THE COMPARATIVE EFFECTS OF 0.5 MAC AND 1.0 MAC CONCENTRATIONS OF SEVOFLURANE AND DESFLURANE ON MIDDLE CEREBRAL ARTERY FLOW PARAMETERS USING TRANS CRANIAL DOPPLERIN PATIENTS UNDERGOING SURGERY FOR SUPRATENTORIAL TUMOURS.

Thesis submitted for the partial fulfillment for the requirement of the Degree of DM (Neuroanesthesiology)

by

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DECLARATION

I hereby declare that this thesis entitled **"The comparative effects of 0.5 MAC and 1.0 MAC concentrations of Sevoflurane and Desflurane on middle cerebral artery flow parameters using Trans Cranial Dopplerin patients undergoing surgery for supratentorial tumours"**, has been prepared by me under the guidance of Dr. Manikandan.S, Additional Professor, Department of Anesthesiology, SreeChitraTirunal Institute for Medical Sciences and Technology, Thiruvananthapuram.

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CERTIFICATE

This is to certify that this thesis entitled **'The comparative effects of 0.5 MAC and 1.0 MAC concentrations of Sevoflurane and Desflurane on middle cerebral arteryusing Trans Cranial Doppler flow parameters in patients undergoing surgery for supratentorial tumours'** is a bonafide work of **Dr Josemine Davis,** DM Neuroanesthesia Resident, and has been done under my guidance and supervision inSreeChitraTirunal Institute for Medical Sciences and Technology, Thiruvananthapuram. He has shown keen interest in preparing this dissertation.

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CERTIFICATE

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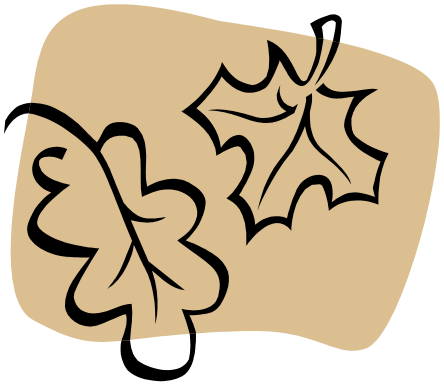
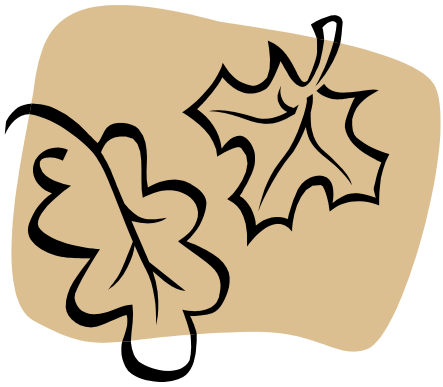


Introduction



INTRODUCTION

Drugs used in neuroanaesthesia and neuro-critical care should have minimal alteration in neurophysiological functions. The favourable characteristics of the drug includes uniform metabolic suppression, blood flow reduction in accordance to metabolic suppression, reduction of ICP, preservation of cerebrovascular autoregulation and absence of epileptogenic potential. The ideal anaesthetic for neuro anaesthesia would maintain cerebral perfusion pressure (CPP) and have no residual anaesthetic effects that hinder postoperative assessment of neurologic status.

Assessment of early postoperative recovery of neurologic and cognitive functions is one of the prerequisites of neuroanesthesia because it expedites the diagnosis of life-threatening complications. In these patients the early post anaesthesia course is frequently complicated by an increase in the arterial pressure of carbon dioxide (PaCO2) due to effects of drugs, depressed postoperative neurological function etc. This increase in PaCO2 causes unfavourable increase in ICP, cerebral hyperemia and oedema. After neurosurgical procedures, cerebral hyperemia may contribute to adverse cerebral outcome by increasing cerebral oedema, intracranial pressure, and the risk of cerebral haemorrhage.

Isoflurane has been the most commonly used volatile anaesthetics since many years for neurosurgical procedures because of its minimal effects on cerebral blood flow (CBF) and intracranial pressure (ICP) in hypocapnic patients.[2,3]Among the newer volatile inhaled anaesthetics, Sevoflurane and Desflurane are both fluorinated inhalational anaesthetics characterized by a low blood/gas partition coefficient that favours rapid emergence from anaesthesia without residual effects. Desflurane has the lowest blood:gas partition

coefficient compared to sevoflurane[1] and desflurane may be preferred in patients having neurosurgery when rapid emergence is desirable.

Recently Sevoflurane has gained popularity in neuroanaesthesia, whereas use of desflurane raises concern because it induces cerebral vasodilation, and in patients with expanding cerebral lesions could lead to suboptimal surgical conditions. But studieshave found that changes caused by desflurane in ICP and cerebral blood flow are similar to that of isoflurane and hence desflurane continues to be used in neuroanaesthesia.[4,5,6] Few published studies have compared how balanced anaesthesia with the hypnotics sevoflurane or desflurane affects perioperative systemic and cerebral hemodynamics in normal patients, but none have carried out a direct comparison of cerebrovascular effects of these drugs in neurosurgical patients.

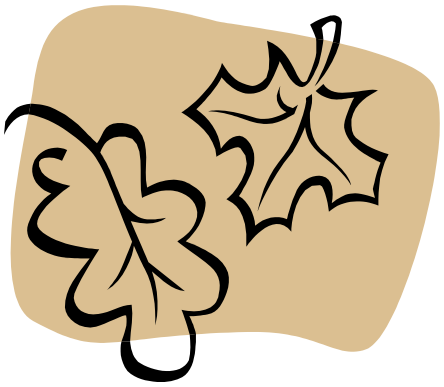
Brain has the ability to maintain its blood flow constant over varying perfusion pressures and it is referred to as ‘cerebral autoregulation’. Factors controlling cerebral blood flow include cerebral metabolism, PaCO2, PaO2, blood viscosity, and myogenic regulation (autoregulation). The limits of autoregulation have been shown to be within cerebral perfusion pressure of 50 to 150mmHg. But studies have proven that inter individual variability is very high and the limits of autoregulation can be altered by cerebral and systemic pathological processes as well as anaesthetic agents. In critical care or anaesthesia setting where patients are sedated and ventilated, the metabolism and partial pressure of blood gases are controlled. Myogenic autoregulation can play an important role in cerebral blood flow in these patients. Thus it should be ensured that drugs used in neuroanaesthesia and critical care setting should have minimal or noadverseeffect on cerebral hemodynamics and autoregulation.

Various methods have been described to assess the phenomenon of autoregulation including Transcranial Doppler assessment of flow velocities, imaging based assessment (MRI, PET, SPECT) and cerebral oxygenation based techniques (NIRS, PbtO2).

TCD has major advantages over other methods because of the simplicity, low cost, repeatability, and does not have any radiation hazards. The new improvements in transcranial Doppler like colour duplex imaging have improved the sensitivity and accuracy. Apart from autoregulatory assessment, several other factors and indices can be derived from flow velocity assessment like Pulsatility index (PI), Resistance index (RI), Estimated zero flow pressure (ZFP) and estimated effective cerebral perfusion pressure (eCPP) which can be useful in assessing the response of distal cerebral vasculature to variety of stimuli including drugs and pathological processes.

This study is designed to assess the effect of clinically useful concentrations of Sevoflurane and Desflurane on cerebral blood flow and autoregulation in patients with supratentorial mass lesions. TCD will be used to assess middle cerebral artery flow velocity (Vmca) and indices of autoregulation -transient hyperaemic response ratio (THRR) and strength of autoregulation (SA) - at two different concentrations of volatile anaesthetics, 0.5 MAC and 1 MAC.

Aims & Objectives



AIMS AND OBJECTIVES

A prospective randomized case control study was performed with the following aims:

1. The aim of this study is to compare the effects of 0.5 minimum alveolar concentration (MAC) and 1 MAC of Sevoflurane and Desflurane on Middle Cerebral Artery (MCA) flow velocities and dynamic cerebral autoregulation using TCD in patients with unilateral supratentorial brain tumour presenting for neurosurgery.
2. To compare the effects of 0.5 (MAC) and 1 MAC of Sevoflurane and Desflurane on Middle Cerebral Artery (MCA) flow velocities and dynamic cerebral autoregulation between the cerebral hemisphere with tumor and normal side.

Basic science

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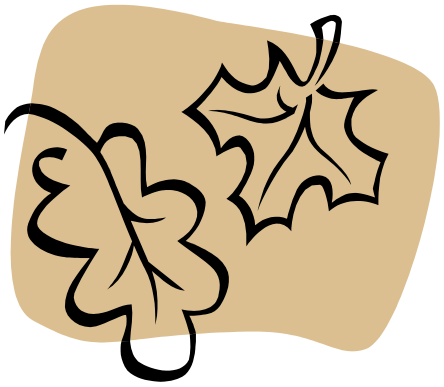
Review of literature



HISTORY OF VOLATILE ANESTHETICS

Inhaled anaesthesia has a long history. Both nitrous oxide and ether were introduced more than 150 years ago, and the introduction of halogenated inhaled anaesthetics during the mid-1950s was a significant step in the development of safe and efficacious anaesthesia. Halothane was the first in this series of potent inhaled anaesthetics; this halogenated hydrocarbon was first synthesised by C. W. Suckling of Imperial Chemical Industries in 1951 and was first used clinically by M. Johnstone in Manchester in 1956. Halothane became popular as a non-flammable, potent, general anaesthetic and replaced other flammable volatile anaesthetics such as diethyl ether and cyclopropane.

