CHAPTER II
REVIEW OF
LITERATURE
Inhalational induction remained standard for over one hundred years but was replaced by intravenous induction as it provided a rapid and predictable loss of consciousness. Intravenous induction is associated with smooth recovery and less postoperative sickness as compared to inhalational agents. The anaesthesiologist has the benefit of rapid induction with no 'second stage' of anaesthesia and its attendant delirium.\(^{19}\)

As intravenous induction is rapid and there is predictable loss of consciousness, it therefore overcomes the feeling of suffocation from application of face mask and the gradual loss of consciousness with inhalational agents which is unpleasant. Moreover, the anaesthesiologist obtains the benefit of rapid induction without second stage of anaesthesia and its attendant delirium. The patients' only fear is venepuncture and pain on injection.

Ideally intravenous induction agent should be water soluble, non irritant, rapidly acting, with no antanalgesic action and minimal cardiovascular and respiratory depression. Ideal intravenous anaesthetic did not exist was evidenced by the number of new such agents that appeared from time to time. Unfortunately, many of these newer drugs, despite having several advantages, suffered from disadvantages. Etomidate though cardiostable is sparingly used
these days because of its suppressive action on adrenals. Althesin and proponadid were solubilized in cremophor and a high incidence of hypersensitivity reactions terminated their use followed by their withdrawal from the market.

Thiopentone used for the first time in late 1930s proved satisfactory in being rapid in onset, reliable and smooth in action. Although it still remains the most commonly used drug for induction the world over, but it can cause marked fall in arterial blood pressure, particularly in the elderly and sick patients or in the presence of hypovolemia. It also causes enzyme induction and exacerbation of acute porphyria. Occasional laryngospasm or bronchospasm have also been reported with its use.19

**PROPOFOL**

Propofol is a new intravenous anaesthetic agent which has been available since 1982 as a 1% solution in an aqueous solution of 10% soyabean oil, 2.25% glycerol and 1.2% purified egg phosphatide. It is devoid of allergic potential as compared to older preparation. The structure of propofol, 2,6-disopropylphenol is shown in figure.

![Chemical structure of propofol, 2,6-disopropylphenol](image)
Administration of propofol 2-2.5 mg kg$^{-1}$ over 15 seconds produces unconsciousness within about 30 seconds. Awakening is more rapid and complete as compared to thiopentone or methohexitone. This rapid return to consciousness with minimal residual central nervous system effects seems to be the most important advantage of propofol over other drugs used as induction agents.

**Pharmacokinetics**

Clearance of propofol, from the plasma exceeds hepatic blood flow, emphasizing that tissue uptake as well as metabolism is important in removal of this drug from the plasma. Less than 0.3% is excreted unchanged in urine along with inactive glucoronide and sulphate conjugates. The elimination half time is 0.5-1.5 hours. Patients older than sixty years of age exhibit a reduced rate of plasma clearance of propofol compared with younger adults. Propofol readily crosses the placenta but is rapidly cleared from the neonatal circulation.

**Uses**

Propofol has become an extremely valuable adjuvant for a variety of diagnostic and therapeutic procedures. Although propofol was initially viewed as an outpatient anaesthetic, it is now more widely used during paediatric, neurosurgical, cardiovascular anaesthesia, ophthalmic surgery as well as for sedation in the intensive care unit.
Dosage

In healthy adults, the induction dose of propofol is 2.0-2.5 mg kg\(^{-1}\) and is modified by factors such as premedication and the state of hydration. Older or debilitated individuals require less propofol for induction (approximately 1.5 mg kg\(^{-1}\)).\(^{21}\)

Propofol 2 mg kg\(^{-1}\) intravenous followed by 150 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) intravenous, results in decreased cerebral perfusion pressure, cerebral blood flow and intracranial pressure. It increases the latency and decreases the amplitude of somatosensory evoked potentials.

It produces reduction in blood pressure that are greater than those evoked by comparable doses of thiopentone. These decreases in blood pressure are often accompanied by corresponding changes in cardiac output or systemic vascular resistance. It is more effective than thiopentone in blunting the magnitude of pressor response. Despite decrease in blood pressure, heart rate remains unchanged. Blood pressure effects of propofol may be exaggerated in hypovolemic patients, elderly patients and in patients with compromised left ventricular function.

