REVIEW

Sevoflurane [version 1; peer review: 2 approved]

Stefan De Hert , Anneliese Moerman

Department of Anesthesiology, Ghent University Hospital, De Pintelaan 185, Ghent, B-9000, Belgium

V1 First published: 25 Aug 2015, 4(F1000 Faculty Rev):626
<https://doi.org/10.12688/f1000research.6288.1>

Latest published: 25 Aug 2015, 4(F1000 Faculty Rev):626
<https://doi.org/10.12688/f1000research.6288.1>

Abstract

Sevoflurane has been available for clinical practice for about 20 years. Nowadays, its pharmacodynamic and pharmacokinetic properties together with its absence of major adverse side effects on the different organ systems have made this drug accepted worldwide as a safe and reliable anesthetic agent for clinical practice in various settings.

Keywords

Sevoflurane, anesthetic, anesthesiology, pharmacodynamic, pharmacokinetic

Open Peer Review**Approval Status**

	1	2
version 1
25 Aug 2015		
1. Roderic Eckenhoff , University of Pennsylvania, Philadelphia, USA		
2. Manfred Seeberger , Klinik Hirslanden, Witellikerstrasse 40, Switzerland		
Any comments on the article can be found at the end of the article.		

Corresponding author: Stefan De Hert (stefan.dehert@ugent.be)

Competing interests: Stefan De Hert has received speakers fees from Abbott and AbbVie. Anneliese Moerman declares that she has no competing interests.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2015 De Hert S and Moerman A. This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: De Hert S and Moerman A. **Sevoflurane [version 1; peer review: 2 approved]** F1000Research 2015, 4(F1000 Faculty Rev):626 <https://doi.org/10.12688/f1000research.6288.1>

First published: 25 Aug 2015, 4(F1000 Faculty Rev):626 <https://doi.org/10.12688/f1000research.6288.1>

Introduction

Although sevoflurane was synthesized in the early 1970s¹, it was not released for clinical use until the early 1990s. This was related partly to the expensive synthesis and the initial concern of apparent toxic effects², which later appeared to be a consequence of a flawed experimental design³. Nowadays, its pharmacodynamic and pharmacokinetic properties together with its absence of major adverse side effects on the different organ systems have made this drug accepted worldwide as a safe and reliable anesthetic agent for clinical practice in various settings.

Physicochemical properties

Sevoflurane (1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy)propane) is a colorless, volatile, and non-flammable liquid with a characteristic smell. It is stable at room temperature and has a boiling point of 58.6°C and a vapor pressure of 157 mm Hg. Hence, in contrast to desflurane, it can be used in standard vaporizers³. Sevoflurane has an oil/gas partition coefficient of 47.2 and its minimal alveolar concentration (MAC), which is the percentage that is necessary to prevent movement in 50% of patients during skin incision, is 2.05%^{4,5}. As a consequence, its potency is considerably lower than that of the older inhalational agents such as halothane and isoflurane, but it is about three times more potent than desflurane.

Upon contact with alkaline carbon dioxide (CO₂) absorbers, sevoflurane undergoes degradation^{6–8}. The most important degradation product is fluoromethyl-2,2-difluoro-1-(trifluoromethyl) vinyl ether, better known as compound A. In experimental studies, compound A has been reported to be nephrotoxic^{9,10}. Although the clinical implications of these findings remained unclear¹¹, the safety issue related to compound A formation led to intense debates for many years before the issue was resolved¹².

In 1996, Abbott Laboratories voluntarily recalled one lot of sevoflurane because evaluation of a bottle of sevoflurane revealed an uncharacteristically pungent odor^{13,14}. This was caused by the formation of hydrogen fluoride as a consequence of a Lewis acid-fluorocarbon reaction. Even in minute amounts, this substance is highly reactive and toxic and can cause respiratory irritation and pulmonary hemorrhage¹⁵. Subsequently, the offending Lewis acid (ferric oxide)-containing part was removed from the sevoflurane handling equipment, and a Lewis acid inhibitor (water) was added to the final product^{16,17}. Although Abbott adapted the production process to create a “high water” sevoflurane (>300 parts per million), the manufacturers that subsequently launched sevoflurane (Minrad and Baxter) did not^{18–20}.

Pharmacological properties

It is beyond the scope of this review to discuss in detail the pharmacological properties of sevoflurane. Several excellent review articles have addressed this topic^{21–25}.

Pharmacodynamics

MAC values of sevoflurane decrease with age, from 3.3% in neonates and 2.5% in infants and young adults to 1.58% to 2.05% in middle-aged adults and 1.45% in adults who are more than 70 years old^{26–31}. In the presence of 65% nitrous oxide in the inspired gas mixture, MAC values for sevoflurane decrease by about 50% in adults³².

Gender does not influence the MAC of sevoflurane, but there is some evidence suggesting that ethnic factors may play a role: MAC values reported in US studies were consistently higher (2.05% to 2.6%)^{5,32} than those reported for Japanese adults (1.58% to 1.71%)^{30,31}.

Pharmacokinetics

As for the volatile anesthetic uptake, distribution and elimination are best described by a five-compartment mammillary model³³. This model consists of the lungs, the vessel-rich group of organs, muscle, fat adjacent to the vessel-rich organs, and peripheral fat. In general, an inverse relationship exists between the blood/gas partition coefficient of a volatile anesthetic and the time required for the inspired and alveolar concentrations to reach equilibrium. Sevoflurane has a low blood/gas partition coefficient (0.69), resulting in a swifter equilibration of the alveolar-to-inspiratory fraction (F_A/F_I ratio) than with enflurane and isoflurane but slightly slower than with nitrous oxide and desflurane^{33,34}.

Because of its pleasant odor and the absence of irritation to the airways, sevoflurane can be used for inhalational induction both in children and in adults³⁵. Studies have shown that induction is as rapid as^{36,37} or even swifter than^{38–40} with halothane.