The second generation of inhaled halogenated anaesthetics (i.e. methoxyflurane, enflurane, and isoflurane) was introduced during the following decades, though methoxyflurane was withdrawn from use in many countries because of case reports of renal impairment caused by free fluoride produced from its in vivo breakdown. The third generation of inhaled halogenated anaesthetics (i.e. desflurane and sevoflurane) was introduced in the 1990s, resulting now in more than a decade of experience with both of these anaesthetics

The ‘ideal inhaled anaesthetic’

The ideal inhaled anaesthetic agent should have ample potency and a low solubility in blood and tissues, thus promoting a rapid equilibration and subsequent rapid elimination and recovery after cessation of administration. In addition, it should provide safe and effective anaesthesia while administered. It should have minimal effects on respiration and circulation; it should not cause airway irritation or produce negative effects on organ functions. The molecule should not have any deleterious effects or possess the potential to cause any injury

to body tissues. The ‘ideal inhaled anaesthetic’ should resist physical and metabolic degradation, both in vitro and in vivo, and it should not react in carbon dioxide (CO_2) absorbers or with filters, tubing, or connections.

The clinical features of the halogenated hydrocarbon gases have led to their widespread use for general anaesthesia since their initial introduction. Most of the desired effects are provided by all of the available agents – isoflurane, sevoflurane, and desflurane. As a class, they provide rapid onset of action, safe and efficacious anaesthesia during administration, and rather minimal effects on circulation and cardiac performance. Through appropriate titration, they may all be used to rapidly increase or decrease the depth of anaesthesia. Following cessation of administration, elimination is governed by wash-out by exhalation and does not require any metabolism. However, subtle differences that have an impact on anaesthesia practice and patient management do exist among the agents.

PHARMACOLOGY OF DESFLURANE

History of Desflurane

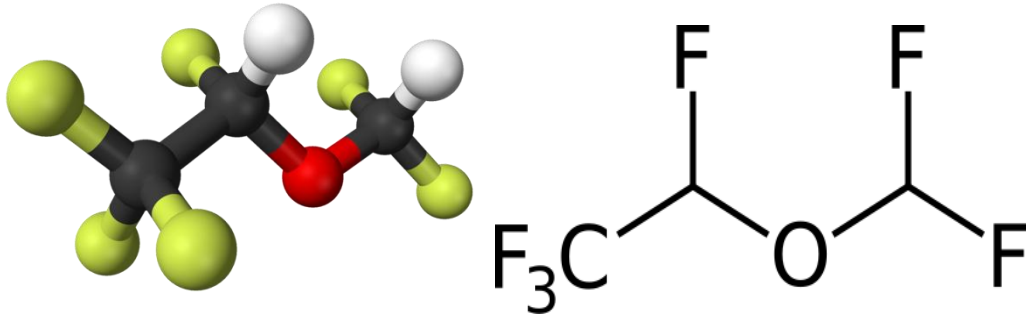
The two ‘newest’ inhalation agents, desflurane and sevoflurane were developed in the 1960s. Concerns regarding inhalation agents in the market in the 1980s and 1990s (halothane with associated hepatitis; isoflurane with coronary steal; enflurane with fluorine nephrotoxicity and seizures) as well as pressure on anaesthesiologists to improve efficiency, outcomes and safety prompted further development of these drugs.Among the 700 compounds developed by Ross Terrell in the 1960s was desflurane designated I-653.[8,9]After its discovery, there was little further development as production involved the use of elemental fluorine, which can be potentially explosive, and the physical property of having a vapour pressure close to 1 atmosphere. It was not until 1988 when the first human trials took place in

London. Because of its high vapour pressure, clinical use necessitated a different type of vaporizer; thus the Tec 6 was developed. Desflurane was introduced for clinical use in 1992[7].

Physico Chemical Properties

Desflurane is a fluorinated methyl ethyl ether that differs from isoflurane only by the substitution of a fluorine atom for the chlorine atom found on the alpha–ethyl component of isoflurane (Figure 1). It is an inhalational general anaesthetic agent,which is a clear, nonflammable liquid with a "strong" odour at room temperature.[1]Desflurane's relatively low boiling point (23.5°C) makes it extremely volatile; however, since this temperature is close to ambient operating theater temperature, full vapour saturation cannot be guaranteed if a conventional vapouriser is employed. A vapouriser, which heats the agent to 39°C at a pressure of 2 atm, is needed to ensure full vapour saturation and addition of a carefully regulated amount of vapour to the fresh gas flow (FGF).[10]

Figure 1 – Molecular structure of Desflurane



Chemical name: (±)-2-Difluoromethyl 1,2,2,2-tetrafluoroethyl ether
Molecular formula and molecular mass: C3H2F6O, 168.04

Vapour Pressure:

669 mm Hg @ 20°C 731 mm Hg @ 22°C
757 mm Hg @ 22.8°C 764 mm Hg @ 23°C
798 mm Hg @ 24°C 869 mm Hg @ 26°C

Stability and Degradation

The effect of fluorination may be seen in a comparison of isoflurane and desflurane, anaesthetics that differ solely by the replacement of a single chlorine atom in isoflurane with a fluorine atom.Desflurane has a lower boiling point, higher vapour pressure, and greater stability in soda lime. It also is less metabolized, less soluble, and less potent. Normal absorbents do not degrade desflurane or isoflurane, but desiccated absorbents can degrade all potent anaesthetics[11].

Carbon monoxide is a by-product of degradation, and desflurane degradation can produce the greatest concentrations of carbon monoxide[12].Degradation results from the action of monovalent absorbent bases (ie, sodium and potassium hydroxide) in both moist and desiccated absorbents. Absorbents containing only the primary divalent base, calcium hydroxide, cause minimal degradation.The consistent use of low fresh gas inflow rates avoids carbon monoxide production because low fresh gas inflow rates sustain moisture through the generation of water from the interaction of carbon dioxide and absorbent base[11]. Dehydration may occur in rarely used absorbent or in machines in which a high flow of oxygen has been left on over the weekend (ie, beware of Monday's absorbent). If a question exists as to desiccation, the absorbent should be replaced with fresh absorbent or rehydrated by pouring a cup of water (230 mL) into each 1.2 kg of absorbent[13]. It is seen that the generation of CO can be avoided with use of soda lime with ≥ 4.8% water content or "Baralyme" which has ≥ 9.7% water content. Desflurane does not require preservatives.

Solubility

Desflurane has the lowest blood/gas solubility of 0.42 as compared to the solubilities of other common anaesthetic agents (diethyl-ether 12.0; halothane 2.3; enflurane 1.9; isoflurane 1.3; sevoflurane 0.67; nitrous oxide 0.47). The lower blood/ gas solubility allows anaesthetic alveolar concentration to remain near inspired concentration permitting a rapid

and large change, with precise control, in the anaesthetic depth, and early awakening.[15,16] The 90% decrement time of desflurane, sevoflurane, isoflurane, and enflurane as a function of the duration of anaesthetic administration is shown in Figure 3.[17]

Table 1. Partition coefficients of inhaled anaesthetic agents in blood and tissues

Type of Tissue	Halothane	Isoflurane	Desflurane	Sevoflurane
Blood	2.4	1.4	0.45	0.65
Brain	3.4	2.1	0.6	1.1
Muscle	3.8	2.1	0.6	1.1
Fat	137	71	15	41

Potency and MAC

MAC, the alveolar concentration of an inhaled anaesthetic at which 50% of subjects move in response to a noxious stimulus, is the usual standard of inhaled anaesthetic potency and sets a lower limit to useful surgical concentrations. Concentrations 10% to 30% greater than MAC produce immobility in nearly all patients.[18]Desflurane has lower anaesthetic potency leading to higher MAC values. MAC for 30 to 60-year-old adults is 0.06 atm (ie, 6%) desflurane, 0.0075 atm halothane, 0.0115 atm isoflurane, 0.0185 atm sevoflurane, and 1.05 atm nitrous oxide.[19]Several physiological factors decrease MAC: decreased body temperature, decreased central nervous system sodium concentrations, pregnancy, and increased age. Thus, the 3-month-old infant has a MAC nearly twice that of an octogenarian.[11]The age specific MAC of Desflurane is given in Table 2.

Table 2: Desflurane MAC is age-specific and decreases with 60% nitrous oxide

Age	MAC in 100% oxygen	MAC in 60% nitrous oxide
0–1 year	8.95–10.65	5.75–7.75

1–12 years	7.2–9.4	5.75–7.0
18–30 years	6.35–7.25	3.75–4.25
30–65 years	5.75–6.25	1.75–3.25
Over 65 years	5.17+/-0.6	1.67+/-0.4

Pharmacokinetics

Pharmacokinetic differences between inhalational agents account for the differences in anaesthesia outcomes and thereby the quality of care provided. Several factors govern how quickly the alveolar concentration (FA) of an inhaled anaesthetic rises toward the concentration inspired (FI).[20-23]Ventilation brings anaesthetic into the lungs. If the effect of ventilation is unopposed, it rapidly raises FA to FI (ie, FA/FI rapidly approaches 1.0).