Propofol is a profound depressant of ventilation, causing many patients to become transiently apneic following rapid intravenous injection. Opioids administered with the preoperative medication may enhance this ventilatory depressant effect. It does not adversely affect hepatic or renal function. It does
not alter tests of coagulation or platelet function. The emulsion form of propofol appears to be devoid of allergic potential. It causes pain on injection but results in phlebitis or thrombosis quiet infrequently.

Propofol does not block the secretion of cortisol following single dose or as continuous infusion. Excitatory responses such as hypertonus, tremor, hiccup or spontaneous movements with induction of anaesthesia with propofol are rare. Nausea and vomiting are infrequent. It decreases intraocular pressure, does not trigger malignant hyperthermia and exacerbation of porphyria has not been reported to occur. The vehicle for propofol does not contain antibacterial preservations, emphasizing the importance of maintaining strict asepsis when handling the drug.20

In 1985, Utting et al studied and compared thiopentone sodium and propofol for induction. They found that an induction dose of propofol 2.5 mg kg⁻¹ was effective and comparable to thiopentone 5.0 mg kg⁻¹. Propofol caused a fall in arterial blood pressure in healthy patients which was significantly greater than that seen after thiopentone. Diastolic pressure fell to a proportionally greater degree suggesting that one of the mechanism involved is fall in peripheral vascular resistance. They observed that fall in blood pressure seen in healthy patients after induction with propofol was dose related and therefore predictable. They found propofol to be an easy drug for the induction of anaesthesia. Pain on injection was a problem in 38% of subjects. Excitatory phenomenon were not
a feature of the drug.\textsuperscript{22}

In a study in 1987, Gerald Edelist compared propofol and thiopentone as induction agents in outpatient surgery. They studied ninety healthy ASA physical status I or II female patients scheduled for therapeutic abortion. Sixty patients received induction dose of propofol (2.5 mg kg\textsuperscript{-1}) and 30 patients received thiopentone (4 mg kg\textsuperscript{-1}). Anaesthesia was maintained with N\textsubscript{2}O and O\textsubscript{2} plus intermittent doses of the agent used for induction. Ninety seven percent of patients induced with propofol had excellent induction as compared to eighty percent patients induced with thiopentone. A large number of patients receiving propofol exhibited minor extraneous muscular movements during induction. Recovery with the propofol group was significantly more rapid than with thiopentone group. The respiratory effects of the two drugs were not significantly different. Propofol caused a significantly greater decrease in pulse rate, systolic, diastolic and mean pressure than thiopentone.\textsuperscript{23}

In the same year, Johnston et al compared propofol and thiopentone for outpatient anaesthesia in ninety three women (ASA physical status I or II) scheduled for dilatation and curettage. The mean duration of anaesthesia was same in the two groups. The mean induction time was longer in the propofol group than in thiopentone group (p <0.001). Apnoea, defined as the cessation of respiration for more than 15 seconds, occurred during induction in 47\% of the propofol group and 23\% in the thiopentone group (p <0.05). Both drugs had
similar effect on heart rate, blood pressure and respiratory rate. Pain occurred in 27% patients in propofol group and 3% in the thiopentone group (p <0.05). Twitching or jerking of the arms or face were seen during induction in 10% of the propofol group versus 6.7% of the thiopentone group. The incidence of nausea and vomiting postoperatively was the same in the two groups (propofol 10% versus thiopentone 6.7%) (p >0.05).24

In 1992, Blake et al studied propofol induction for laryngeal mask insertion. They studied dose requirement for successful insertion of LMA and its cardiorespiratory effects. Forty eight patients (ASA I-II) were randomly given one of the four induction doses of propofol: 1.5, 2.0, 2.5 or 2.8 mg kg⁻¹ lean body weight. The propofol bolus was given over 20 seconds and first attempt at LMA insertion was made at 90 seconds. MAP, HR, SaO₂ and the time of insertion of LMA were recorded. LMA was inserted at 90 seconds in 69% and by 180 seconds in all but one patient. Insertion was less successful after 1.5 mg kg⁻¹ but did not vary with other dosages.25

