50 μmol/L (67). Further research in this area would benefit from understanding safety thresholds for modern-day volatiles, how these would change in patients with renal dysfunction, and how long these agents could be safely administered in the ICU.

Neuroanesthetists and intensivists are aware of the conflicting physiological effects of these agents. Volatiles cause dose-dependent cerebrovasodilation with increase in cerebral blood flow and intracranial pressure but also reduce the cerebral metabolic oxygen consumption with improved regional blood flow. Work within a neuro ICU is limited to three small observational studies of adult patients with stroke or intracerebral or subarachnoid hemorrhage with normal intracranial pressure. Two studies using isoflurane showed no significant changes in intracranial pressure and improved regional cerebral blood flow and central venous saturation, with mixed findings of no to small reduction in cerebral perfusion pressure necessitating more vasopressor support (37, 69). This compares to a recent sevoflurane study where 8 out of 25 patients had significant reductions in blood pressure and rise in intracranial pressure (38).

The effects of volatile agents being either neuroprotective or neurotoxic is a matter of significant debate. There are considerable *in vitro* and *in vivo* data demonstrating pre- and postconditioning effects of these agents at limiting hypoxic ischemic damage (53, 70, 71). However, rodent and primate data have shown inhalational and intravenous (ketamine, propofol, benzodiazepines) agents may cause neurodegeneration and apoptosis in the developing brain as well as cognitive dysfunction in elderly patients (70, 72–74). This may be mediated through activation of type-A γ-aminobutyric acid pathways or *N*-methyl-D-aspartate receptor blockade. Clinical studies have produced conflicting results regarding long-term behavioral and cognitive problems with difficulties differentiating the impact of anesthesia from surgical trauma, neuroinflammation, underlying effects of disease, comorbidities, and environment (74, 75). These effects may be associated with dose, timing, and number of exposures to the developing brain (70, 74). Although firm conclusions cannot be drawn, in 2012 the SmartTots group (partnership of International Anesthesia Research Society and U.S. Food and Drug Administration) recommended avoiding elective surgical procedures in children younger than 3 years of age. Recently, results for the international multicenter GAS (General Anesthesia Spinal) trial were reported in infants younger than 60 weeks postmenstrual age who underwent inguinal herniorrhaphy using either sevoflurane general anesthesia or awake regional anesthesia (76). Cognitive testing at 2 years of age demonstrated no difference between these anesthesia techniques. Currently, the PANDA (Pediatric Anesthesia and Neurodevelopment Assessment) study will prospectively assess neuropsychological function in infants who have undergone inguinal hernia repair compared with a sibling with no anesthesia exposure. Initial pilot results from feasibility assessment of the PANDA project have shown no differences in neuropsychological assessment in 28 exposed children matched to an unexposed sibling (77). Data are limited within the pediatric critical care literature, and the impact of these findings will be highly relevant to neonatal and pediatric ICUs.

Conclusions

Volatiles have expanded beyond the operating room secondary to technological advances attracting the attention of clinicians and researchers trying to improve sedation therapy and outcomes. Their unique pharmacological properties may account for shorter patient awakening and extubation times in comparison to the current standard of care. However, like all sedatives, these agents can induce deep levels of sedation that have respiratory depressant effects and reduce patient mobility. At this time, it would be prudent to conduct further research to ensure patient safety with a focus on mortality, duration of mechanical ventilation, clinically relevant end-organ protection, and early and long-term cognitive dysfunction before widespread adoption of this exciting technique. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1. Ford WW. Ether inhalers in early use. *N Engl J Med* 1946;234:713–726.
2. Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, Davidson JE, Devlin JW, Kress JP, Joffe AM, *et al*.; American College of Critical Care Medicine. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013;41:263–306.
3. Barr J. Propofol: a new drug for sedation in the intensive care unit. *Int Anesthesiol Clin* 1995;33:131–154.
4. Sleigh J, Harvey M, Voss L, Denny B. Ketamine: more mechanisms of action than just NMDA blockade. *Trends in Anaesthesia and Critical Care* 2014;4:76–81.
5. Jackson DL, Proudfoot CW, Cann KF, Walsh TS. The incidence of sub-optimal sedation in the ICU: a systematic review. *Crit Care* 2009;13: R204.
6. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, Taichman DB, Dunn JG, Pohlman AS, Kinniry PA, *et al*. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* 2008; 371:126–134.
7. Wade DM, Howell DC, Weinman JA, Hardy RJ, Mythen MG, Brewin CR, Borja-Boluda S, Matejowsky CF, Raine RA. Investigating risk factors for psychological morbidity three months after intensive care: a prospective cohort study. *Crit Care* 2012;16:R192.