Uptake of potent inhaled anaesthetics opposes the effect of ventilation. For example, if uptake removes 2/3 of the anaesthetic delivered by ventilation, FA/FI will equal 1/3 or 0.33. Uptake equals the product of three factors: solubility, pulmonary capillary blood flow (i.e. cardiac output or Q), and the anaesthetic partial pressure gradient driving anaesthetic from the alveoli into the blood returning from the body to the lungs (A – v). An increase in any of these factors increases uptake and decreases FA/FI. Tissue uptake determines A – v. In the first minutes of anaesthesia, highly vascular tissues (brain, heart, liver, kidney, the so-called vessel rich group or VRG) take up large volumes of anaesthetic because these tissues receive the most anaesthetic (they get 3/4 of the cardiac output). But this also means that they equilibrate rapidly and cease taking up anaesthetic after 5-10 minutes. After this time, muscle (the muscle group or MG tissues) and fat (FG) determine uptake. Because of the much greater capacity of fat to hold anaesthetic, the FG takes up anaesthetic for a much longer period than the MG [11]. Metabolism of anaesthetic also can increase uptake.

In humans, metabolism degrades approximately 0.02% of desflurane taken up[24],0.2% of isoflurane,[25]5% of sevoflurane.[26]Metabolism accounts for uptake of an appreciable fraction of older anaesthetics (40% of halothane[21,27] and 75% of methoxyflurane[21]).

Thus it is evident that smaller blood and tissue solubilities promote a more rapid increase in FA toward FI during administration, (Figure 2) and a more rapid decrease in FA during elimination (Figure 3). A second factor, pungency, limits the rapidity of an inhalation induction of anaesthetics but does not influence rapidity of recovery from anaesthetics. Desflurane being the least soluble of all volatile anaesthetic agents would provide the fastest induction but its pungency precludes its use for induction. Thus, among inhaled anaesthetics, induction is most rapid with sevoflurane because it has both a low solubility and minimal or no pungency. Recovery is most rapid with desflurane because it has the smallest tissue and blood solubilities. The rate of recovery with desflurane also equals or exceeds the rate of recovery from comparable levels of anaesthesia maintained with intravenous agents such as propofol. A rapid recovery decreases the time needed to move the patient through the operating room and PACU.[28]In a comparison of patients given desflurane versus sevoflurane, those given desflurane have a significantly more rapid recovery of protective pharyngeal reflexes.[29]

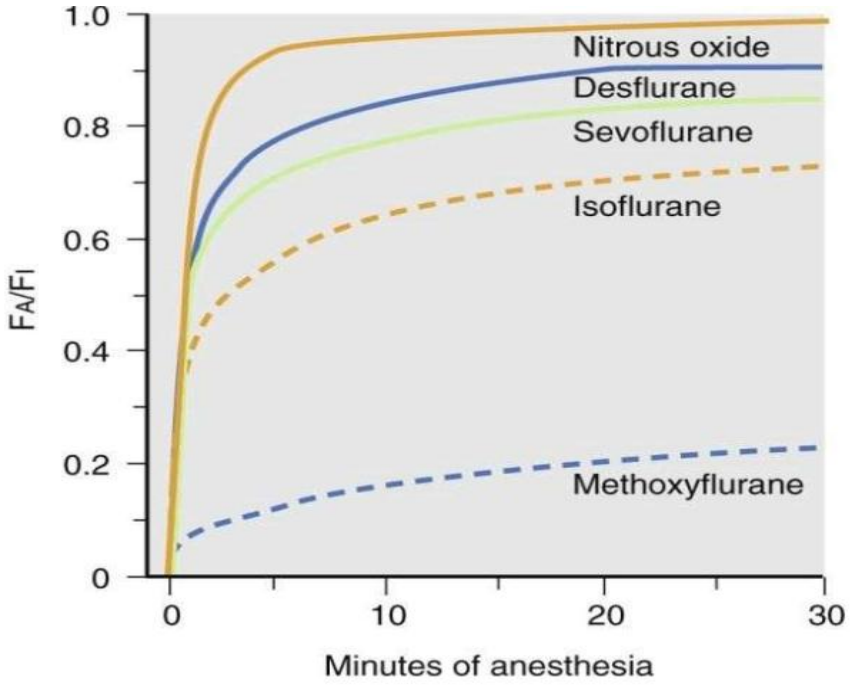


Figure 2: The rise in alveolar (FA) anaesthetic concentration toward the inspired (FI) concentration is most rapid with the least soluble anaesthetic, nitrous oxide, and slowest with the most soluble anaesthetic, methoxyflurane. All data are from human studies.

Elimination

Desflurane has low solubility in blood and other body tissues and has lower solubility in all body compartments as compared with sevoflurane and isoflurane. This difference in tissue solubilities has a significant effect on anaesthetic accumulation as demonstrated by a pharmacokinetic modelling study by Lockwood[30] in which the amount of residual total body anaesthetic varied considerably across the inhaled anaesthetics. After 4 h of anaesthesia, the model predicted body content to be 28 g nitrous oxide, 26 g desflurane (because of its higher MAC), 14 g sevoflurane, or 15 g isoflurane, and 99.9% brain elimination times were 9 h for nitrous oxide, 33 h for desflurane, 52 h for sevoflurane, and 71 h for isoflurane. Although desflurane remains in the body for a shorter time than sevoflurane and isoflurane, these results indicate that significant amounts of all inhaled anaesthetics remain in the body for a prolonged period of time after cessation of administration.

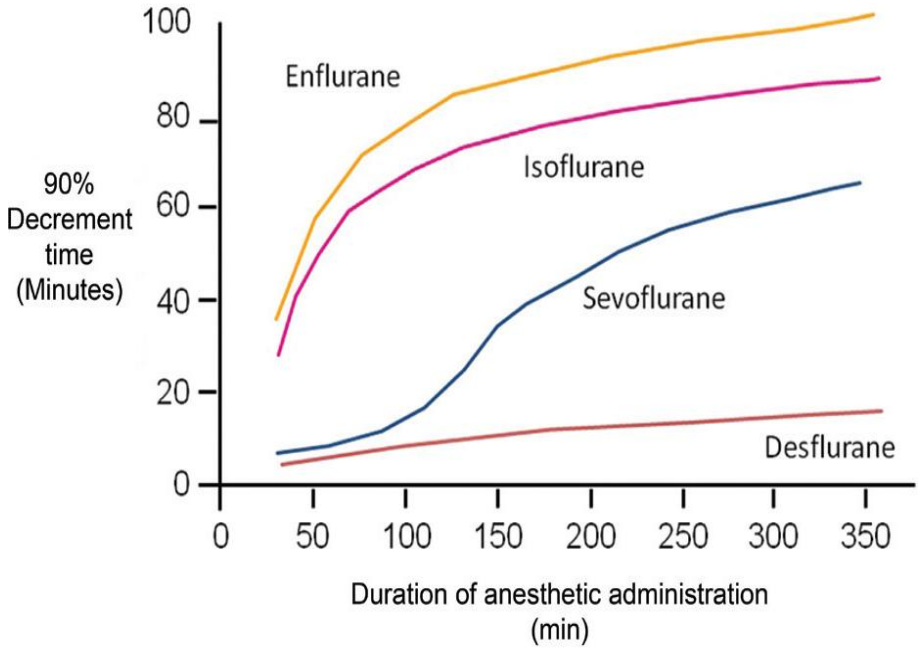


Figure 3: Faster 90% terminal decrement times with desflurane

Metabolism and safety

Desflurane is only minimally metabolised (0.02%) and has the lowest in vivo metabolism of the available inhaled halogenated anaesthetics (see Table 3).[31-35] However, all of the halogenated inhalational anaesthetics (i.e. halothane, enflurane, isoflurane, and desflurane) can produce metabolic hepatocellular injury in humans. During metabolism of these anaesthetics, tissue acetylation occurs because of the formation of reactive intermediates, and proteins modified by acetylation may constitute neo-antigens with the potential for triggering an antibody-mediated immune response. The likelihood of suffering post-operative immune hepatitis depends on the amount of the anaesthetic metabolised and is therefore considerably less with isoflurane, and lowest for desflurane, compared with halothane.[36]

Table 3. Metabolism of inhaled anaesthetic agents

Inhaled anaesthetic agent	Percent metabolised
Halothane	15%–20%
Enflurane	2%
Isoflurane	0.17%
Desflurane	0.02%
Sevoflurane	5%

CLINICAL EFFECTS

Cardiovascular system

The cardiovascular system (CVS) effects of desflurane can be divided into 2 types: The direct effects of the anaesthetic and a transient response involving sympathetic nervous

system (SNS) activation.[37] The direct effects of desflurane on the CVS are remarkably similar to those of isoflurane.[38] In pigs and dogs, desflurane decreases myocardial contractility, cardiac output, and blood pressure (BP) in a dose-dependent fashion.[39,40] As with isoflurane, desflurane produces vasodilation, which results in dose dependent reductions in systemic vascular resistance and arterial BP in healthy volunteers and patients with coronary artery disease.[41-44] β-adrenergic activation leads to significant elevations of BP and heart rate (HR)[45] mediated by release of plasma adrenaline and noradrenaline. The degree of sympathetic stimulation is related in part to the absolute concentration of desflurane (>1.25 MAC) and the rapid rise in desflurane concentration, as rapid increase leads to more sympathetic stimulation.[46] There is evidence that these sympathetic responses normalize after a few minutes and that subsequent repetition does not cause the same response (i.e., they were attenuated) again.[47] Sympathetic response by desflurane can be prevented by increasing the desflurane concentration slowly, in 0.5–1.0% increments every 2–3 breaths, avoiding the overpressurising technique. Prior administration of alfentanil, fentanyl, sufentanil, clonidine, or β-adrenergic blocking drugs can minimize the sympathetic and/or CVS response.[48,49]