In 1991, Hannallah et al studied the induction dose, induction characteristics, and cardiovascular and respiratory effects of propofol in ninety, 3-12 years old unpremedicated children. Propofol in a dose of 1-3 mg kg⁻¹ was injected in antecubital vein over 10-30 seconds. Successful induction was defined by loss of eyelash reflex occurring within 50 seconds of conclusion of propofol injection and followed by subsequent acceptance of face mask without
excessive movement. The effective dose of propofol resulting in loss of eyelash reflex in 50% and 95% of children were 1.3 and 2.0 mg kg$^{-1}$. The corresponding $ED_{50}$ and $ED_{95}$ for induction that included acceptance of face mask was 1.54 and 2.3 mg respectively. There was a 6.6% incidence of mild to moderate pain on injection and 12.7% incidence of involuntary movement. Apnoea (cessation of breathing >20 seconds) was seen in 20% of the patients. Blood pressure decreased by more than 20% of baseline value in 48% of subjects. They concluded that propofol was an effective induction agent in children. A dose of 2.5-3.0 mg kg$^{-1}$ was recommended to ensure a smooth transition to an inhalation maintenance technique.$^{26}$

In order to avoid cremophor-related reactions and reduce the incidence of pain on injection, di-isopropylphenol (ICI 35,868, propofol) was reformulated as an emulsion. In 1984, Cummings et al investigated the dose requirement for propofol in this new formulation for induction of anaesthesia. One hundred and fifty patients received an induction dose of propofol in this new formulation. The dose required to induce anaesthesia in 95% of healthy, unpremedicated patient was 2.5 mg kg$^{-1}$. Induction was associated with cardiovascular and respiratory depression. There were no adverse reactions although there were number of minor side effects. The incidence of pain on injection was low (3%) and the overall quality of induction was assessed as good or adequate in 92% of patients.$^{21}$
The induction of sleep by inhalation has a tradition in anaesthesia which encompasses our very roots. While it is unlikely that inhalational induction of anaesthesia will replace use of rapidly acting intravenous induction agents, but insertion of an intravenous needle (or cannula), and even injection of intravenous anaesthetics (e.g. methohexitone, etomidate, propofol), may cause considerable discomfort, especially in children. While the use of local anaesthetics can reduce the discomfort, poor veins and lack of cooperation can make intravenous induction of anaesthesia impractical for many patients. Inhalational induction of anaesthesia by mask may be preferable in some of these patients, assuming that this could be accomplished rapidly and smoothly. Finally inhalational induction may be desirable on those occasions where there is danger of airway obstruction following rapid loss of consciousness. Intravenous anaesthetic agents routinely provide a means of rapid, pleasant induction. However these drugs may induce unacceptable degrees of hypotension, have a hangover effect, and tend to cause apnoea, rendering the administration of inhalational agent for subsequent maintenance of anaesthesia more difficult. Furthermore, they may occasionally cause severe adverse reactions.

With inhalational anaesthetic agents, unconsciousness ensues when an effective drug concentration is achieved in brain tissue. Because of the high lipid solubility of these agents, there is dose relation between drug concentration in arterial blood and in brain, and unless there is severe lung disease, concentration
in alveoli and pulmonary end capillary are virtually equal. Rate of onset of anaesthesia is therefore dependent primarily upon the rate at which alveolar drug concentration increases.

Alveolar concentration increases slowly with the conventional inhalational techniques as drug concentration is diluted by the air present in the lungs at functional residual capacity. Uptake of drug by blood produces a large reduction in alveolar concentration so it is necessary to administer an inspired concentration much higher than alveolar concentration for rapid induction.\(^8\)

A new technique for inhalational induction by means of a single vital capacity breath was described in 1982 by Ruffle, which was rapid, safe and readily accepted by the patient. This study was conducted in ASA class I or II patients over 10 years of age without opiate premedication. The circle or non-rebreathing system was flushed with 4% halothane in oxygen. The patients were instructed to exhale to the residual volume and hold breath while mask was placed tightly on face. The patient inhaled slowly through mouth to minimise the odour, coughing and breath holding. After inspiring a vital capacity of 4% halothane, patients were asked to hold the breath. Loss of consciousness occurred after 15-20 seconds followed by regular spontaneous breathing. Nitrous oxide was then added to inspired gas. Inspired halothane concentration of 3-4% for the next 3-4 minutes produced surgical plane of anaesthesia.\(^{27}\)
This single breath technique has advantages over intravenous induction of anaesthesia. Venepuncture is avoided while the patient is awake; the risk of anaphylaxis with intravenous agents is avoided; there is a generally smooth transition from induction to maintenance phase; and the hangover effect associated with intravenous anaesthetic agents, particularly barbiturates, is also avoided.8