8. Girard TD, Shintani AK, Jackson JC, Gordon SM, Pun BT, Henderson MS, Dittus RS, Bernard GR, Ely EW. Risk factors for post-traumatic stress disorder symptoms following critical illness requiring mechanical ventilation: a prospective cohort study. *Crit Care* 2007;11: R28.
9. Long AC, Kross EK, Davydow DS, Curtis JR. Posttraumatic stress disorder among survivors of critical illness: creation of a conceptual model addressing identification, prevention, and management. *Intensive Care Med* 2014;40:820–829.
10. Roberts RJ, Barletta JF, Fong JJ, Schumaker G, Kuper PJ, Papadopoulos S, Yogaratnam D, Kendall E, Xamplas R, Gerlach AT, *et al*. Incidence of propofol-related infusion syndrome in critically ill adults: a prospective, multicenter study. *Crit Care* 2009;13:R169.
11. Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, Bratty JR, Takala J; Dexmedetomidine for Long-Term Sedation Investigators. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA* 2012;307:1151–1160.
12. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, Shintani AK, Thompson JL, Jackson JC, Deppen SA, *et al*. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA* 2007;298:2644–2653.
13. Preckel B, Bolten J. Pharmacology of modern volatile anaesthetics. *Best Pract Res Clin Anaesthesiol* 2005;19:331–348.
14. Campagna JA, Miller KW, Forman SA. Mechanisms of actions of inhaled anesthetics. *N Engl J Med* 2003;348:2110–2124.
15. Breheny FX, Kendall PA. Use of isoflurane for sedation in intensive care. *Crit Care Med* 1992;20:1062–1064.
16. Soukup J, Schärff K, Kubosch K, Pohl C, Bomplitz M, Kompardt J. State of the art: sedation concepts with volatile anesthetics in critically Ill patients. *J Crit Care* 2009;24:535–544.
17. Sackey PV, Martling CR, Radell PJ. Three cases of PICU sedation with isoflurane delivered by the 'AnaConDa'. *Paediatr Anaesth* 2005;15: 879–885.
18. Redaelli S, Mangili P, Ormas V, Sosio S, Peluso L, Ponzoni F, Patroniti N, Pesenti A. Prolonged sedation in ARDS patients with inhaled anesthetics: our experience [abstract]. *Crit Care* 2013;17:386.
19. Chabanne R, Perbet S, Futier E, Ben Said NA, Jaber S, Bazin JE, Pereira B, Constantin JM. Impact of the anesthetic conserving device on respiratory parameters and work of breathing in critically ill patients under light sedation with sevoflurane. *Anesthesiology* 2014; 121:808–816.
20. National Institute for Occupational Safety and Health (NIOSH). Criteria for a recommended standard occupational exposure to waste anesthetic gases and vapors. Cincinnati, OH: NIOSH, Department of Health and Human Services, Centers for Disease Control and Prevention; 1977.
21. Occupational Safety and Health Administration (OSHA). Waste anesthetic gases. Washington, DC: U.S. Department of Labor; 1991 [accessed 2014 Dec] Publication 9138. Available from: https://www.osha.gov/dts/osta/anestheticgases/index.html
22. Pickworth T, Jerath A, DeVine R, Kherani N, Wąsowicz M. The scavenging of volatile anesthetic agents in the cardiovascular intensive care unit environment: a technical report. *Can J Anaesth* 2013;60:38–43.
23. Migliari M, Bellani G, Rona R, Isgrò S, Vergnano B, Mauri T, Patroniti N, Pesenti A, Foti G. Short-term evaluation of sedation with sevoflurane administered by the anesthetic conserving device in critically ill patients. *Intensive Care Med* 2009;35:1240–1246.
24. Sackey PV, Martling CR, Nise G, Radell PJ. Ambient isoflurane pollution and isoflurane consumption during intensive care unit sedation with the Anesthetic Conserving Device. *Crit Care Med* 2005;33:585–590.
25. L'her E, Dy L, Pili R, Prat G, Tonnelier JM, Lefevre M, Renault A, Boles JM. Feasibility and potential cost/benefit of routine isoflurane sedation using an anesthetic-conserving device: a prospective observational study. *Respir Care* 2008;53:1295–1303.
26. Meiser A, Sirtl C, Bellgardt M, Lohmann S, Garthoff A, Kaiser J, Hügler P, Laubenthal HJ. Desflurane compared with propofol for postoperative sedation in the intensive care unit. *Br J Anaesth* 2003; 90:273–280.