Elimination of a volatile anesthetic is also related to its blood solubility. Between 95% and 98% of sevoflurane is eliminated through the lung. The driving force for this elimination is the difference in partial pressures between the inspired gas mix and the pulmonary capillary blood. In humans, 2% to 5% of the absorbed dose of sevoflurane is metabolized by the liver, resulting in the formation of inorganic fluoride and the organic fluoride metabolite hexafluoroisopropanol⁴¹. The latter is conjugated with glucuronic acid and excreted rapidly via the kidneys. The biotransformation of sevoflurane occurs predominantly through cytochrome P450(CYP)2E1^{42,43}. Serum inorganic fluoride concentrations after sevoflurane anesthesia are dose-dependent, reaching 10 to 20 $\mu\text{mol/L}$ after 1 to 2 MAC hours and up to 20 to 90 $\mu\text{mol/L}$ with prolonged exposure⁴¹. Although most studies could not show nephrotoxic effects after sevoflurane anesthesia⁴⁴, some controversial reports⁴⁵ of mild renal dysfunction after the use of sevoflurane resulted in a recommendation by the US Food and Drug Administration for caution in the use of sevoflurane in patients with coexisting renal disease. Interestingly, the majority of data report no differences in pharmacokinetics between patients with and those without kidney diseases^{46,47}. Percutaneous losses account for less than 1% of the total uptake of sevoflurane⁴⁸.

Effects on vital systems

Like the effects of other anesthetic agents, those of sevoflurane on the vital systems are mostly depressant.

Respiration

A decrease in ventilation leading to apnea at concentrations of between 1.5 and 2.0 MAC can be observed. The ventilatory depression with sevoflurane is the result of a combination of central depression of medullary respiratory neurons⁴⁹ and depression of diaphragmatic function⁵⁰ and contractility⁵¹.

Sevoflurane provides bronchodilation and attenuates bronchial smooth muscle constriction by histamine or acetylcholine and can

be safely used in patients with asthma²¹. Hypoxic pulmonary vasoconstriction is inhibited by sevoflurane in a dose-dependent manner and is not mediated by cyclo-oxygenase²¹⁻²³.

Circulation

Sevoflurane decreases blood pressure in a dose-dependent manner by decreasing total peripheral resistance. At clinically relevant concentrations, cardiac output is usually preserved²¹⁻²³. Heart rate remains unchanged or even decreases. Coronary blood flow remains preserved and regional blood flow to other vascular beds appears to be maintained at least when systemic hemodynamics are preserved. For sevoflurane (unlike for desflurane), no sympathetic nervous system activation is observed²¹⁻²³. Although sevoflurane has been reported to prolong the QT and the QTc interval⁵², it has no effect on the normal cardiac conduction pathways and therefore is considered a safe agent that can also be used in cardiac electrophysiological procedures²⁵.

Central nervous system

Sevoflurane is a cerebral vasodilator. In neurosurgical patients, sevoflurane decreased middle cerebral artery flow velocity and caused no epileptiform electroencephalogram activity and no increase of intracranial pressure⁵³. Cerebral autoregulation is maintained at low concentrations of sevoflurane⁵⁴, but higher doses seem to decrease autoregulatory capacity⁵⁵.

Safety

Overall, sevoflurane is considered to be a safe and reliable agent that has also been used in uncommon medical conditions such as pheochromocytoma, acute intermittent porphyria, carnitine deficiency, muscular dystrophy, multiple sclerosis, primary aldosteronism, and myotonic dystrophy²³.

In the early years of its use, a number of reports on malignant hyperthermia with sevoflurane were published. In many of them, it was difficult to isolate the potential effects of sevoflurane from the influence of the concurrent use of other triggers such as succinylcholine. Animal studies have suggested that the malignant hyperthermia trigger of sevoflurane was substantially lower than that of other volatile anesthetic agents⁵⁶. However, a recent Japanese database study did not find evidence that sevoflurane would be a weaker triggering agent for malignant hyperthermia⁵⁷. Since its introduction in clinical practice, sevoflurane has been safely used in millions of people, and reports of sevoflurane-related malignant hyperthermia are scarce. Nevertheless, it seems wise to avoid exposure to sevoflurane in patients with a known susceptibility.

In the early years of clinical sevoflurane use, it was reported that sevoflurane in the presence of the CO₂ absorbers soda lime (calcium, sodium, and potassium hydroxide mixture), or baralyme (barium, sodium, calcium, and potassium hydroxide mixture) degrades to compound A. This degradation occurs in the anesthesia machine as a result of the extraction of an acidic proton (from the inhalational anesthetic) by a strong base (soda lime or baralyme)⁵⁸. The rate of degradation at a given temperature and moisture level is two to four times greater with baralyme compared with soda lime^{58,59}. The order of solubility of inhalation anesthetics in dry soda lime is sevoflurane > enflurane > desflurane ≥ halothane > isoflurane⁴. As

a consequence, more sevoflurane is absorbed into the CO₂ absorber than is observed with other inhalational anesthetics. The production and subsequent inhalation of compound A correlate inversely with the inflow rate⁶⁰ and directly with the absorbent temperature⁶¹. In addition, low fresh gas flows of sevoflurane are associated with increased temperatures in the CO₂ absorber⁶². Therefore, compound A production can be limited by decreasing the temperature of the absorbent⁶³. For these reasons, US and Canadian package labels and licensing authorities have recommended minimal fresh gas inflow rates of 1 or 2 L/min, although other licensing authorities have not made such a recommendation. Compound A production can also be reduced by the amount of absorbent (smaller canisters)⁶⁴ and adapting the composition of the absorbent by eliminating potassium and sodium hydroxide⁶⁵⁻⁶⁷. The clinical implications of compound A production have been a point of debate for many years⁶⁸, but the introduction of the new-generation absorbers¹¹ has made this issue largely obsolete.