Again in 1982, Ruffle et al compared the onset of hypnosis with halothane using single breath, triple breath and conventional technique. Eight healthy volunteers in the age group of 25-45 years were selected in whom general anaesthesia was induced thrice in a single day. In all trials volunteers breathed halothane for a total of four minutes. Each volunteer reached unconsciousness on all trials. Onset of unconsciousness was most rapid with three vital capacity breaths of 4% halothane (average 69 seconds), intermediate with a single vital capacity breath (112 seconds) and slowest with gradually increasing concentration of halothane (average 166 seconds). These times were significantly different (p <0.01). Excitement on induction was seen only with the conventional induction technique in three of the eight volunteers. Vital signs and oxygen saturation remained at safe levels for all trials. Oxygen saturation never dropped below 89%. Blood pressure never dropped below 90/53. Volunteers unanimously preferred the more rapid inductions.28

Ruffle, again in the year 1985 studied the cardiopulmonary and anaesthetic responses of nine healthy volunteers, breathing 1,2,3 or 4%
halothane in oxygen. In supine position all subjects breathing room air were asked to exhale to residual volume and then take a vital capacity breath of 1,2,3 or 4% halothane in oxygen. After a breath holding time ranging from 30-90 seconds, they exhaled and then breathed spontaneously the same anaesthetic mixture for up to 2 minutes. The ECG, arterial pressures, heart sounds and oxygen saturation were monitored. The maximum effect was seen after breathing 4% halothane. All volunteers were amnesic after their first breath and unresponsive to command after 2 minutes. Little or no excitement occurred. A maximum decrease of 12 mm Hg in systolic pressure was observed in patients breathing 4% halothane. Bradycardia, hypoxia and clinically important hypercarbia did not occur. No volunteers found this technique to be unpleasant. They found that rapid induction of general anaesthesia with 2-4% halothane in oxygen to be effective, safe and well accepted by healthy young adults.29

Wilton and Thomas in the year 1986 studied inhalational induction of anaesthesia, using a single vital capacity breath of 4% halothane in 66% nitrous oxide and 33% oxygen in 100 unpremedicated outpatients. They found this technique acceptable to most of the patients studied with a mean induction time of 83±21 seconds (measured from beginning of inspiration to loss of eyelash reflex). Relative cardiovascular stability was a notable finding of the technique, with a slight decrease in the mean arterial pressure of only 10%. Anaesthetic induction time was unaffected by age, weight or smoking habits.30
The halogenated agents are comparatively young in anaesthetic terms and their structural analogues are still being explored in search for the elusive ideal inhalational anaesthetic agent.\textsuperscript{31}

Ideal inhalational agent should be prepared readily and inexpensively; it should be stable without preservatives; with a long shelf-life to permit storage and use in a range of climatic conditions; it must be nonflammable and non-explosive in concentrations used clinically; it should be potent to allow high concentration of oxygen to be used concurrently and possess a low blood gas partition coefficient to produce rapid induction and emergence and should be flexible in adjusting the depth of anaesthesia; it should be pleasant to inhale, permitting a smooth gaseous induction and devoid of adverse pharmacological effects on the cardiovascular and respiratory system; it should cause readily controlled depression of central nervous system producing analgesia but should lack stimulant activity; the compound should resist biotransformation and devoid of organ-specific toxicity.\textsuperscript{3}

Halothane, enflurane and isoflurane meet several of these criteria, but all have serious imperfections. Halothane is decomposed by light and must be stored in amber coloured bottles with 0.01\% thymol as stabiliser. The high initial manufacturing cost of isoflurane was a barrier to early commercial success. Enflurane and isoflurane are not pleasant to inhale but halothane, although more pleasant, is the least flexible in altering the depth of anaesthesia as it possesses
the highest blood/gas solubility coefficient. All three depress the respiratory response to hypoxia in dose dependent manner. All cause hypotension, halothane mainly as a direct depression of cardiac output, and isoflurane mainly by production of peripheral vasodilatation; with enflurane occupying an intermediate position.\textsuperscript{11}