Desflurane caused fewer episodes of intraoperative hypotension, without the occurrence of more hypertensive episodes, than sevoflurane when studied using an experimental inhalation bolus technique in morbidly obese patients.[50] When used for hypotensive anaesthesia, with desflurane HR was statistically unchanged from baseline throughout surgery, with a significantly faster return to baseline arterial BP at the end of anaesthesia, as compared to sevoflurane and propofol.[51]

In a manner similar to ischemic preconditioning, volatile anaesthetics can trigger an acute cardioprotective memory effect, called “anaesthetic or pharmacologic preconditioning,” which lasts beyond their elimination.[52] Volatile anaesthetics also have post-conditioning

effects that may contribute to protection when administered after the onset of ischemia, such as mitigation of Ca2+ overload, free-radical production, and neutrophil adhesion.[53-55]

Cardioprotective effects of volatile anaesthetic agents are measured by cardiac biomarkers. The most popular biomarker for myocardial damage is cardiac troponin (cTn), with nearly total myocardial tissue specificity and extreme sensitivity, reflecting even very small amounts of myocardial necrosis.[56] Under desflurane anaesthesia, patients undergoing off-pump coronary artery bypass surgery had less myocardial damage as evidenced by a significant ($P < 0.001$) reduction in postoperative median (25th–75th percentiles) peak of cTn, reduced ($P = 0.04$) number of patients requiring postoperative inotropes, and a reduced number of patients needing prolonged hospitalization (>7 days).[57]

Pulmonary system

The respiratory system may be adversely affected by inhalational anaesthetic agents by causing respiratory depression, airway irritation, and bronchospasm. In healthy volunteers, at concentrations up to 1.66 MAC, desflurane (with or without nitrous oxide) produced a dose-dependent decrease in tidal volume with an increase in respiratory frequency.[58]*In vitro* data have shown that desflurane produces dose-dependent relaxation of pre-constricted proximal and distal canine tracheal smooth muscle, with the latter being relaxed approximately 30% more than the former**.**[58]

Desflurane can irritate the airway when given in high concentration above threshold for respiratory irritation (1–1.5 MAC) to patients.[59] Irritation of the airway, coughing, breath-holding, and laryngospasm do not occur at end-tidal concentration of 5.4% or less.[60] Concentrations that may have been irritating during the induction of anaesthesia do not necessarily increase the incidence of airway irritation during maintenance.[61] The threshold for

irritation seems to be influenced by age, opioid administration, and smoking. Increasing age decreases airway responsiveness to irritants.[62] Administration of a small dose of fentanyl, 1 mcg/kg, can significantly decrease the incidence of airway irritation with a decrease in coughing by 80%.[63] Similar incidence of respiratory events is there with laryngeal mask airway (LMA) in adult patients receiving up to 100 µg of fentanyl, prior to induction and concomitant N2O during the procedure, with use of desflurane and sevoflurane.[61,64,65] With use of LMA, on awakening, desflurane provides more rapid recovery of pharyngeal reflexes as compared with sevoflurane.[66]

In vitro, increasing concentrations of all volatile anaesthetics directly depress hypoxic pulmonary vasoconstriction (HPV) in a dose-dependent manner. *In vivo*, however, volatile anaesthetics may affect HPV, directly as well as indirectly, by their influence on cardiac output, venous oxygen saturation, and shunt fraction. The influence of propofol and desflurane anaesthesia on postoperative lung function and pulse oximetry value in overweight patients was evaluated and it was found that, for superficial surgical procedures of up to 120 min, propofol impairs early postoperative lung function and pulse oximetry values more than with desflurane. Increasing obesity decreases pulmonary function at 2 h after propofol but not after desflurane anaesthesia.[67,68]

Neurological system

The comparative effects of Sevoflurane and Desflurane on the CNS are discussed in a separate section of review of literature. The same is dealt with in brief, here. The effects of desflurane on cerebral physiology and function are similar to those of isoflurane. Both agents appear to reduce cerebral vascular resistance and increase intracranial pressure.

In humans, both agents are dose-related cerebral vasodilators but at >1.5 MAC the vasodilation seen with desflurane exceeds that with halothane.[69,70] Cerebrospinal fluid (CSF) production is increased slightly more with desflurane than isoflurane.[71] Cerebral vascular

autoregulation appears to be delayed but maintained at least up to 0.5 MAC; at 1.5 MAC autoregulation is abolished, as is the case with isoflurane.[72] In humans, anesthetizing concentrations of desflurane and isoflurane provide a dose-related depression of EEG activity[73,74] and evoked potentials,[75] though neither agent predisposes to convulsive activity. Normal concentrations of desflurane (up to 1 MAC) do not abolish somato-sensory evoked potentials.[76] In humans, desflurane produced central respiratory depression (ventilatory response to CO2) comparable with that seen with enflurane and greater than that seen with isoflurane.[77] Desflurane should be administered at 1 MAC or less, and in conjunction with a barbiturate induction and hyperventilation (hypocapnia) until cerebral decompression in patients with known or suspected increases in CSF pressure. CBF alterations on variation of PaCO2 indicate that cerebrovascular CO2 reactivity is not impaired by application of 1 MAC desflurane.[78]

Hepatic and renal effects

Studies in humans have not shown evidence of hepatic injury secondary to anaesthesia with desflurane. Absence of hepatotoxicity[79] is consistent with the minimal biodegradation of desflurane, the sustained hepatic arterial blood flow,[80] and the rapid elimination of desflurane after termination of anaesthesia. A recent study in rats demonstrated that unlike halothane, biodegradation of desflurane produces no covalently-bound fluorine (the agent which may be responsible for hepatic damage) and thus the potential for hepatotoxicity seems to be low.[81] This low potential has also been shown in human volunteers and patients with post anaesthetic renal function tests in human volunteers[82] and patients[83] showing no change after desflurane anaesthesia.

Neuromuscular effects

Desflurane produces dose-related muscle relaxation comparable with that seen with isoflurane.[84,85] In addition, it potentiates the action of non-depolarizing neuromuscular

blocking agents to a slightly greater degree than that seen with isoflurane. For example, 90% response time was more prolonged after vecuronium and desflurane as compared with isoflurane.[86,87] After mivacurium too, 90% response time is also prolonged in the presence of desflurane.[88]

Obstetrics

Desflurane has been used for caesarean section with no significant maternal complications and only slightly longer neonatal time to sustained respirations, compared with enflurane and nitrous oxide.[89] Desflurane has been well tolerated when used for control of labour pain.[90]

Malignant hyperthermia

Desflurane has been shown to be a trigger of malignant hyperthermia, though the onset may be delayed compared with that after halothane.[91]

Elderly population

More rapid recovery from prolonged anaesthesia may be an advantage in the elderly in whom hepatic and renal function are decreasing and cognitive impairment (e.g., delirium, confusion) is a problem during recovery.[92] Desflurane does not increase pre-existing hepatic or renal injury, does not rely upon metabolism for its elimination, and minimally influences metabolism of other drugs.[19] Several studies have demonstrated a faster, clearheaded, and more predictable recovery in elderly patients after desflurane as compared with sevoflurane. Chen et al. published a study that evaluated cognitive recovery profiles in elderly patients after general anaesthesia with desflurane or[93] sevoflurane. The data revealed that desflurane was associated with a faster early recovery than sevoflurane, but recovery of cognitive function was similar after both inhaled anaesthetics.[93] In another investigation of anaesthesia recovery time in elderly patients, Fredman et al. showed that upon arrival in the PACU a

significantly larger percentage of patients receiving desflurane was judged to be awake and with stable vital signs,[94] thus becoming fast-track eligible, compared with those receiving either isoflurane or propofol (73% vs. 43% and 44%, respectively). Heavner et al. studied elderly patients receiving two or more hours of desflurane or sevoflurane anaesthesia and compared emergence from these agents. Early (as measured by times to extubation, eye opening, squeezing fingers on command, and orientation) but not intermediate recovery (as measured by the digit-symbol substitution test and time to discharge) was significantly better in patients receiving desflurane.[95]

Obese population

Compared to non-obese patients, obese patients are at higher risk of aspiration, hypoventilation, airway obstruction, and desaturation during early recovery from anaesthesia. Rapid recovery and early return of airway reflexes may be desirable in these patients. There is a link between overweight and elderly patients as body weight may stay stable with increase in fat percentage with age.[96] Several studies have demonstrated a more rapid and predictable recovery, with faster washout, in obese/overweight[98] and morbidly obese[97] patients after desflurane as compared with sevoflurane. Desflurane has thus gained popularity for bariatric surgery due to favourable profiles of emergence and recovery. Small concentrations (5–10% of MAC) can impair pharyngeal function and the ability to manage foreign material in the pharynx. McKay *et al.* demonstrated that the more rapid and predictable recovery of desflurane compared with sevoflurane also applies to the return of protective airway reflexes in overweight/obese patients [99].