Special populations

The pediatric patient

There seems to be no significant difference in sevoflurane pharmacokinetics between children and adults²⁴. Because of its pleasant odor, lack of airway irritation, and maintenance of stable hemodynamics, sevoflurane is the agent of choice for mask induction. In general, complications upon emergence are infrequent, although some studies mention a significantly higher incidence of excitement/agitation with sevoflurane^{69,70}. However, this observation has been linked to the fact that the prompt recovery from anesthesia with sevoflurane also facilitates earlier awareness of postoperative pain^{69,71}. This causal relationship was confirmed in a number of studies demonstrating that adequate pain treatment was associated with significantly fewer episodes of emergence agitation^{72,73}.

The ambulatory patient

Ambulatory surgery has increased rapidly in recent years and this has put an emphasis on the use of short-acting drugs in anesthetic practice, allowing fast recovery and early mobilization. Differences in early recovery between sevoflurane, desflurane, and propofol have been reported to be small but in favor of the inhaled anesthetics⁷⁴, although the clinical implications of these small differences are debatable. Postoperative nausea and vomiting are higher with volatile anesthetics than with propofol, but adequate anti-emetic prophylaxis can prevent or blunt this side effect.

The obese patient

The prevalence of obesity is increasing dramatically, not only in industrialized countries but also in developing ones. As a consequence, we encounter a growing number of morbidly obese patients who need different types of surgery. Obese patients are traditionally reported to have slower emergence from anesthesia because of a delayed release of volatile anesthetics from the excess fat tissue. However, comparable recovery times have been reported in obese and non-obese subjects after anesthetic procedures lasting 2 to 4 hours⁷⁵.

The new inhalation drugs have a much lower lipid solubility compared with the older volatile anesthetic agents, resulting in a more rapid and consistent recovery profile⁷⁶. For sevoflurane, no significant

differences in F_A/F_I ratio have been observed, but the wash-out curve—that is, the alveolar-to-expiratory fraction (F_A/F_{AO} ratio)—was reported to be slower in obese patients compared with non-obese patients. However, 5 minutes after sevoflurane discontinuation, no differences in wash-out were observed between obese and non-obese patients⁷⁷. Several studies have compared kinetic profiles of sevoflurane and desflurane. Some studies observed more rapid emergence from anesthesia with desflurane but this was not confirmed in other studies (reviewed in 78). Finally, an advantage of sevoflurane in this setting is that it allows progressive induction of anesthesia via face mask⁷⁹.

Organ protection

The heart

The finding in the late 1990s that sevoflurane was capable of limiting the extent of myocardial infarction after myocardial ischemia triggered a new research direction investigating potential cardioprotective effects of volatile anesthetic agents. Experimental studies have clearly indicated that volatile anesthetic agents are capable of protecting the myocardium against the consequences of ischemia-reperfusion injury by decreasing the extent of myocardial damage, decreasing the extent of reperfusion injury, and better preserving myocardial function. Subsequent research was directed toward unraveling the underlying mechanisms and intracellular pathways of these cardioprotective effects^{80–85}.

Although the experimental evidence of cardioprotection with volatile anesthetic agents was quite straightforward, the implications for clinical practice remain a point of debate. The potential cardioprotective effects related to the use of volatile anesthetics were first explored in the setting of cardiac surgery. In coronary artery surgery patients, the results of preconditioning protocols were conflicting: some authors demonstrated a protective effect whereas others failed to observe such an effect. Later, it became clear that this might be attributed to the preconditioning protocol used. It also seems that the administration of the volatile anesthetic agent throughout the entire procedure results in a more pronounced protective effect than when administered intermittently. It is beyond the scope of this review to discuss these studies in detail. The interested reader is referred to a number of reviews on the topic^{86–95}.

For non-cardiac surgery, the potential clinical implication of the cardioprotective properties of volatile anesthetics is even more debatable. One small study in vascular surgery patients observed a lower incidence of cardiac complications in patients treated with sevoflurane compared with those anesthetized with propofol⁹⁶. Others, however, observed no difference in the extent of myocardial damage when comparing a volatile anesthetic regimen with a total intravenous regimen^{97,98}. This clearly indicates that only in the presence of myocardial ischemia/reperfusion injury can a potential beneficial effect of volatile anesthetics be expected⁹⁹. Interestingly, in the study by Lurati Buse and colleagues⁹⁸, in which 385 patients were randomly assigned to receive anesthesia with either sevoflurane or propofol, the incidences of perioperative myocardial ischemia were comparable (40.8% in the sevoflurane group and 40.3% in the propofol group). Within 12 months, 14 patients had a major cardiac event in the sevoflurane-treated group (7.6%) and 17 in the propofol-treated group (8.5%). However, given that a potential cardioprotective effect of volatile anesthetic agents relates to a modulation of the

extent of myocardial ischemia/reperfusion injury, the analysis of the major cardiac events needs to be focused on the occurrence of these events in the subgroup of patients who had perioperative myocardial ischemia. To further clarify this issue, the authors performed an additional analysis of their data. They found that the incidence of major cardiac complications in patients with evidence of perioperative myocardial ischemia was similar in both groups: 8 out of 67 patients (11.9%) in the sevoflurane group and 9 out of 72 patients (12.9%) in the propofol group. The remaining 6 and 8 patients with postoperative major cardiac complications had not shown any evidence of perioperative myocardial ischemia (Seeberger M, unpublished observations).

Other organ systems

Clinical studies on the protective effects of sevoflurane on other organ systems are scarce and limited to a small number of patients. Three studies from the same group suggest protective effects after liver^{100,101} and lung¹⁰² ischemia with sevoflurane, but the potential implications on long-term outcome remain to be established.