27. Röhm KD, Wolf MW, Schöllhorn T, Schellhaass A, Boldt J, Piper SN. Short-term sevoflurane sedation using the Anaesthetic Conserving Device after cardiothoracic surgery. *Intensive Care Med* 2008;34: 1683–1689.
28. Kong KL, Willatts SM, Prys-Roberts C. Isoflurane compared with midazolam for sedation in the intensive care unit. *BMJ* 1989;298:1277–1280.
29. Hellström J, Öwall A, Sackey PV. Wake-up times following sedation with sevoflurane versus propofol after cardiac surgery. *Scand Cardiovasc J* 2012;46:262–268.
30. Jerath A, Beattie SW, Chandy T, Karski J, Djaiani G, Rao V, Yau T, Wasowicz M; Perioperative Anesthesia Clinical Trials Group. Volatile-based short-term sedation in cardiac surgical patients: a prospective randomized controlled trial. *Crit Care Med* 2015;43:1062–1069.
31. Steurer MP, Steurer MA, Baulig W, Piegeler T, Schläpfer M, Spahn DR, Falk V, Dreessen P, Theusinger OM, Schmid ER, *et al*. Late pharmacologic conditioning with volatile anesthetics after cardiac surgery. *Crit Care* 2012;16:R191.
32. Soukup J, Selle A, Wienke A, Steighardt J, Wagner NM, Kellner P. Efficiency and safety of inhalative sedation with sevoflurane in comparison to an intravenous sedation concept with propofol in intensive care patients: study protocol for a randomized controlled trial. *Trials* 2012;13:135.
33. Sackey PV, Martling CR, Granath F, Radell PJ. Prolonged isoflurane sedation of intensive care unit patients with the Anesthetic Conserving Device. *Crit Care Med* 2004;32:2241–2246.

34. Mesnil M, Capdevila X, Bringuier S, Trine PO, Falquet Y, Charbit J, Roustan JP, Chanques G, Jaber S. Long-term sedation in intensive care unit: a randomized comparison between inhaled sevoflurane and intravenous propofol or midazolam. *Intensive Care Med* 2011;37: 933–941.
35. Spencer EM, Willatts SM. Isoflurane for prolonged sedation in the intensive care unit: efficacy and safety. *Intensive Care Med* 1992;18: 415–421.
36. Spencer EM, Willatts SM, Prys-Roberts C. Plasma inorganic fluoride concentrations during and after prolonged (greater than 24 h) isoflurane sedation: effect on renal function. *Anesth Analg* 1991;73: 731–737.
37. Bösel J, Purrucker JC, Nowak F, Renzland J, Schiller P, Pérez EB, Poli S, Brunn B, Hacke W, Steiner T. Volatile isoflurane sedation in cerebrovascular intensive care patients using AnaConDa(®): effects on cerebral oxygenation, circulation, and pressure. *Intensive Care Med* 2012;38:1955–1964.
38. Purrucker JC, Renzland J, Uhlmann L, Bruckner T, Hacke W, Steiner T, Bösel J. Volatile sedation with sevoflurane in intensive care patients with acute stroke or subarachnoid haemorrhage using AnaConDa®: an observational study. *Br J Anaesth* 2015;114:934–943.
39. Bellgardt M, Bomberg H, Herzog-Niescery J, Dasch B, Vogelsang H, Weber TP, Steinfort C, Uhl W, Wagenpfeil S, Volk T, *et al*. Survival after long-term isoflurane sedation as opposed to intravenous sedation in critically ill surgical patients. *Eur J Anaesthesiol* 2015;32: 1–8.
40. Kikuchi C, Dosenovic S, Bienengraeber M. Anaesthetics as cardioprotectants: translatability and mechanism. *Br J Pharmacol* 2015;172:2051–2061.
41. Cason BA, Gamperl AK, Slocum RE, Hickey RF. Anesthetic-induced preconditioning: previous administration of isoflurane decreases myocardial infarct size in rabbits. *Anesthesiology* 1997;87: 1182–1190.
42. Knapp J, Bergmann G, Bruckner T, Russ N, Böttiger BW, Popp E. Pre- and postconditioning effect of sevoflurane on myocardial dysfunction after cardiopulmonary resuscitation in rats. *Resuscitation* 2013;84:1450–1455.
43. Meybohm P, Gruenewald M, Albrecht M, Müller C, Zitta K, Foesel N, Maracke M, Tacke S, Schrezenmeir J, Scholz J, *et al*. Pharmacological postconditioning with sevoflurane after cardiopulmonary resuscitation reduces myocardial dysfunction. *Crit Care* 2011;15:R241.