(Bilotta et al. found desflurane to be associated with a faster recovery after anaesthesia for craniotomy in overweight and obese patients.[98] Early post-operative cognitive

recovery was more delayed in patients receiving sevoflurane-based anaesthesia than in those receiving desflurane-based anaesthesia as assessed by the Short Orientation Memory Concentration Test (SOMCT) and by an assessment utilising the Rancho Los Amigos Scale (RLAS).]In another recent study in overweight patients (BMI 25–35), Zoremba et al. demonstrated the beneficial physiochemical properties of desflurane that allow rapid elimination and produce only minor residual effects after cessation of administration.[100] Patients receiving desflurane as the main anaesthetic during superficial surgery lasting 40–120 min exhibited improved lung function and oxygen saturation during the first two post-operative hours as compared with propofol. Moreover, even 24 h after surgery, forced expiratory volume in 1 s [FEV(1)], peak expiratory flow, MEF, forced inspiratory vital capacity, and peak inspiratory flow were reduced to a greater degree in the propofol group ($P < 0.01$ for all measures). The analysis of data according to patient BMI revealed further differences. At 2 h after extubation, increasing BMI was associated with decreasing FEV(1) and MEF in patients anaesthetised with propofol but not desflurane ($P < 0.01$).

Paediatric population

Desflurane is not approved for induction and maintenance of anaesthesia in non-intubated children due to an increased incidence of respiratory adverse reactions, including coughing, laryngospasm, and secretions. Desflurane is primarily used as maintenance agent for intubated children during paediatric anaesthesia. Caution should be exercised when desflurane is used for maintenance anaesthesia with laryngeal mask airway (LMA) in children 6 years old or younger because of the increased potential for adverse respiratory events, e.g., coughing and laryngospasm, especially with removal of the LMA under deep anaesthesia. In a study comparing desflurane with sevoflurane, there were no significant differences in hemodynamic parameters, renal and hepatic functions, postoperative recovery,

and postoperative nausea and vomiting between the two groups. The recovery time was shorter in the desflurane group compared to the sevoflurane group.[101]

Chronic obstructive airway disease

Inhalational anaesthetics have bronchodilatory effects and their use is recommended in Chronic obstructive airway disease patients with hyper reactive airways.[102] Inhalational anaesthetics are equipotent (isoflurane, desflurane, and sevoflurane) in treating intraoperative bronchospasm, but desflurane may provoke coughing, bronchospasm, laryngospasm, and bronchial hypersecretion. Desflurane exhibits a bronchodilator effect at 1 MAC concentration but at higher MAC values increases airway resistance.[103]

Emergence and Recovery

Dexter and Tinker compared the emergence profiles of desflurane, propofol, and isoflurane when these agents were used for anaesthesia maintenance and found that desflurane maintenance was associated with a significantly more rapid emergence than that seen when propofol was utilised as the primary anaesthetic agent.[104] In a similar, more recent meta-analysis that compared sevoflurane with desflurane, Macario et al. examined studies in which the duration of anaesthesia was up to 3.1 h. The analysis indicated that there were no significant differences in post-anaesthesia care unit (PACU) time or post-operative nausea and vomiting (PONV) frequency between patients receiving either desflurane or sevoflurane. However, in agreement with the previous meta-analysis by Dexter et al., patients receiving desflurane exhibited a more rapid emergence; they followed commands, were extubated, and were oriented 1.0–1.2 min earlier than were patients receiving sevoflurane.[105]

Emergence time has particular implications in the ambulatory surgery setting. In a systematic review of ambulatory literature, Gupta et al. compared post-operative recovery after propofol-, isoflurane-, desflurane-, and sevoflurane-based anaesthesia in adults. In agreement with previous reviews, this analysis revealed faster early recovery in patients

receiving desflurane or sevoflurane anaesthesia.[106]In a recent meta-analysis, Agoliati et al. showed desflurane to have beneficial effects on extubation time and in the reduction of 'prolonged extubation time' as compared with both isoflurane and sevoflurane.[107] In this analysis, desflurane reduced the mean extubation time by 34% and reduced the variability in extubation time by 36% relative to isoflurane, which were associated with reductions in the incidence of prolonged extubation times by 95% and 97%, respectively. Sevoflurane reduced the mean extubation time as compared with isoflurane, though the effects were not as profound as those observed with desflurane. With sevoflurane, mean extubation time was reduced by 13% and variability in extubation time was reduced by 8.7%, which were associated with reductions in the incidence of prolonged extubation times by 51% and 35%, respectively. Thus, the use of desflurane is associated with a more predictable emergence and the avoidance of unanticipated delay caused by prolonged time to extubation. Similarly, Dexter et al. demonstrated through a modelling study that desflurane may reduce the average extubation time and the variability of extubation time by 20%–25% relative to sevoflurane.[108]

The quicker emergence with desflurane has been shown to be associated with a more rapid recovery of protective reflexes. A study conducted by McKay et al. published in 2005 compared desflurane with sevoflurane in ASA I-II patients scheduled for general anaesthesia not requiring muscle relaxation.. The time from discontinuation of anaesthetic administration to appropriate response to command was significantly longer after sevoflurane (5.5 ± 3.1 vs. 3.4 ± 1.9 min; $P < 0.01$). In addition, the time from first response to command to ability to swallow 20 ml of water without coughing or drooling was longer after sevoflurane; at 2 min after responding to command, all patients who had received desflurane were able to swallow without coughing or drooling, whereas 55% of patients who had received sevoflurane coughed and/or drooled ($P < 0.001$). At 6 min after responding to

command, 18% of patients given sevoflurane still could not swallow without coughing or drooling ($P < 0.05$).[66]

Pharmaco economic considerations

The utilisation of inhaled anaesthetics has been shown to have lower direct costs as compared with intravenous-based anaesthesia.[109,110] For example, Rosenberg et al. showed a significant cost difference in which the drug acquisition cost for the maintenance period of general anaesthesia with a desflurane-based technique was $11.24/h, whereas the cost of a propofol-based technique was $44.08/h.[110] Similarly, Dolk et al. showed that inhaled anaesthesia is associated with a lower cost as compared with a propofol-based technique, and the cost difference became even more pronounced when waste was taken into account.[109] The cost aspects need to be put into perspective. Propofol is today available as a generic drug in most countries, and thus the acquisition cost has decreased. Also, sevoflurane is available today as a generic drug and thus the cost associated with inhaled anaesthetics will decrease. Further, reducing fresh gas flow has been repeatedly shown to have a profound effect on inhaled anaesthetic consumption.[111,112]In a recent retrospective analysis of inhaled anaesthesia costs in Australia, Weinberg et al. analysed and compared consumption of inhaled anaesthetics and direct acquisition costs of isoflurane, sevoflurane, and desflurane.[113] This analysis revealed isoflurane used at a low 0.5 l/min fresh gas flow rate to be the least expensive option, and both sevoflurane and desflurane were more expensive. When comparing a 1-l/min fresh gas flow rate of desflurane anaesthesia with a 2-l/min sevoflurane anaesthesia, the desflurane cost was found to be comparable or even slightly lower in cost than the sevoflurane anaesthesia regimen.

Indirect cost savings from desflurane use in terms of faster recovery, extubation, return of cognition and swallowing, shorter PACU stay should also be considered while calculating pharmaco economics.

Summary and conclusions

A decade of clinical use has helped to demonstrate the clinical features of desflurane. The expected physiochemical properties associated with the low blood and tissue solubility of desflurane are now well-documented in clinical practice. For example, desflurane provides rapid intraoperative control of haemodynamics; the sympathetic stimulation described following its introduction has been shown to be easily attenuated by co-administration of low clinical doses of fast-acting opioids (e.g. fentanyl or alfentanil); and its use in spontaneous breathing patients may be associated with some airway irritation. In addition, there is a large and reassuring body of clinical evidence demonstrating that desflurane is associated with rapid emergence/recovery; early recovery is rapid and predictable, with a reduced risk for delayed extubation; and a more rapid return of the protective swallowing reflex when compared with sevoflurane and propofol-based anaesthesia. Desflurane may possess advantages in obese and elderly patients, as well as for long-duration procedures by reducing anaesthetic accumulation in fat compartments.

Early postoperative recovery and early neurological assessment is of importance in neurosurgical patients. Desflurane would be the ideal volatile agent in this regard; however some concerns remain as to the cerebrovascular effects of desflurane, in comparison to the currently used agents, isoflurane and sevoflurane. This study purports to address this issue, by comparing the cerebrovascular effects of desflurane and sevoflurane in neurosurgical patients.