Neurotoxicity in the young and aged brain

Preclinical evidence in rodents and non-human primates has caused concern regarding the safety of anesthesia in infants and children. Indeed, animal studies suggest that neurodegeneration with possible cognitive sequelae may constitute a potential long-term risk of anesthesia in neonatal and young pediatric patients (reviewed in 103,104). No hard clinical data suggest that the use of anesthetics in the neonate or young child is associated with signs of developmental neurotoxicity¹⁰³. It has been argued that the increased risk of poor outcome in some human cohort studies is because of the inflammation and stress associated with the surgery rather than the anesthetic¹⁰⁵. It is expected that the results of two ongoing large-scale studies—the Multi-site Randomized Controlled Trial comparing Regional and General Anesthesia for Effects on Neurodevelopment Outcome and Apnea in Infants (GAS) study and the Pediatric Anesthesia and NeuroDevelopment Assessment (PANDA) study—will give more insight into the problem¹⁰⁴.

Similarly, experimental studies, observing effects of anesthetic agents on memory formation and the induction of neurodegenerative changes on a cellular level, have raised concerns about the effects of anesthesia and surgery on the elderly brain. The incidence of postoperative cognitive dysfunction (POCD) varies according to the definitions used in the various studies but is reported to be higher in major surgery (reviewed in 106–108). Whether general anesthesia contributes to POCD remains uncertain. A recent meta-analysis of 26 randomized trials comparing general to regional anesthesia was unable to identify general anesthesia as an independent risk factor for POCD¹⁰⁹. It is conceivable that surgical trauma and underlying pathology are of greater importance. Given the complexity and still-unknown elements of the pathogenesis of POCD, further research on the topic is needed.

Conclusions

Since its introduction in clinical practice, sevoflurane has gained wide acceptance as an anesthetic for various types of surgery. Its ease of administration, versatility, and stable hemodynamic profile make it a safe and easily applicable anesthetic agent.

Competing interests

Stefan De Hert has received speakers fees from Abbott and AbbVie. Anneliese Moerman declares that she has no competing interests.

Grant information

The author(s) declared that no grants were involved in supporting this work.

