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

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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 amnergic 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
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, 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

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**Figure 1.** Modern theory of volatile activity involves complex interaction with multiple proteins on the pre- and postsynaptic nerve membrane as well as nonneuronal tissue. Volatiles reduce presynaptic excitation and neurotransmitter release through inhibition of sodium (Na⁺) and several isoforms of calcium (Ca²⁺) voltage-gated channels (VGCCs) 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-isoxazolepropionic 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

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

**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 (EtCO₂) carbon dioxide, inspired (FiO₂) and end-tidal (EtO₂) 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).
### Table 2. Summary of the Main Findings from Several Key Randomized Controlled Trials Assessing Volatile-based Sedation

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size, ICU Setting</th>
<th>Duration of Sedation (h)</th>
<th>Sedation Agents</th>
<th>Main Study Findings</th>
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<tbody>
<tr>
<td><strong>Short-term sedation trials (&lt;24 h)</strong></td>
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</table>
| 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]†  
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)†  
No difference in shivering, nausea, vomiting, renal insufficiency, or patient mortality  
No difference in ICU or hospital length of stay  
No statistically significant difference in risk-adjusted models of oxygenation index (PaO2/FIO2) at 4 h and first postoperative day, postoperative respiratory complications, postoperative nausea and vomiting, or ICU or hospital length of stay  
No difference in postextubation pain scores, opioid requirement, nausea, vomiting, shivering, or postoperative ICU or hospital length of stay  
No correlation between plasma fluoride level and serum creatinine  
No difference in ICU discharge time or systolic blood pressure  |
| Meiser et al., 2003 (26) | 60, SICU                 | 9.7–11.5                 | Desflurane 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  |
| Röhm et al., 2008 (27)  | 70, CICU                 | 8.1–8.4                  | 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 stay  
Memory tool test  
No difference in postextubation pain scores, opioid requirement, nausea, vomiting, shivering, or postoperative ICU or hospital length of stay  |
| Hellström et al., 2012 (29) | 100, CICU              | 2.8–3.1                  | Sevoflurane vs. propofol| Time to extubation (min): sevoflurane 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  |
| 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 (PaO2/FIO2) at 4 h and first postoperative day, postoperative respiratory complications, postoperative nausea and vomiting, or ICU or hospital length of stay  
No difference in postextubation pain scores, opioid requirement, nausea, vomiting, shivering, or postoperative 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)
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.

Critical Care Perspective

### 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 anesthetic agents 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

#### Table 2. (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size, ICU Setting</th>
<th>Duration of Sedation (h)</th>
<th>Sedation Agents</th>
<th>Main Study Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sackey et al., 2004 (33)</td>
<td>40, MSICU</td>
<td>32–52</td>
<td>Isoflurane vs. midazolam</td>
<td>Time to extubation (min): isoflurane 10 ± 5 vs. midazolam 250 ± 2701</td>
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<tr>
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<td>Time to obey verbal command (min): isoflurane 10 ± 8 vs. midazolam 110 ± 1300</td>
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<td>Time within target sedation (%): isoflurane 54 vs. midazolam 59</td>
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<td>Opiate requirement (mg/h): isoflurane 2.7 ± 2 vs. midazolam 4.2 ± 3.8</td>
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<td>No difference in patient mortality</td>
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<tr>
<td>Mesnil et al., 2011 (34)</td>
<td>60, MSICU</td>
<td>50–57</td>
<td>Sevoflurane vs. propofol vs. midazolam</td>
<td>Time to extubation (min): sevoflurane 33.6 ± 13.1 vs. propofol 326.1 ± 360.2 vs. midazolam 599.6 ± 5871</td>
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<td>24-h postextubation morphine use (mg): sevoflurane 20 (4–30) vs. propofol 40 (9–60) vs. midazolam 76 (55–111)1</td>
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<td>No. hypnotic dose changes/day (n): sevoflurane 1.5 (0–2.5) vs. propofol 5 (4–8.5) vs. midazolam 3.5 (2–5)1</td>
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<td></td>
<td>Vasoactive drug use (%): sevoflurane 35 vs. propofol 48 vs. midazolam 421</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>No difference in renal or liver function</td>
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</table>

**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.

†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.
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 induced 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. Suspicions 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**

Volatile 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 old-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
References