PHARMACOLOGY OF SEVOFLURANE

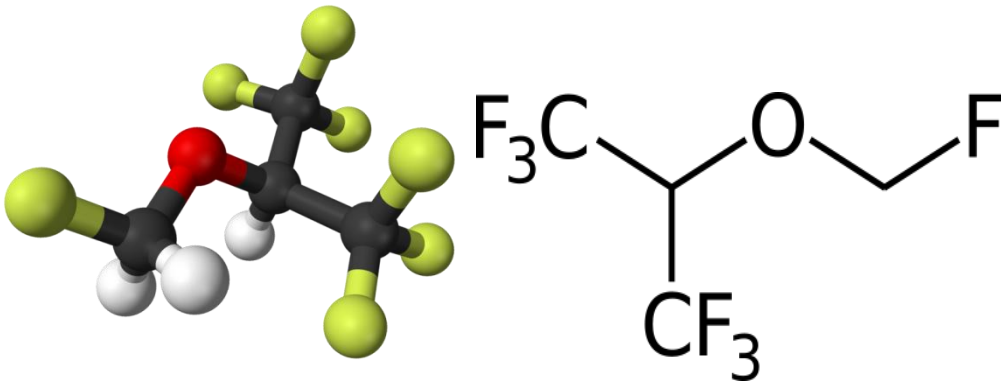
History

Research to develop a safe, non-inflammable inhaled anaesthetic agent began in the 1930s when chemists discovered that the substitution of fluorine for other halogens "lowers the boiling point, increases stability, and generally decreases toxicity".[114] Sevoflurane was first synthesized in 1968 by Regan at Travenol Laboratories, Illinois, while he was investigating a series of halomethyl poly fluoro isopropyl ethers. The compound was initially reported by his co-workers in 1971.[115] Development was later to be impeded by apparent toxic effects, eventually shown to be a consequence of flawed experimental design.[116] Work was slow because of the problems of biotransformation and stability with soda lime. Eventually sevoflurane was released for clinical use in Japan in May 1990.

Physico chemical properties

Sevoflurane, volatile liquid for inhalation, a non-flammable and non-explosive liquid administered by vaporization, is a halogenated general inhalation anaesthetic drug (Fig 4). Sevoflurane is related structurally to isoflurane and enflurane and not surprisingly shares many of the physical properties of these drugs. Sevoflurane has a boiling point of 58.6^{o} C and a saturated vapour pressure (SVP) of 160 mm Hg a t 20^{o} C. These values are similar to those of halothane, enflurane and isoflurane. The blood:gas partition coefficient of sevoflurane is 0.69.[117] This is approximately half that of isoflurane (1.43) and compares favourably with the blood:gas solubility of both desflurane (0.42) and nitrous oxide (0.44). The low blood:gas solubility of sevoflurane should provide for rapid induction of, and recovery from, anaesthesia.

Figure 4. Molecular structure of Sevoflurane



Chemical name: Fluoromethyl 2,2,2,-trifluoro-1-(trifluoromethyl) ethyl ether
Molecular formula - $C_4H_3F_7O$

Sevoflurane, Physical Constants are:

Molecular weight	200.05
Vapour pressure	-157 mm Hg at 20°C
	-197 mm Hg at 25°C
	-317 mm Hg at 36°C

Distribution Partition Coefficients at 37°C:

Blood/Gas	0.63 - 0.69
Water/Gas	0.36
Olive Oil/Gas	47 - 54
Brain/Gas	1.15

Stability and degradation

Upon contact with alkaline CO_2 absorbents (soda lime or Baralyme), used to remove CO_2 from the anaesthesia circuit, sevoflurane undergoes degradation. The most important degradation product, fluoromethyl-2,2-difluoro- 1- (trifluoromethyl) vinyl ether (CF_2 = $C(CF_3)$ OCH_2F) [compound A], has been reported to be nephrotoxic in rats. There is controversy surrounding whether this also applies to humans. Studies in patients have reported mean concentrations of compound A ranging from 8 to 40 ppm[118-123] in the inspired gas mix with maximum values of up to 61 ppm, especially when a closed breathing system or a low-flow anaesthesia technique was employed. At the end of anaesthesia the concentrations

of compound A declined rapidly towards <3 ppm in the exhaled gases.[123] The concentration of compound A has increased with higher sevoflurane concentrations,[124] use of Baralyme versus soda lime,[125,126]lowerer fresh gas inflows, higher temperature and lower water content of absorbant. Recently, it was reported that contact with inappropriately dry absorbent (<5 to 10% water content) lead to the instantaneous, exothermic degradation of sevoflurane. As a result, the concentration of sevoflurane in the inhaled gas mix declined and induction of anaesthesia was slowed. In an experimental setting in swine, an inspiratory concentration of 357+/- 49 ppm of compound A was found.[127] However, there was no formation of carbon monoxide, as described in the case of desflurane. As a precautionary measure, low flows less than 1 ltr/min is not recommended to be used while employing sevoflurane as the anaesthetic agent.

Solubility

The most important pharmacokinetic (uptake, equilibration and elimination) characteristic of an inhalational anaesthetic is its blood solubility, expressed by its blood gas partition coefficient. With a blood gas partition coefficient of 0.69, sevoflurane is less soluble than the older volatile anaesthetics, but more soluble than desflurane (0.42) or nitrous oxide (0.47).[128]The blood solubility of sevoflurane is not dependent on patient age[129]. Its solubility in plastic or rubber tubing used in anaesthesia apparatus is lower than those of the older inhalational anaesthetics.[130] Clinically, sevoflurane pharmacokinetics are not altered by solubility in these materials.

Potency and MAC

The most common measure of anaesthetic potency of an inhalation anaesthetic is the minimum alveolar concentration (MAC) of anaesthetic in volumes (percentage) which are necessary to prevent movement in 50% of patients during skin incision. As is the case with other inhalational anaesthetics, the anaesthetic potency of sevoflurane is correlated with its

lipid solubility. With an oil gas partition coefficient of 47.2 its MAC has been reported to be 2.05%.[117,131]. Thus, its potency is considerably lower than that of halothane and isoflurane, but is about 3times more potent than desflurane. The MAC of sevoflurane decreases with age and addition of Nitrous Oxide as shown in table- 4 below.

Table-4: Effect of age on minimum alveolar concentration (MAC) of sevoflurane

Age of Patient (years)	**Sevoflurane in O2**	**Sevoflurane in 65% N2O/35% O2***
<3	3.3-2.6%%	2.0%
3-<5	2.5%	Not available
5 - 12	2.4%	Not available
25	2.5%	1.4%
35	2.2%	1.2%
40	2.05%	1.1%
50	1.8%	0.98%
60	1.6%	0.87%
80	1.4%	0.70%

Pharmacokinetcis

The systemic uptake of volatile anaesthetics and their subsequent distribution and elimination have usually been described by multi compartrnent models. Absorption of the anaesthetic agent by the lung is equivalent to the continuous infusion of an intravenous agent. The kinetic profile of a volatileagent is mainly determined by its physicochemical properties. The rate of induction of anaesthesia as well as the rate of recovery from anaesthesia is inversely related to anaesthetic solubility in the blood and fatty tissues. In addition, agent distribution is dependent on circulatory factors (e.g. organ perfusion) which themselves are modified by the agent.

Uptake

After 30 minutes of inhalation the FA/FI ratio of sevoflurane was approximately 0.8, i.e. equilibration was 80% complete in healthy adults. Consistent with their physicochemical properties, the increase of the FA/FI ratio was more rapid with sevoflurane than with

enflurane and isoflurane, with only nitrous oxide and desflurane yielding higher values, 98 and 90%, respectively.[132]

In contrast to isoflurane, enflurane and desflurane, sevoflurane has a pleasant odour and is not irritating to the airways. As a result, inhalational

induction with sevoflurane is possible in children and studies have shown that inhalational induction with sevoflurane is more rapid [133] than with halothane. When 4.5 to **7** Vol% of sevoflurane have been added to the inspired gas mix during induction, it has taken about 1 to **7** minutes until a concentration of 4 to 6 Vol% was reached in the exhaled gas mixture.[133-135] However, the brief period of apnoea required for intubation has led to a drop in concentration to about 2 Vo1%.[135] Therefore, it is postulated that during rapid inhalational induction, the correlation between end-tidal concentration and blood concentration of sevoflurane is lost.

Distribution and Elimination

Similar to uptake, the elimination of a given volatile anaesthetic is related to its solubility in blood and tissues. Between 95 and 98% of the amount of sevoflurane taken up is eliminated through the lungs. The driving force is the difference in partial pressures between the inspired gas mix and the pulmonary capillary blood. As only 2 to 5% of the absorbed dose of sevoflurane is metabolised, metabolic clearance can be ignored.

As in the case of enflurane, halothane, methoxyflurane and isoflurane, distribution and elimination of sevoflurane is best described by a 5-compartment. The 5 compartments consist of the lungs, the vessel-rich group of organs (including the liver), muscle, fat adjacent to vessel-rich organs, and 'peripheral' fat. Using this model the alveolar elimination of sevoflurane and other volatile agents was analysed by means of 5 differential equations which described the rate of change of a given agent's concentration in each compartment as well as its elimination rate from the lungs and the vessel-rich groups of organs. In addition,

by incorporating the tissue/blood partition coefficients of the various agents, the perfusion and tissue volumes of the various compartments were estimated.[132]

Compared with isoflurane and halothane, sevoflurane has a shorter wash-out time but FA/FI ratiosdecreased more rapidly with desflurane than with sevoflurane. Percutaneous losses account for less than 1% of the total uptake of Sevoflurane. In a recently published study, Eger et a1.[136] were able to show that sevoflurane-induced anaesthesia of 2 hours' duration results in faster elimination and more rapid awakening than similar anaesthesia lasting 8 hours. With the 2-hour duration the FA/FA0 ratio fell below 0.1 after approximately 22 minutes; this period was increased to 55 minutes after 8 hours of anaesthesia.