References

1. Wallin RF, Regan BM, Napoli MD, *et al.*: **Sevoflurane: a new inhalational anesthetic agent.** *Anesth Analg.* 1975; **54**(6): 758–66.
[PubMed Abstract](#) | [Publisher Full Text](#)
2. Hitt B, Mazze R, Cook T, *et al.*: **Thermoregulatory defect in rats during anesthesia.** *Anesth Analg.* 1977; **56**(1): 9–15.
[PubMed Abstract](#) | [Publisher Full Text](#)
3. Patel SS, Goa KL: **Sevoflurane. A review of its pharmacodynamic and pharmacokinetic properties and its clinical use in general anaesthesia.** *Drugs.* 1996; **51**(4): 658–700.
[PubMed Abstract](#) | [Publisher Full Text](#)
4. Strum DP, Eger EI 2nd: **Partition coefficients for sevoflurane in human blood, saline, and olive oil.** *Anesth Analg.* 1987; **66**(7): 654–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
5. Scheller MS, Saidman LJ, Partridge BL: **MAC of sevoflurane in humans and the New Zealand white rabbit.** *Can J Anaesth.* 1988; **35**(2): 153–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
6. Munday IT, Ward PM, Foden ND, *et al.*: **Sevoflurane degradation by soda lime in a circle breathing system.** *Anaesthesia.* 1996; **51**(7): 622–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
7. Cunningham DD, Huang S, Webster J, *et al.*: **Sevoflurane degradation to compound A in anaesthesia breathing systems.** *Br J Anaesth.* 1996; **77**(4): 537–43.
[PubMed Abstract](#) | [Publisher Full Text](#)
8. Eger EI 2nd, Ionescu P, Laster MJ, *et al.*: **Baralyme dehydration increases and soda lime dehydration decreases the concentration of compound A resulting from sevoflurane degradation in a standard anesthetic circuit.** *Anesth Analg.* 1997; **85**(4): 892–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
9. Gonsowski CT, Laster MJ, Eger EI 2nd, *et al.*: **Toxicity of compound A in rats. Effect of a 3-hour administration.** *Anesthesiology.* 1994; **80**(3): 556–65.
[PubMed Abstract](#) | [Publisher Full Text](#)
10. Gonsowski CT, Laster MJ, Eger EI 2nd, *et al.*: **Toxicity of compound A in rats. Effect of increasing duration of administration.** *Anesthesiology.* 1994; **80**(3): 566–73.
[PubMed Abstract](#) | [Publisher Full Text](#)
11. Marini F, Bellugi I, Gambi D, *et al.*: **Compound A, formaldehyde and methanol concentrations during low-flow sevoflurane anaesthesia: comparison of three carbon dioxide absorbers.** *Acta Anaesthesiol Scand.* 2007; **51**(5): 625–32.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
12. Gentz BA, Malan TP Jr: **Renal toxicity with sevoflurane: a storm in a teacup?** *Drugs.* 2001; **61**(15): 2155–62.
[PubMed Abstract](#) | [Publisher Full Text](#)
13. Leary JP: **Contaminated sevoflurane use reported from NY state.** *APSF Newsletter.* 1996; **11**: 37.
[Reference Source](#)
14. Callan CM: **Sevo manufacturer outlines circumstances, response.** *APSF Newsletter.* 1996; **11**: 37.
[Reference Source](#)
15. Bertolini J: **Hydrofluoric acid: a review of toxicity.** *J Emerg Med.* 1992; **10**(2): 163–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
16. McLeskey CH: **Anesthesiologist executive reports how Abbott made sevoflurane safer: water stops formation of highly toxic acid.** *APSF Newsletter.* 2000; **15**: 39.
[Reference Source](#)
17. Kharash ED, Subbarao GN, Cromack KR, *et al.*: **Sevoflurane formulation water content influences degradation by Lewis acids in vaporizers.** *Anesth Analg.* 2009; **108**(6): 1796–802.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
18. Kharash ED: **Sevoflurane: the challenges of safe formulation.** *APSF Newsletter.* 2007; **22**: 42.
[Reference Source](#)
19. Baker MT: **Sevoflurane: are there differences in products?** *Anesth Analg.* 2007; **104**(6): 1447–51.
[PubMed Abstract](#) | [Publisher Full Text](#)
20. Baker MT: **Sevoflurane-Lewis acid stability.** *Anesth Analg.* 2009; **108**(6): 1725–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
21. Eger EI 2nd: **New inhaled anesthetics.** *Anesthesiology.* 1994; **80**(4): 906–22.
[PubMed Abstract](#) | [Publisher Full Text](#)
22. Frink EJ, Brown BR: **Sevoflurane.** *Baillieres Clin Anaesthesiol.* 1993; **7**(4): 899–913.
[Publisher Full Text](#)
23. Young CJ, Apfelbaum JL: **Inhalational anesthetics: desflurane and sevoflurane.** *J Clin Anesth.* 1995; **7**(7): 564–77.
[PubMed Abstract](#) | [Publisher Full Text](#)
24. Behne M, Wilke HJ, Harder S: **Clinical pharmacokinetics of sevoflurane.** *Clin Pharmacokinet.* 1999; **36**(1): 13–26.
[PubMed Abstract](#) | [Publisher Full Text](#)
25. Delgado-Herrera L, Ostroff RD, Rogers SA: **Sevoflurane: approaching the ideal inhalational anesthetic. A pharmacologic, pharmacoeconomic, and clinical review.** *CNS Drug Rev.* 2001; **7**(1): 48–120.
[PubMed Abstract](#) | [Publisher Full Text](#)
26. Mapleson WW: **Effect of age on MAC in humans: a meta-analysis.** *Br J Anaesth.* 1996; **76**(2): 179–85.
[PubMed Abstract](#) | [Publisher Full Text](#)
27. Katoh T, Ikeda K: **Minimum alveolar concentration of sevoflurane in children.** *Br J Anaesth.* 1992; **68**(2): 139–41.
[PubMed Abstract](#) | [Publisher Full Text](#)
28. Inomata S, Watanabe S, Taguchi M, *et al.*: **End-tidal sevoflurane concentration for tracheal intubation and minimum alveolar concentration in pediatric patients.** *Anesthesiology.* 1994; **80**(1): 93–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
29. Lerman J, Sikich N, Kleinman S, *et al.*: **The pharmacology of sevoflurane in infants and children.** *Anesthesiology.* 1994; **80**(4): 814–24.
[PubMed Abstract](#)
30. Katoh T, Ikeda K: **The minimum alveolar concentration (MAC) of sevoflurane in humans.** *Anesthesiology.* 1987; **66**(3): 301–3.
[PubMed Abstract](#) | [Publisher Full Text](#)
31. Kimura T, Watanabe S, Asakura N, *et al.*: **Determination of end-tidal sevoflurane concentration for tracheal intubation and minimum alveolar anesthetic concentration in adults.** *Anesth Analg.* 1994; **79**(2): 378–81.
[PubMed Abstract](#) | [Publisher Full Text](#)
32. Fragen RJ, Dunn KL: **The minimum alveolar concentration (MAC) of sevoflurane with and without nitrous oxide in elderly versus young adults.** *J Clin Anesth.* 1996; **8**(5): 352–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
33. Yasuda N, Lockhart SH, Eger EI 2nd, *et al.*: **Comparison of kinetics of sevoflurane and isoflurane in humans.** *Anesth Analg.* 1991; **72**(3): 316–24.
[PubMed Abstract](#)
34. Shiraishi Y, Ikeda K: **Uptake and biotransformation of sevoflurane in humans: a comparative study of sevoflurane with halothane, enflurane, and isoflurane.** *J Clin Anesth.* 1990; **2**(6): 381–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
35. Doi M, Ikeda K: **Airway irritation produced by volatile anaesthetics during brief inhalation: comparison of halothane, enflurane, isoflurane and sevoflurane.** *Can J Anaesth.* 1993; **40**(2): 122–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
36. Baum VC, Yemen TA, Baum ID: **Immediate 8% sevoflurane induction in children: a comparison with incremental sevoflurane and incremental halothane.** *Anesth Analg.* 1997; **85**(2): 313–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
37. Sigston PE, Jenkins AM, Jackson EA, *et al.*: **Rapid inhalation induction in children: 8% sevoflurane compared with 5% halothane.** *Br J Anaesth.* 1997; **78**(4): 362–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
38. Yurino M, Kimura H: **Vital capacity rapid inhalation induction technique: comparison of sevoflurane and halothane.** *Can J Anaesth.* 1993; **40**(5 Pt 1): 440–3.
[PubMed Abstract](#) | [Publisher Full Text](#)
39. Yurino M, Kimura H: **A comparison of vital capacity breath and tidal breathing techniques for induction of anaesthesia with high sevoflurane concentrations in nitrous oxide and oxygen.** *Anaesthesia.* 1995; **50**(4): 308–11.
[PubMed Abstract](#) | [Publisher Full Text](#)
40. Nishiyama T, Nagase M, Tamai H, *et al.*: **Rapid induction with 7% sevoflurane inhalation-not the single-breath method.** *J Anaesth.* 1995; **9**(1): 36–9.
[PubMed Abstract](#) | [Publisher Full Text](#)