### SEVOFLURANE

Sevoflurane introduced recently overcomes the adverse effects of currently used inahalational agents. Sevoflurane was first synthesised in 1968 by Regan at Travenol Laboratories, Illinois, while he was investigating a series of halomethyl poly-flouro isopropyl ethers. This compound was initially reported by his co-workers in 1971.\textsuperscript{17} The first volunteer trials reported by Holaday and Smith in 1981, were encouraging.\textsuperscript{32} However further work was slow because of the problem of biotransformation and instability with sodalime. Buxter Travenol sold the rights of sevoflurane to Anaquest who in turn sold these to Maruishi Company. Maruishi continued research and development, eventually releasing sevoflurane for clinical use in Japan in May 1990. The continuing search for an inhaled agent with rapid induction, emergence and recovery characteristics has stimulated the recent reexamination of sevoflurane.\textsuperscript{15}

It is a halogenated methyl propyl ether with the following structure:
Chemical structure of sevoflurane

The molecule does not contain an asymmetric carbon atom and therefore does not exist as optical isomers. In this respect it is unique amongst currently available anaesthetics.

Physical properties

Sevoflurane is related structurally to isoflurane and enflurane and shares many of the physical properties of these drugs. Sevoflurane has a boiling point of 58.6°C and a saturated vapour pressure of 160 mm Hg at 20°C, similar to those of halothane, enflurane and isoflurane. Therefore, it can be delivered using standard vaporizer technology.\textsuperscript{16} The blood:gas partition coefficient of sevoflurane is 0.69 which in common with desflurane is substantially lower than other agents.\textsuperscript{18} The low blood:gas solubility of sevoflurane provides rapid induction and recovery from anaesthesia. The minimal alveolar concentration of sevoflurane is reported to be between 1.71% and 2.05%. This value was reduced to 0.66% in an adult population by addition of approximately 60% nitrous oxide. The MAC for sevoflurane, in common with other anaesthetic, is somewhat higher
in children.33

### Comparison of sevoflurane with existing volatile anaesthetics

Scale: 0=Worst, +++=Best

<table>
<thead>
<tr>
<th>Property</th>
<th>Halothane</th>
<th>Enflurane</th>
<th>Isoflurane</th>
<th>Desflurane</th>
<th>Sevoflurane</th>
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<tr>
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<tr>
<td>Cost (at low flow)</td>
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**Cardiovascular effects:** In volunteers, about 1MAC sevoflurane caused a decrease in systemic arterial pressure, diastolic more than systolic, and did not appreciably increase heart rate.32

**Respiratory effects:** Sevoflurane causes less increase in respiratory rate with a larger tidal volume and longer inspiratory and expiratory times. The agent does not irritate the upper airway and is suitable for inhalation induction.34

**CNS effects:** EEG effects of sevoflurane are similar to other inhaled anaesthetics. However, there have been reports of possible convulsions occurring during induction of anaesthesia.32
Effects on muscle: Sevoflurane potentiates non depolarising muscle relaxants. Malignant hyperpyrexia has been reported during sevoflurane anaesthesia in a four year old child. So the agent should be avoided in susceptible individuals.35

RENAL EFFECTS

Clinical experience with methoxyflurane suggested that renal impairment could occur if a "threshold" serum flouride concentration of 50 μmol l⁻¹ was exceeded, although clinically evident renal dysfunction was rarely observed at concentration less than 80μmol l⁻¹.36 After administration of sevoflurane anaesthesia for 1 hour, Holaday and Smith found a mean serum flouride concentration of 22 μmol l⁻¹ in six volunteers.32 A positive correlation has been demonstrated between peak concentration of flouride ions and duration of exposure to sevoflurane. After 1.1 MAC hour of sevoflurane, Shruishi and Ikeda found that the mean peak serum inorganic flouride concentration was only 19.3 μmol l⁻¹. No alterations in urinary enzymes or postoperative renal functions were detected after sevoflurane anaesthesia (0.8-2%) lasting 9-10 hours, despite a mean peak serum flouride concentration in excess of 50 μmol l⁻¹.37

It appears that renal toxicity is not a consequence of exceeding a threshold serum concentration of flouride ions. The apparent lack of renal toxicity with sevoflurane in humans may be related to its rapid elimination and site of metabolism. The rapid elimination of sevoflurane reduces the total amount of drug available for in vivo metabolism by hepatic microsomal enzymes, resulting
in a rapid decrease in organic flouride concentration after sevoflurane administration, and preventing exposure to flouride ions for a long enough duration to lead to clinically detectable toxicity. Recent evidence from Kharasch, Hankins and Thhumel suggested that intrarenal production of flouride ions may be more important in the aetiology of methoxyflurane induced toxicity than peak serum flouride concentration. 38