Metabolism and Toxicity

Fluoride

Rapid hepatic metabolism of sevoflurane results in the formation of inorganic fluoride and the organic fluoride metabolite hexafluoroisopropanol (HFIP).[137]In the blood HFIP is conjugated with glucuronic acid and excreted rapidly by the kidneys. Cytochrome P450 (CYP) 2E, is predominantly

responsible for the biotransformation of sevoflurane.[138-141] In humans, 2 to 5% of the absorbed dose of sevoflurane is metabolised, [137] compared with 75, 46, 8.5, 0.2 to 2 and 0.02 to 0.2% for methoxyflurane, halothane, enflurane, isoflurane and desflurane. Serum inorganic fluoride concentrations after sevoflurane anaesthesia have been reported to be dose dependent and reach about 10 to 20 pmol/L (after 1 to 2 MAC hours), 20 to 40 pmol/L (after 2 to 7 MAC hours) and may be as high as 20 to 90 pmol/L with prolonged exposure.[137]

Serum fluoride concentrations >50mmol/L after methoxyflurane anaesthesia have resulted in a diminished concentrating ability of the kidney. Therefore, it is controversial whether a serum fluoride threshold of >50mmol/L applies in the case of sevoflurane.[142] In the case of methoxyflurance, other factors have been implicated: for instance, Kharaschet a1.[143]

suggested that the intra renal biotransformation of methoxyflurane was crucial for its nephrotoxic effect. In contrast, sevoflurane is predominantly metabolised by the liver rather than intra renally. A number of studies could not show nephrotoxic effects after sevoflurane anaesthesia [144].

Compound A

Degradation of sevoflurane after contact with CO2 absorbent leads to formation of compound A which has been reported to be nephrotoxic in rats. Depending on length of exposure, values of 25 to 50 ppm [145] or 114 ppm[146] are considered critical in rats. While no signs of nephrotoxicity were found

in studies with volunteers,[147,148] surgical patients or in children a group of investigators have reported albuminuria, glucosuria, and liberation of the tubular enzymes a-glutathione S-transferase (a-GST) after exposure of volunteers to 2.5 to 10 MAC hours of sevoflurane.[149-151] These findings, however, remain quite controversial, and have not been reproduced. The standard for assessing renal function is glomerular filtration rate, measured by creatinine clearance. Using this standard, there have been no case reports or studies documenting compound A associated renal impairment. The FDA has recommended the use of sevoflurane with fresh gas inflows of more than 2 L/min in order to minimise the formation of compound A; however, other licensing authorities have not made this recommendation. In contrast with older inhalational anaesthetics, the metabolism of sevoflurane has not resulted in the formation of trifluoroacetic acid (TFA); hence, the hepatotoxic potential of sevoflurane is considered to be minima1.[118,152]

Clinical effects

Respiratory system

Sevoflurane produces dose-dependent ventilatory depression [153] and also reduces respiratory drive in response to hypoxia and increases in carbon dioxide partial pressure,

comparable with levels achieved with other ether anaesthetics. It relaxes bronchial smooth muscle, although perhaps not as effectively as halothane. Sevoflurane is a more potent ventilatory depressant than halothane. Depression of carbon dioxide response curves is similar with halothane and sevoflurane at a minimum alveolar anaesthetic concentration (MAC) equivalent of 1.1, but at a MAC of 1.4, sevoflurane produces more severe depression.[154] No difference in $PaCO_2$ was seen with sevoflurane and halothane at a MAC of 1.1, but at a MAC of 1.4, $PaCO_2$ was higher and minute ventilation lower in spontaneously ventilated patients receiving sevoflurane than in those receiving halothane. Tidal volume with sevoflurane decreases with increasing depth of anaesthesia as it does with halothane. At 1.4 MAC, tidal volumes are similar with the two agents. However, respiratory frequency in patients given sevoflurane was found to increase, but not enough to compensate for the reduction in tidal volume.

Nishino and Kochi [155] measured the end-tidal carbon dioxide partial pressures ($PETCO_2$) at three points: resting, apnoeic threshold, and on-switch threshold. The apnoeic threshold was significantly less than the resting $PETCO_2$. The on-switch threshold, the $PETCO_2$ at which the respiratory drive reappears after post hyperventilation apnoea, was also found to be significantly greater than resting $PETCO_2$. Surgical stimulation does not have a linear effect on these three points. Resting $PETCO_2$ was decreased under sevoflurane anaesthesia. Likewise, the apnoeic threshold was decreased with the apnoeic threshold significantly less than resting $PETCO_2$. However, after surgical stimulus there was no significant difference between on-switch threshold and resting $PETCO_2$.

The effect of sevoflurane on diaphragm function has been assessed in dogs. Ide et al.[156] studied the effects of three sevoflurane concentrations (1, 1.5, and 2 MAC) on diaphragmatic function by measuring transdiaphragmatic pressure after phrenic nerve stimulation at 0.5, 10, 20, 30, 50, and 100 Hz. Sevoflurane exposure at the three

concentrations did not have a significant effect on transdiaphragmatic pressure at 0.5, 10, 20, 30, and 50 Hz, which are in the physiologic range of intrinsic neural firing. However, at 2.0 MAC with a supraphysiologic stimulation of 100 Hz, a decrease in transdiaphragmatic pressure was observed. [156] In contrast, halothane has no effect on diaphragmatic function, while at the other extreme; enflurane causes a very pronounced decrease in force generation by the diaphragm.[157]

Airway irritation due to sevoflurane exposure in humans was assessed by Doi and Ikeda[158], using respiratory plethysmography. Changes in respiratory frequency, tidal volume, and end-expiratory volume due to inhalation of various anaesthetics were evaluated. In general, inhalation of anaesthetics caused an increase in respiratory frequency, decrease in tidal volume, and decrease in end-expiratory volume. A 30% change in tidal volume or respiratory frequency for 10 or longer or a 30% change in end-expiratory volume constituted a significant change. Isoflurane was associated with the most frequent number of changes, followed by enflurane, halothane, then sevoflurane. Sevoflurane had the least effect on tidal volume, had no effect on respiratory rate, and did not initiate a cough reflex.

Sevoflurane appears to be effective in reversing bronchospasm. Mitsuhata and colleagues[159] have successfully demonstrated that anaphylaxis-induced increase in pulmonary resistance is attenuated by sevoflurane anaesthesia at 1 MAC. Furthermore, no significant difference in attenuation was found between sevoflurane and isoflurane.

Sevoflurane has been found to be quite appropriate for use in inhalational induction techniques. Its use was especially amenable to the vital capacity rapid inhaled induction of anaesthesia.[160]When sevoflurane was used in this technique, induction took half the time of conventional inhalational induction (54 s vs 108 s) and was not associated with cardiovascular instability. When compared with halothane, the anaesthetic most often used in an inhaled induction of anaesthesia, sevoflurane has a more rapid induction and fewer

complications, such as coughing and movement, using the vital capacity rapid inhaled induction technique.[161] Volunteers subjected to sevoflurane induction found the smell of the anaesthetic to be more acceptable than did those subjected to halothane.[161]

Cardiovascular system

Sevoflurane decreases mean arterial pressure predominantly through decreased peripheral resistance, with cardiac output being well maintained over the normal anaesthetic maintenance range. A degree of myocardial depression occurs at higher concentrations, as a result of an effect on calcium channels. Sevoflurane does not sensitize the myocardium to the arrhythmogenic effects of catecholamines. Sevoflurane has little effect on normal myocardial blood flow, is a less potent coronary arteriolar dilator than isoflurane, and does not appear to cause “coronary steal” . In contrast with other halogenated ethers, sevoflurane appears to be associated with a lower heart rate, which helps to reduce myocardial oxygen consumption and assists myocardial perfusion.[162]

In another review [163] Sevoflurane was not associated with increases in heart rate in adult patients and volunteers, whereas higher MACs of isoflurane and desflurane and rapid increases in the inspired concentrations of these two anaesthetics have been associated with tachycardia. Increasing concentrations of sevoflurane progressively decrease blood pressure in a manner similar to the other volatile anaesthetics, and in unstimulated volunteers this decrease may be slightly less than with isoflurane at a higher MAC. Sevoflurane appears similar to isoflurane in its effect on regional blood flows, including the hepatic, renal, and cerebral circulation. In animals, sevoflurane appears to be a slightly less potent coronary vasodilator than isoflurane, and in a dog model, sevoflurane has not been associated with coronary flow redistribution ("steal"). Sevoflurane decreases myocardial contractility in a manner similar to equi-anaesthetic concentrations of isoflurane and desflurane, and does not potentiate epinephrine induced cardiac arrhythmias. Sevoflurane reduces baroreflex function

in a manner similar to other volatile anaesthetics.[163] In several multicenter studies where patients with CAD or patients at high risk for CAD were randomized to receive either sevoflurane or isoflurane for cardiac or noncardiacsurgery , the incidence of myocardial ischemia, infarction, and cardiac outcomes did not differ between treatment groups. Thus, sevoflurane has not been associated with untoward cardiovascular changes in volunteers and patients undergoing elective surgery compared with other volatile anaesthetics, and it appears to offer a more stable heart rate profile than either isoflurane or desflurane.[163]