41. Kharash ED: **Biotransformation of sevoflurane.** *Anesth Analg.* 1995; **81**(6 Suppl): S27–38.
[PubMed Abstract](#) | [Publisher Full Text](#)
42. Kharash ED, Karol MD, Lanni C, *et al.*: **Clinical sevoflurane metabolism and disposition. I. Sevoflurane and metabolite pharmacokinetics.** *Anesthesiology.* 1995; **82**(6): 1369–78.
[PubMed Abstract](#) | [Publisher Full Text](#)
43. Kharash ED, Armstrong AS, Gunn K, *et al.*: **Clinical sevoflurane metabolism and disposition. II. The role of cytochrome P450 2E1 in fluoride and hexafluoroisopropanol formation.** *Anesthesiology.* 1995; **82**(6): 1379–88.
[PubMed Abstract](#) | [Publisher Full Text](#)
44. Malan TP Jr: **Sevoflurane and renal function.** *Anesth Analg.* 1995; **81**(6 Suppl): S39–45.
[PubMed Abstract](#) | [Publisher Full Text](#)
45. Kharash ED, Hankins DC, Thummel KE: **Human kidney methoxyflurane and sevoflurane metabolism. Intrarenal fluoride production as a possible mechanism of methoxyflurane nephrotoxicity.** *Anesthesiology.* 1995; **82**(3): 688–99.
[PubMed Abstract](#) | [Publisher Full Text](#)
46. Conzen PF, Nuscheler M, Melotte A, *et al.*: **Renal function and serum fluoride concentrations in patients with stable renal insufficiency after anesthesia with sevoflurane or enflurane.** *Anesth Analg.* 1995; **81**(3): 569–75.
[PubMed Abstract](#)
47. Nishiyama T, Aibiki M, Hanaoka K: **Inorganic fluoride kinetics and renal tubular function after sevoflurane anesthesia in chronic renal failure patients receiving hemodialysis.** *Anesth Analg.* 1996; **83**(3): 574–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
48. Lockhart SH, Yasuda N, Peterson N, *et al.*: **Comparison of percutaneous losses of sevoflurane and isoflurane in humans.** *Anesth Analg.* 1991; **72**(2): 212–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
49. Doi K, Kasaba T, Kosaka Y: **[A comparative study of the depressive effects of halothane and sevoflurane on medullary respiratory neurons in cats].** *Masui.* 1988; **37**(12): 1466–77.
[PubMed Abstract](#)
50. Ide T, Kochi T, Isono S, *et al.*: **Diaphragmatic function during sevoflurane anaesthesia in dogs.** *Can J Anaesth.* 1991; **38**(1): 116–20.
[PubMed Abstract](#) | [Publisher Full Text](#)
51. Ide T, Kochi T, Isono S, *et al.*: **Effect of sevoflurane on diaphragmatic contractility in dogs.** *Anesth Analg.* 1992; **74**(5): 739–46.
[PubMed Abstract](#)
52. **F** Kleinsasser A, Kuenszberg E, Loekinger A, *et al.*: **Sevoflurane, but not propofol, significantly prolongs the Q-T interval.** *Anesth Analg.* 2000; **90**(1): 25–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
53. Artru AA, Lam AM, Johnson JO, *et al.*: **Intracranial pressure, middle cerebral artery flow velocity, and plasma inorganic fluoride concentrations in neurosurgical patients receiving sevoflurane or isoflurane.** *Anesth Analg.* 1997; **85**(3): 587–92.
[PubMed Abstract](#) | [Publisher Full Text](#)
54. Kitaguchi K, Ohsumi H, Kuro M, *et al.*: **Effects of sevoflurane on cerebral circulation and metabolism in patients with ischemic cerebrovascular disease.** *Anesthesiology.* 1993; **79**(4): 704–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
55. **F** Conti A, Iacopino DG, Fodale V, *et al.*: **Cerebral haemodynamic changes during propofol-remifentanyl or sevoflurane anaesthesia: transcranial Doppler study under bispectral index monitoring.** *Br J Anaesth.* 2006; **97**(3): 333–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
56. Kunst G, Graf BM, Schreiner R, *et al.*: **Differential effects of sevoflurane, isoflurane, and halothane on Ca²⁺ release from the sarcoplasmic reticulum of skeletal muscle.** *Anesthesiology.* 1999; **91**(1): 179–86.
[PubMed Abstract](#) | [Publisher Full Text](#)
57. **F** Migita T, Mukaida K, Kobayashi M, *et al.*: **The severity of sevoflurane-induced malignant hyperthermia.** *Acta Anaesthesiol Scand.* 2012; **56**(3): 351–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
58. Liu J, Laster MJ, Eger EI 2nd, *et al.*: **Absorption and degradation of sevoflurane and isoflurane in a conventional anesthetic circuit.** *Anesth Analg.* 1991; **72**(6): 785–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
59. Frink EJ Jr, Malan TP, Morgan SE, *et al.*: **Quantification of the degradation products of sevoflurane in two CO₂ absorbents during low-flow anesthesia in surgical patients.** *Anesthesiology.* 1992; **77**(6): 1064–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
60. Bito H, Ikeda K: **Effect of total flow rate on the concentration of degradation products generated by reaction between sevoflurane and soda lime.** *Br J Anaesth.* 1995; **74**(6): 667–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
61. Fang ZX, Kandel L, Laster MJ, *et al.*: **Factors affecting production of compound A from the interaction of sevoflurane with Baralyme® and soda lime.** *Anesth Analg.* 1996; **82**(4): 775–81.
[PubMed Abstract](#) | [Publisher Full Text](#)
62. **F** Luttrupp HH, Johansson A: **Soda lime temperatures during low-flow sevoflurane anaesthesia and differences in dead-space.** *Acta Anaesthesiol Scand.* 2002; **46**(5): 500–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