44. Yannopoulos D, Segal N, Matsuura T, Sarraf M, Thorsgard M, Caldwell E, Rees J, McKnite S, Santacruz K, Lurie KG. Ischemic post-conditioning and vasodilator therapy during standard cardiopulmonary resuscitation to reduce cardiac and brain injury after prolonged untreated ventricular fibrillation. *Resuscitation* 2013;84:1143–1149.
45. De Hert SG, Van der Linden PJ, Cromheecke S, Meeus R, Nelis A, Van Reeth V, ten Broecke PW, De Blier IG, Stockman BA, Rodrigus IE. Cardioprotective properties of sevoflurane in patients undergoing coronary surgery with cardiopulmonary bypass are related to the modalities of its administration. *Anesthesiology* 2004;101:299–310.
46. Soro M, Gallego L, Silva V, Ballester MT, Lloréns J, Alvariño A, García-Perez ML, Pastor E, Aguilar G, Martí FJ, *et al*. Cardioprotective effect of sevoflurane and propofol during anaesthesia and the postoperative period in coronary bypass graft surgery: a double-blind randomised study. *Eur J Anaesthesiol* 2012;29:561–569.
47. Yu CH, Beattie WS. The effects of volatile anesthetics on cardiac ischemic complications and mortality in CABG: a meta-analysis. *Can J Anaesth* 2006;53:906–918.
48. Hellström J, Öwall A, Bergström J, Sackey PV. Cardiac outcome after sevoflurane versus propofol sedation following coronary bypass surgery: a pilot study. *Acta Anaesthesiol Scand* 2011;55: 460–467.
49. Beck-Schimmer B, Breitenstein S, Urech S, De Conno E, Wittlinger M, Puhan M, Jochum W, Spahn DR, Graf R, Clavien PA. A randomized controlled trial on pharmacological preconditioning in liver surgery using a volatile anesthetic. *Ann Surg* 2008;248:909–918.
50. Julier K, da Silva R, Garcia C, Bestmann L, Frascarolo P, Zollinger A, Chassot PG, Schmid ER, Turina MI, von Segesser LK, *et al*. Preconditioning by sevoflurane decreases biochemical markers for myocardial and renal dysfunction in coronary artery bypass graft surgery: a double-blinded, placebo-controlled, multicenter study. *Anesthesiology* 2003;98:1315–1327.
51. Kim M, Park SW, Kim M, D'Agati VD, Lee HT. Isoflurane post-conditioning protects against intestinal ischemia-reperfusion injury and multiorgan dysfunction via transforming growth factor-β1 generation. *Ann Surg* 2012;255:492–503.
52. De Conno E, Steurer MP, Wittlinger M, Zalunardo MP, Weder W, Schneiter D, Schimmer RC, Klaghofer R, Neff TA, Schmid ER, *et al*. Anesthetic-induced improvement of the inflammatory response to one-lung ventilation. *Anesthesiology* 2009;110:1316–1326.
53. Kitano H, Kirsch JR, Hurn PD, Murphy SJ. Inhalational anesthetics as neuroprotectants or chemical preconditioning agents in ischemic brain. *J Cereb Blood Flow Metab* 2007;27:1108–1128.
54. Voigtsberger S, Lachmann RA, Leutert AC, Schläpfer M, Booy C, Reyes L, Urner M, Schild J, Schimmer RC, Beck-Schimmer B. Sevoflurane ameliorates gas exchange and attenuates lung damage in experimental lipopolysaccharide-induced lung injury. *Anesthesiology* 2009;111:1238–1248.
55. Fortis S, Spieth PM, Lu WY, Parotto M, Haitsma JJ, Slutsky AS, Zhong N, Mazer CD, Zhang H. Effects of anesthetic regimes on inflammatory responses in a rat model of acute lung injury. *Intensive Care Med* 2012;38:1548–1555.
56. Englert JA, Macias AA, Amador-Munoz D, Pinilla Vera M, Isabelle C, Guan J, Magaoay B, Suarez Velandia M, Coronata A, Lee A, *et al*. Isoflurane ameliorates acute lung injury by preserving epithelial tight junction integrity. *Anesthesiology* 2015;123:377–388.
57. Wu L, Zhao H, Wang T, Pac-Soo C, Ma D. Cellular signaling pathways and molecular mechanisms involving inhalational anesthetics-induced organoprotection. *J Anesth* 2014;28:740–758.