HEPATIC EFFECTS

The other major breakdown product of sevoflurane metabolism is hexaflouroisopropanol, an organic flouride molecule which is excreted in the urine as a glucoronide conjugate. Although this molecule is potentially hepatotoxic, conjugation of hexaflouroisopropanol occurs so rapidly that clinically significant liver damage seems theoretically impossible.39

METABOLISM AND TOXICITY

Sevoflurane is a comparatively unstable molecule and undergoes a moderate degree of metabolism (approximately 5%) and also breaks down in the presence of sodalime and baralyme at elevated temperatures. Both processes result in potentially toxic products. However, unlike other anaesthetic ethers, sevoflurane does not posses a CF₂H group, and so does not result in the production of carbon monoxide in association with excessively dry carbon dioxide absorbants.
Sevoflurane is metabolised by the liver to produce hexafluoroisopropanol and inorganic flouride ions. In humans, upto 5% of administered doses of sevoflurane undergoes metabolism, catalyzed by the 2 E1 isoform of cytochrome P450. Studies in animals have demonstrated that this enzyme can be induced by phenobarbitone, isoniazid and ethanol, leading to increased serum inorganic flouride concentration and urinary excretion of flouride ions.40

Sevoflurane appears to be a practical and well tolerated induction agent in all age groups investigated to date. In children, it will challenge halothane as inhalational induction agent of choice. Although the use of sevoflurane for inhalational induction in adults is likely to be more limited, it provides a viable alternative to intravenous induction techniques.15

In 1992, Yurino and Kimura compared vital capacity rapid inhalational induction of anaesthesia with sevoflurane and isoflurane in forty six volunteers, out of which 25 inhaled sevoflurane and 21 isoflurane. Subjects were unpremedicated and breathed approximately 1.7 MAC equivalents of either vapour. There were no significant differences in the patients' cardiovascular, respiratory and electrocardiographic variables. The mean time for induction of anaesthesia with sevoflurane (120 seconds) was significantly shorter than with isoflurane (145 seconds), reflecting lower blood gas solubility of sevoflurane. There were fewer induction complications in the sevoflurane group. Subjects in
the sevoflurane group found the induction of anaesthesia more pleasant and were willing to undergo it again compared to subjects in the isoflurane group. They found sevoflurane superior to isoflurane in their study.41

In the following year, Yurino and Kimura again compared induction of anaesthesia using the vital capacity rapid inhalational induction technique with sevoflurane and halothane. Subjects were unpremedicated and breathed approximately 2.6MAC equivalent of either agent. There were no differences in the patients' cardiovascular or respiratory variables. The mean time for induction of anaesthesia with halothane (153±46 seconds) was slower than with sevoflurane (81±52 seconds, p <0.05), reflecting higher blood gas solubility of halothane. There were fewer induction complications such as coughing and movements in the sevoflurane than in the halothane group. Subjects in the sevoflurane group found the smell of anaesthetic more acceptable than those in the halothane group (65% vs 13%). Patients in both the groups had no objection to undergo the procedure again. They concluded that both halothane and sevoflurane were effective in vital capacity rapid inhalational induction of anaesthesia without premedication. However, the slower speed of induction with halothane frustrated the anesthesiologist because of longer induction time, and increased the chances of pronounced excitatory phenomenon.42

In the same year again, Yurino and Kimura compared vital capacity rapid inhalational induction (VCRII) of anaesthesia technique and the conventional
spontaneous inhalational induction technique, each using 4.5% sevoflurane in N₂O and oxygen in unpremedicated patients. Patients in vital capacity rapid inhalational induction group required only half the time of conventional inhalational induction (54 sec. and 108 seconds respectively) and were not associated with cardiovascular instability. The two techniques were found acceptable by most of the volunteers studied. But, induction with sevoflurane using VCRII technique resulted in fewer complications and was more pleasant.⁴³