63. Ruzicka JA, Hidalgo JC, Tinker JH, *et al.*: **Inhibition of volatile sevoflurane degradation product formation in an anesthesia circuit by a reduction in soda lime temperature.** *Anesthesiology.* 1994; **81**(1): 238–44.
[PubMed Abstract](#)
64. **F** Yamakage M, Kimura A, Chen X, *et al.*: **Production of compound A under low-flow anesthesia is affected by type of anesthetic machine.** *Can J Anesth.* 2001; **48**(5): 435–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
65. Neumann MA, Laster MJ, Weiskopf RB, *et al.*: **The elimination of sodium and potassium hydroxides from desiccated soda lime diminishes degradation of desflurane to carbon monoxide and sevoflurane to compound A but does not compromise carbon dioxide absorption.** *Anesth Analg.* 1999; **89**(3): 768–73.
[PubMed Abstract](#) | [Publisher Full Text](#)
66. Murray JM, Renfrew CW, Bedi A, *et al.*: **Amsorb: A new carbon dioxide absorbent for use in anesthetic breathing systems.** *Anesthesiology.* 1999; **91**(5): 1342–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
67. **F** Stabernack CR, Brown R, Laster MJ, *et al.*: **Absorbents differ enormously in their capacity to produce compound A and carbon monoxide.** *Anesth Analg.* 2000; **90**(6): 1428–35.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
68. Eger EI 2nd: **Compound A: does it matter?** *Can J Anesth.* 2001; **48**(5): 427–30.
[PubMed Abstract](#) | [Publisher Full Text](#)
69. Lerman J, Davis PJ, Welborn LG, *et al.*: **Induction, recovery, and safety characteristics of sevoflurane in children undergoing ambulatory surgery. A comparison with halothane.** *Anesthesiology.* 1996; **84**(6): 1332–40.
[PubMed Abstract](#) | [Publisher Full Text](#)
70. **F** Picard V, Dumont L, Pellegrini M: **Quality of recovery in children: sevoflurane versus propofol.** *Acta Anaesthesiol Scand.* 2000; **44**(3): 307–10.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
71. Welborn LG, Hannallah RS, Norden JM, *et al.*: **Comparison of emergence and recovery characteristics of sevoflurane, desflurane, and halothane in pediatric ambulatory patients.** *Anesth Analg.* 1996; **83**(5): 917–20.
[PubMed Abstract](#) | [Publisher Full Text](#)
72. Davis PJ, Greenberg JA, Gendelman M, *et al.*: **Recovery characteristics of sevoflurane and halothane in preschool-aged children undergoing bilateral myringotomy and pressure equalization tube insertion.** *Anesth Analg.* 1999; **88**(1): 34–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
73. Johannesson GP, Florén M, Lindahl SG: **Sevoflurane for ENT-surgery in children. A comparison with halothane.** *Acta Anaesthesiol Scand.* 1995; **39**(4): 546–550.
[PubMed Abstract](#) | [Publisher Full Text](#)
74. **F** Gupta A, Stierer T, Zuckerman R, *et al.*: **Comparison of recovery profile after ambulatory anesthesia with propofol, isoflurane, sevoflurane and desflurane: a systematic review.** *Anesth Analg.* 2004; **98**(3): 632–41.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
75. Cork RC, Vaughan RW, Bentley JB, *et al.*: **General anesthesia for morbidly obese patients—an examination of postoperative outcomes.** *Anesthesiology.* 1981; **54**(4): 310–3.
[PubMed Abstract](#) | [Publisher Full Text](#)
76. **F** Sollazzi L, Perilli V, Modesti C, *et al.*: **Volatile anesthesia in bariatric surgery.** *Obes Surg.* 2001; **11**(5): 623–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
77. **F** Casati A, Marchetti C, Spreafico E, *et al.*: **Effects of obesity on wash-in and wash-out kinetics of sevoflurane.** *Eur J Anaesthesiol.* 2004; **21**(3): 243–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
78. Lemmens HJ: **Perioperative pharmacology in morbid obesity.** *Curr Opin Anaesthesiol.* 2010; **23**(4): 485–91.
[PubMed Abstract](#) | [Publisher Full Text](#)
79. **F** Salihoglu Z, Karaca S, Kose Y, *et al.*: **Total intravenous anesthesia versus single breath technique and anesthesia maintenance with sevoflurane for bariatric operations.** *Obes Surg.* 2001; **11**(4): 496–501.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
80. Zaugg M, Lucchinetti E, Uecker M, *et al.*: **Anaesthetics and cardiac preconditioning. Part I. Signalling and cytoprotective mechanisms.** *Br J Anaesth.* 2003; **91**(4): 551–65.
[PubMed Abstract](#) | [Publisher Full Text](#)
81. Tanaka K, Ludwig LM, Kersten JR, *et al.*: **Mechanisms of cardioprotection by volatile anesthetics.** *Anesthesiology.* 2004; **100**(3): 707–21.
[PubMed Abstract](#) | [Publisher Full Text](#)
82. Stowe DF, Kevin LG: **Cardiac preconditioning by volatile anesthetic agents: a defining role for altered mitochondrial bioenergetics.** *Antioxid Redox Signal.* 2004; **6**(2): 439–48.
[PubMed Abstract](#) | [Publisher Full Text](#)
83. Bienengraeber MW, Weihrauch D, Kersten JR, *et al.*: **Cardioprotection by volatile anesthetics.** *Vascul Pharmacol.* 2005; **42**(5–6): 243–52.
[PubMed Abstract](#) | [Publisher Full Text](#)
84. Pratt PF Jr, Wang C, Weihrauch D, *et al.*: **Cardioprotection by volatile anesthetics: new applications for old drugs?** *Curr Opin Anaesthesiol.* 2006; **19**(4): 397–403.
[PubMed Abstract](#) | [Publisher Full Text](#)