58. Li L, Peng L, Zuo Z. Isoflurane preconditioning increases B-cell lymphoma-2 expression and reduces cytochrome c release from the mitochondria in the ischemic penumbra of rat brain. *Eur J Pharmacol* 2008;586:106–113.
59. Li L, Zuo Z. Isoflurane postconditioning induces neuroprotection via Akt activation and attenuation of increased mitochondrial membrane permeability. *Neuroscience* 2011;199:44–50.
60. Kadoi Y, Goto F. Sevoflurane anesthesia did not affect postoperative cognitive dysfunction in patients undergoing coronary artery bypass graft surgery. *J Anesth* 2007;21:330–335.
61. Zhang L, Huang H, Cheng J, Liu J, Zhao H, Vizcaychipi MP, Ma D. Pre-treatment with isoflurane ameliorates renal ischemic-reperfusion injury in mice. *Life Sci* 2011;88:1102–1107.
62. Lee HT, Kim M, Jan M, Emala CW. Anti-inflammatory and antinecrotic effects of the volatile anesthetic sevoflurane in kidney proximal tubule cells. *Am J Physiol Renal Physiol* 2006;291:F67–F78.
63. Sindhvananda W, Phisaiphun K, Prapongsena P. No renal protection from volatile-anesthetic preconditioning in open heart surgery. *J Anesth* 2013;27:48–55.
64. Schuster F, Moegele S, Johannsen S, Roewer N. Malignant hyperthermia in the intensive care setting. *Crit Care* 2014;18:411.
65. Sackey PV, Martling CR, Carlswärd C, Sundin O, Radell PJ. Short- and long-term follow-up of intensive care unit patients after sedation with isoflurane and midazolam–a pilot study. *Crit Care Med* 2008; 36:801–806.
66. Cousins MJ, Mazze RI. Methoxyflurane nephrotoxicity: a study of dose response in man. *JAMA* 1973;225:1611–1616.
67. Röhm KD, Mengistu A, Boldt J, Mayer J, Beck G, Piper SN. Renal integrity in sevoflurane sedation in the intensive care unit with the anesthetic-conserving device: a comparison with intravenous propofol sedation. *Anesth Analg* 2009;108:1848–1854.
68. Perbet S, Bourdeaux D, Sautou V, Pereira B, Chabanne R, Constantin JM, Chopineau J, Bazin JE. A pharmacokinetic study of 48-hour sevoflurane inhalation using a disposable delivery system (AnaConDa®) in ICU patients. *Minerva Anestesiol* 2014;80: 655–665.
69. Villa F, Iacca C, Molinari AF, Giussani C, Aletti G, Pesenti A, Citerio G. Inhalation versus endovenous sedation in subarachnoid hemorrhage patients: effects on regional cerebral blood flow. *Crit Care Med* 2012; 40:2797–2804.
70. Chiao S, Zuo Z. A double-edged sword: volatile anesthetic effects on the neonatal brain. *Brain Sci* 2014;4:273–294.

71. Payne RS, Akca O, Roewer N, Schurr A, Kehl F. Sevoflurane-induced preconditioning protects against cerebral ischemic neuronal damage in rats. *Brain Res* 2005;1034:147–152.
72. Creeley C, Dikranian K, Dissen G, Martin L, Olney J, Brambrink A. Propofol-induced apoptosis of neurones and oligodendrocytes in fetal and neonatal rhesus macaque brain. *Br J Anaesth* 2013;110:i29–i38.
73. Mandal PK, Ritchie K, Fodale V. Anesthetics and its impact on the brain and Alzheimer's disease. *J Alzheimers Dis* 2014;39: 223–225.
74. Wilder RT, Flick RP, Sprung J, Katusic SK, Barbaresi WJ, Mickelson C, Gleich SJ, Schroeder DR, Weaver AL, Warner DO. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. *Anesthesiology* 2009;110:796–804.
75. Bartels M, Althoff RR, Boomsma DI. Anesthesia and cognitive performance in children: no evidence for a causal relationship. *Twin Res Hum Genet* 2009;12:246–253.
76. Davidson AJ, Disma N, de Graaff JC, Withington DE, Dorris L, Bell G, Stargatt R, Bellinger DC, Schuster T, Arnup SJ, *et al*.; GAS consortium. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. *Lancet* 2016;387:239–250.
77. Sun LS, Li G, DiMaggio CJ, Byrne MW, Ing C, Miller TL, Bellinger DC, Han S, McGowan FX. Feasibility and pilot study of the Pediatric Anesthesia NeuroDevelopment Assessment (PANDA) project. *J Neurosurg Anesthesiol* 2012;24:382–388.