In a study in 1995, Yurino and Kimura compared vital capacity breath and tidal breathing techniques for induction of anaesthesia with high sevoflurane concentration (7.5%) in nitrous oxide and oxygen. In this study, thirty five subjects were randomly assigned to a vital capacity breath group (19) or to a tidal breathing group (16). The mean time for induction was faster with vital capacity breath (41 seconds) than with tidal breathing (52 seconds, p <0.05). Involuntary movements were observed in three patients in the tidal breathing group but none in the vital capacity breath group. Coughing occurred in a quarter of the subjects in the tidal breathing group and in one subject of the vital capacity group. The vital capacity group had rapid and pleasant induction without premedication. They suggested that the vital capacity breath technique was necessary for inhalational induction of anaesthesia as it allowed the subject to pass reliably and rapidly through the initial stages of excitement.⁴⁴
In another study in 1995, Yurino and Kimura compared induction time and characteristics of sevoflurane and combination of sevoflurane and nitrous oxide. They evaluated 40 volunteers in a randomised study using 7.5% sevoflurane in O₂ or combination of sevoflurane with nitrous oxide using a single breath induction technique. Sevoflurane in nitrous oxide and oxygen reduced induction time by 15% compared to sevoflurane in oxygen alone (41±16 and 48±17 seconds respectively), which was not statistically significant. There were few induction complications, such as coughing, laryngospasm, breath holding, movements of a limb and excessive salivation in either group. Thus the addition of nitrous oxide neither increased the number of complications nor decreased the induction time which might be explained on the fact that sevoflurane might act as quickly as nitrous oxide due to its blood gas solubility (0.69) which is closer to that of N₂O (0.47).⁴⁵

In 1992, Smith, Ding and White compared induction and recovery characteristics in three group of patients who received either propofol or sevoflurane as induction agents. However the anaesthesia was maintained with isoflurane and N₂O in group I and sevoflurane in N₂O in group II and group III. Inhaled induction of anaesthesia with sevoflurane - N₂O was rapid (109±25 seconds to loss of consciousness) and without any untoward haemodynamic changes or episodes of coughing and laryngospasm. Emergence time after discontinuation of isoflurane - N₂O was significantly longer than after propofol
sevoflurane - N₂O or sevoflurane N₂O alone. They concluded that induction of anaesthesia with either propofol or sevoflurane - N₂O was rapid and without any significant side effect. Emergence and early recovery after maintenance of anaesthesia with sevoflurane - N₂O was significantly faster than that after isoflurane - N₂O combination.⁴⁶

In 1994, Jellish and Fontenot studied sevoflurane versus propofol for induction and maintenance of anaesthesia in adult patients. They found the time for induction of anaesthesia with sevoflurane to be 3.1±0.18 minutes and with propofol to be 2.2±0.18 minutes. In gyst, sevoflurane was found to be as safe as propofol for induction of anaesthesia in adult patients, thus proving to be smooth, rapid and a potential alternative to intravenous induction.⁴⁷

In a study in 1995, Lien, Belmont and Hemmings compared the efficacy of sevoflurane with propofol for the induction and maintenance of anaesthesia. A total of 50 patients of ASA I or ASA II in the age group of 18-70 years were included in the study. During preoxygenation, patients received 2 μg kg⁻¹ Fentanyl. Patients in the sevoflurane group received 60% N₂O and oxygen with a total gas flow of 6 litre per minute and increasing concentration of sevoflurane. Patients in the propofol group received propofol (2.0-2.5mg kg⁻¹) as a slow intravenous bolus while breathing 100% O₂. Patient were monitored for the speed of induction and haemodynamic aberrations. The time required for induction of
anaesthesia were significantly different (2.0±1.1 min vs. 0.8±0.5min for sevoflurane and propofol respectively). They concluded that sevoflurane was an effective anaesthetic agent for induction and maintenance of anaesthesia.48

In another study in the same year, Hall, Stewart and Harmer compared the induction characteristics of sevoflurane in nitrous oxide and oxygen, with sevoflurane in oxygen alone or with propofol infusion. A vital capacity technique was used for the gaseous induction group using Mapelson A system and a reservoir bag. Time to achieve four ends points i.e. cessation of finger tapping, loss of eyelash reflex, jaw relaxation and regular settled breathing after LMA insertion was recorded. They also recorded sequential blood pressure and pulse rate, the incidence of adverse airway events and acceptability of induction technique. Propofol had a faster time to cessation of finger tapping (p <0.05) and jaw relaxation (p <0.01) but patients in sevoflurane in N₂O and O₂ group had the faster time to regular settled breathing though statistically insignificant. Cardiovascular stability was good and comparable in all groups. Although there were few adverse airway events in each group but none caused oxygen saturation to fall below 96%. There was more excitation in gaseous induction groups but patient satisfaction with induction was high.49