85. Pagel PS, Hudetz JA: **Delayed cardioprotection by inhaled anesthetics.** *J Cardiothorac Vasc Anesth.* 2011; **25**(6): 1125–40.
[PubMed Abstract](#) | [Publisher Full Text](#)
86. Zaugg M, Lucchinetti E, Garcia C, *et al.*: **Anaesthetics and cardiac preconditioning. Part II. Clinical implications.** *Br J Anaesth.* 2003; **91**(4): 556–76.
[PubMed Abstract](#) | [Publisher Full Text](#)
87. De Hert SG, Turani F, Mathur S, *et al.*: **Cardioprotection with volatile anesthetics: mechanisms and clinical implications.** *Anesth Analg.* 2005; **100**(6): 1584–93.
[PubMed Abstract](#) | [Publisher Full Text](#)
88. De Hert SG: **The concept of anaesthetic-induced cardioprotection: clinical relevance.** *Best Pract Res Clin Anaesthesiol.* 2005; **19**(3): 445–59.
[PubMed Abstract](#) | [Publisher Full Text](#)
89. De Hert SG: **Anesthetic preconditioning: how important is it in today's cardiac anesthesia?** *J Cardiothorac Vasc Anesth.* 2006; **20**(4): 473–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
90. De Hert S: **Cardioprotection in anaesthesia.** *Minerva Anaesthesiol.* 2008; **74**: 259–70.
91. De Hert S, Preckel B, Schlack WS: **Update on inhalational anaesthetics.** *Curr Opin Anaesthesiol.* 2009; **22**(4): 491–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
92. Frässdorf J, De Hert S, Schlack W: **Anaesthesia and myocardial ischaemia/ reperfusion injury.** *Br J Anaesth.* 2009; **103**(1): 89–98.
[PubMed Abstract](#) | [Publisher Full Text](#)
93. De Hert SG: **Is anaesthetic cardioprotection clinically relevant? Another futile search for a magic bullet?** *Eur J Anaesthesiol.* 2011; **28**(9): 616–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
94. Bein B: **Clinical application of the cardioprotective effects of volatile anaesthetics: PRO—get an extra benefit from a proven anaesthetic free of charge.** *Eur J Anaesthesiol.* 2011; **28**(9): 620–2.
[PubMed Abstract](#) | [Publisher Full Text](#)
95. Van Rompaey N, Barvais L: **Clinical application of the cardioprotective effects of volatile anaesthetics: CON—total intravenous anaesthesia or not total intravenous anaesthesia to anaesthetise a cardiac patient?** *Eur J Anaesthesiol.* 2011; **28**(9): 623–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
96. **F** Van der Linden PJ, Dierick A, Wilmin S, *et al.*: **A randomized controlled trial comparing an intraoperative goal-directed strategy with routine clinical practice in patients undergoing peripheral arterial surgery.** *Eur J Anaesthesiol.* 2010; **27**(9): 788–93.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
97. **F** Zangrillo A, Testa V, Aldrovandi V, *et al.*: **Volatile agents for cardiac protection in noncardiac surgery: a randomized controlled study.** *J Cardiothorac Vasc Anesth.* 2011; **25**(6): 902–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
98. **F** Lurati Buse GA, Schumacher P, Seeberger E, *et al.*: **Randomized comparison of sevoflurane versus propofol to reduce perioperative myocardial ischemia in patients undergoing noncardiac surgery.** *Circulation.* 2012; **126**(23): 2696–704.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
99. De Hert SG: **Cardioprotection by volatile anesthetics: what about noncardiac surgery?** *J Cardiothorac Vasc Anesth.* 2011; **25**(6): 899–901.
[PubMed Abstract](#) | [Publisher Full Text](#)
100. **F** Beck-Schimmer B, Breitenstein S, Urech S, *et al.*: **A randomized controlled trial on pharmacological preconditioning in liver surgery using a volatile anesthetic.** *Ann Surg.* 2008; **248**(6): 909–18.
[PubMed Abstract](#) | **F1000 Recommendation**
101. **F** Beck-Schimmer B, Breitenstein S, Bonvini JM, *et al.*: **Protection of pharmacological postconditioning in liver surgery: results of a prospective randomized controlled trial.** *Ann Surg.* 2012; **256**(5): 837–44; discussion 844–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
102. **F** De Conno E, Steurer MP, Wittlinger M, *et al.*: **Anesthetic-induced improvement of the inflammatory response to one-lung ventilation.** *Anesthesiology.* 2009; **110**(6): 1316–26.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
103. **F** Mellon RD, Simone AF, Rappaport BA: **Use of anesthetic agents in neonates and young children.** *Anesth Analg.* 2007; **104**(3): 509–20.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
104. Sun L: **Early childhood general anaesthesia exposure and neurocognitive development.** *Br J Anaesth.* 2010; **105**(Suppl 1): i61–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | **Free Full Text**
105. **F** Davidson AJ: **Neurotoxicity and the need for anesthesia in the newborn: does the emperor have no clothes?** *Anesthesiology.* 2012; **116**(3): 507–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
106. Hussain M, Berger M, Eckenhooff RG, *et al.*: **General anesthetic and the risk of dementia in elderly patients: current insights.** *Clin Interv Aging.* 2014; **9**: 1619–28.
[PubMed Abstract](#) | [Publisher Full Text](#) | **Free Full Text**
107. Strøm C, Rasmussen LS, Sieber FE: **Should general anaesthesia be avoided in the elderly?** *Anaesthesia.* 2014; **69**(Suppl 1): 35–44.
[PubMed Abstract](#) | [Publisher Full Text](#)
108. Mashour GA, Woodrum DT, Avidan MS: **Neurological complications of surgery and anaesthesia.** *Br J Anaesth.* 2015; **114**(2): 194–203.
[PubMed Abstract](#) | [Publisher Full Text](#)
109. **F** Guay J: **General anaesthesia does not contribute to long-term post-operative cognitive dysfunction in adults: A meta-analysis.** *Indian J Anaesth.* 2011; **55**(4): 358–63.
[PubMed Abstract](#) | [Publisher Full Text](#) | **Free Full Text** | **F1000 Recommendation**

Open Peer Review

Current Peer Review Status:

Version 1

Reviewer Report 25 August 2015

<https://doi.org/10.5256/f1000research.6744.r10111>

© 2015 Seeberger M. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Manfred Seeberger

Department of Anaesthesiology and Intensive Care Medicine, Klinik Hirslanden, Witellikerstrasse 40, Zurich, 8032, Switzerland

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 25 August 2015

<https://doi.org/10.5256/f1000research.6744.r10110>

© 2015 Eckenhoff R. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Roderic Eckenhoff

Department of Anesthesiology and Critical Care, University of Pennsylvania, Philadelphia, PA, 19104-6112, USA

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research