In the same year, Thwaites, Edmends and Smith conducted a randomized double blind comparison of 8% sevoflurane and propofol as induction agent in 102 unpremedicated patients for day case cystoscopy. Anaesthesia was induced
with intravenous propofol or inhalation of 8% sevoflurane and was maintained in all patients with 2% sevoflurane via face mask. Induction of anaesthesia with sevoflurane was significantly slower compared with propofol (mean 84 seconds vs. 57s) but was associated with lower incidence of apnoea (16% versus 65%) and a shorter time to establish spontaneous ventilation (94±34 seconds vs. 126±79 secs.) Induction complications were uncommon in each group. According to postoperative questionnaire, the majority of the patients found both techniques acceptable.50

In 1998, Nakata et al determined the anesthetic duration of sevoflurane to achieve good conditions for the placement of cuffed oropharyngeal airway (COPA) or laryngeal mask airway (LMA). Forty adult ASA physical status I or II patients presenting for elective surgery received single breath vital capacity inhaled induction with sevoflurane via face mask; thereafter ventilation was manually assisted. The patients randomly received either COPA or LMA placement. The mean time required for acceptable COPA placement was significantly shorter than that for LMA (100 sec vs 160 sec).51

In another study in the same year, Dashfield et al studied induction and recovery characteristics following inhalational induction with 8% sevoflurane in N2O and oxygen and compared it with intravenous propofol in forty patients presenting for arthroscopy of the knee. They randomly allocated the patients to receive either induction agent, and the anaesthesia was maintained with
sevoflurane in N₂O and O₂. The sevoflurane group had a faster onset of anaesthesia. The time to eye opening or psychomotor tests were found similar in both the groups. They observed a significant higher incidence of nausea and vomiting in sevoflurane group. They concluded that sevoflurane had no important clinical advantages and caused more nausea and vomiting than propofol.⁵²

In 1999, Sivalingam et al compared conditions for LMA insertion with propofol or sevoflurane with or without alfentanil. This prospective, randomised parallel groups study was conducted in one hundred unpremedicated ASA I or II patients scheduled for elective surgery. All patients were divided equally into four groups receiving either propofol 2.5 mg kg⁻¹; or vital capacity breath induction with sevoflurane (>7% in the inspiratory gas) in 65% N₂O and oxygen; or gaseous induction with sevoflurane plus alfentanil 5μg kg⁻¹ or propofol 2.5 mg kg⁻¹ and alfentanil 5 μg kg⁻¹. The conditions for LMA were assessed and graded on a three point scale using six variables which included jaw opening, ease of LMA insertion, coughing, gagging, laryngospasm or airway obstruction and patient movements. The overall conditions for LMA insertion was assessed as excellent, satisfactory or poor on the basis of total score in each group. Excellent or satisfactory conditions were observed in 100% of patients in sevoflurane -alfentanil group, 88% in the propofol alfentanil group and 64% patients each in the propofol and sevoflurane group (p <0.001). Sevoflurane alfentanil combination provided better conditions for laryngeal mask insertion when
compared with sevoflurane alone, or a propofol alfentanyl combination.\textsuperscript{53}

In another study in the same year, Molloy, Buggy and Scanlon compared the conditions for LMA insertion obtained by vital capacity breath inhalational induction of sevoflurane with propofol induction. In this study, eighty eight ASA I or II patients aged 18-65 years undergoing general anaesthesia for elective surgery were randomised into two groups. Patients in group P (n=44) received 2.5 mg/kg propofol intravenous and in group S (n=44) received 8% sevoflurane in 50% \textsubscript{N\textsubscript{2}O} and oxygen. Ventilation was not assisted. Laryngeal mask airway insertion was attempted at one minute intervals from loss of both verbal response and eyelash reflex, by an anaesthesiologist unaware of the induction technique. Complications, such as coughing and head movement, were also noted at each attempt. They observed that mean time to successful insertion of LMA was 1.3 minutes in P group and 2.2 minutes in S group (p <0.05). Eleven out of 44 patients in P group required addition propofol compared with four (9%) in S(p <0.05). They observed similar incidence of complications in both the groups. Further, they observed that LMA was inserted in all the patients by 3 minutes, it was successful in all patients. They concluded that vital capacity breath inhalational induction with 8% sevoflurane is effective for LMA insertion in most cases but takes slightly longer time than propofol.\textsuperscript{54}