Central Nervous system

The comparative effects of Sevoflurane and Desflurane on the CNS are discussed in a separate section. The same is dealt with in brief, here. Sevoflurane has CNS effects similar to those of isoflurane and desflurane. Intracranial pressure increases at high inspired concentrations of sevoflurane (analogous to isoflurane); however, this effect is minimal over the 0.5–1-MAC range .[164] Sevoflurane is not associated with convulsive or epileptic activity.[164]

Renal and hepatic effects

Renal and hepatic blood flow is well preserved with sevoflurane, and organ toxicity has not been observed to date. Sevoflurane has been well studied with respect to its influence on hepatic perfusion. Initial studies by Manohar and Parks[165] evaluated organ blood flow using radiolabeled microspheres in a porcine model. Exposure to 1.0 or 1.5 minimum alveolar anaesthetic concentration (MAC) sevoflurane with 50% nitrous oxide produced an increase in hepatic arterial flow at both anaesthetic levels, whereas there were modest decreases in intestinal blood flow. Crawford et al. [166] studied hepatic blood flow in sevoflurane-anesthetized rats and found preservation of total hepatic blood flow with increases in hepatic arterial flow (25% at 1.0 MAC; 31% at 1.5 MAC). However, these

animals had concomitant hypercarbia during spontaneous ventilation. In a subsequently study by Conzen et al.[167], sevoflurane and isoflurane maintained total liver blood flow at an anaesthetic concentration that reduced mean arterial pressure to 70 mm Hg, but decreased total liver flow when mean arterial pressure was reduced to 50 mm Hg.

Sevoflurane appears to be similar to isoflurane in terms of preserving or increasing hepatic arterial blood flow compared to unanesthetized values. Sevoflurane and isoflurane preserved hepatic arterial blood flow better than enflurane and significantly better than halothane. All anaesthetics reduced portal blood flow, with halothane producing the most pronounced results. Sevoflurane maintained hepatic blood flow and O_2 delivery at concentrations less than 2.0 MAC, comparable to results observed with isoflurane. Sevoflurane 2.0 MAC anaesthesia reduced O_2 delivery, which was not balanced by a further reduction in hepatic O_2 consumption, as occurred with isoflurane anaesthesia. Portal venous blood flow was reduced substantially only at the 2.0 MAC level. Hepatic arterial flow, which was shown to be well maintained in the study by Frink et al. [168], was actually increased over control values with increasing anaesthetic depth (this same phenomenon has been noted in other studies during isoflurane anaesthesia). Data from these animal models suggest that sevoflurane maintains good hepatic blood flow and liver oxygenation at concentrations less than 2.0 MAC in a fashion comparable to that observed with isoflurane anaesthesia. Although there are no available data on hepatic blood flow measurements in humans, previous studies in animals with other inhaled anaesthetics (e.g., halothane and isoflurane) have generally mirrored the effects found in subsequent studies in humans.

Potential renal toxicity of sevoflurane is of concern because sevoflurane is metabolized to inorganic fluoride, a potential nephrotoxin and the proposed etiologic agent of fluorinated anaesthetic nephrotoxicity. Sevoflurane administered to rats resulted in postanaesthesia renal concentrating ability and urinary excretion of NAG unchanged from

preanaesthesia values. Prolonged sevoflurane exposure in humans has not resulted in significant postanaesthesia renal dysfunction or evidence of renal injury. When compound A, a vinyl compound produced by the breakdown of sevoflurane in soda lime and Baralyme , was administered to Wistar rats by total body exposure, microscopic damage to renal corticomedullaryjunctional cells was described. The significance of this damage is unclear because functional correlates of this injury were not described, the long-term effects of these changes are not known, potential species differences complicate the application of these findings to humans, and the concentrations of Compound A producing damage were in excess of those produced in anaesthetic circuits containing soda lime. Studies documenting the presence and concentration of Compound A in the anaesthesia circuit during sevoflurane anaesthesia in humans have detected no-postanaesthesia renal dysfunction. Sevoflurane itself appears to have minimal nephrotoxic potential.[169]

Obstetric effects

There are limited data on sevoflurane in the obstetric population . However, sevoflurane appears to have similar uterine effects to isoflurane, and no differences in maternal or fetal outcome were observed when equianaesthetic concentrations (0.5 MAC) of these two agents were compared during elective Caesarean section.[170]

Neuro Muscular Junction

Sevoflurane produces clinically useful neuromuscular block and potentiates neuromuscular blockers to a similar degree to other anaesthetics. It can trigger malignant hyperpyrexia in susceptible individuals.[171]

Paediatric population

Sevoflurane is well tolerated by infants, children, and adults when it is administered by mask.[172] Coughing and breath holding occur infrequently during inhalational anaesthesia with sevoflurane; laryngospasm and bronchospasm are exceedingly rare events. Thus

sevoflurane is considered most suitable agent for induction of anaesthesia in children, especially with faster induction as compared to Halothane; due to its low solubility. In 68 infants and children aged 1 moth to 12 years who were anesthetized by inhalation of sevoflurane in 95% oxygen, the incidence of coughing during induction of anaesthesia was 1.5%.[172] In a subsequent multicentre comparison of sevoflurane and halothane (both in 66% nitrous oxide), the incidence of coughing in 250 children anesthetized with sevoflurane was 3%, compared with 7% in 125 children anesthetized with halothane.[172] In a third study, the incidence of coughing during induction of anaesthesia with sevoflurane in 95% oxygen was 15%, compared with 10% for sevoflurane in 66% nitrous oxide and 17% for halothane in 66% nitrous oxide.[172] These data are consistent with published data on the airway irritability of inhalants in adults. Breath holding occurs infrequently (approximate 2.5%) during sevoflurane anaesthesia.[172] Induction of anaesthesia with sevoflurane with or without nitrous oxide is well tolerated in unmedicated children, with an incidence of airway complications that is similar to or less than that with halothane.

Although sevoflurane does not irritate the upper airway, it may cause transient involuntary movements (excitement) and agitation during induction of anaesthesia . These spontaneous movements vary between random movements of one extremity (most frequent occurrence) to flexion movements of all four extremities requiring restraint (rare occurrence). Episodes of agitation have been regarded as minor or moderate adverse events by investigators.[172]The incidence of agitation during sevoflurane anaesthesia appears to depend on the presence of nitrous oxide. When anaesthesia is induced with sevoflurane in 95% oxygen, the incidence of agitation is 20%-35%[172], which is fivefold greater than the 5%-7% incidence with sevoflurane in 66% nitrous oxide. Since most inhalational inductions include nitrous oxide, agitation is unlikely to complicate induction of anaesthesia with sevoflurane in the clinical setting.

Isolated instances of transient apnoea have been reported during sevoflurane anaesthesia in children. A 3-yr-old male who was scheduled for circumcision developed 3 min of apnoea during an inhalational induction with sevoflurane and 66% nitrous oxide. [172] This event followed administration of a caudal block. When apnoea occurred, the inspired concentration of sevoflurane was decreased and, after a period of manual ventilation, spontaneous ventilation resumed. This example serves to remind us that sevoflurane, like all inhalants, is a potent respiratory depressant and, in the absence of pain or other stimulation, deep sevoflurane anaesthesia may induce hypoventilation and apnoea.

Summary

Introduction of sevoflurane and desflurane during the last decades offered new perspectives to clinical anaesthesia. The most interesting new feature of these agents is their low blood/tissue solubility that is responsible for their interesting pharmacokinetic behaviour. Both agents are characterized by a very rapid onset of and recovery from anaesthesia. Sevoflurane reduces brain metabolism, diminishes cerebral regional blood flow, and does not alter brain volume.. Neither sevoflurane nor desflurane causes ‘coronary steal’. Sevoflurane is especially suitable in children due to its low airway-irritating properties. With regard to the liver, sevoflurane and desflurane are as safe as isoflurane. Sevoflurane produces transient elevation of fluoride levels, but without clinical significance. Compound A, a product that results from a reaction between sevoflurane and carbon dioxide absorbent, does not show cytotoxicity to human proximal tubular cells in clinical settings. Low-flow anaesthesia with sevoflurane is even safe in patient with impaired renal function.

EFFECTS OF DESFLURANE AND SEVOFLURANE ON CEREBRAL BLOOD FLOW AND ICP: COMPARATIVE PHARMACOLOGY

Introduction

In general, all volatile anaesthetic agents are cerebral vasodilators, but important differences exist among different agents. At low concentrations, all agents reduce CMRO2 and hence CBF due to flow metabolism coupling. As the concentration of volatile agent is increased, the vasodilation increases and at some point, overtakes the vasoconstriction due to CMRO2 reduction and flow metabolism coupling. If the flow metabolism uncoupling occurs at a low MAC, (halothane, enflurane) that volatile agent will cause a greater increase in CBF and consequently ICP. Isoflurane is among the most commonly used volatile anaesthetics for neurosurgical procedures because of its minimal effects on cerebral blood flow (CBF) and intracranial pressure (ICP) in hypocapnic patients. [2,3]Sevoflurane is widely used in neuroanaesthesia, whereas desflurane raises concern because it induces cerebral vasodilation, and in patients with expanding cerebral lesions could lead to suboptimal surgical conditions. But others have found that changes caused by desflurane in ICP and cerebral blood flow are similar to that of isoflurane and hence desflurane continues to be used in neuroanaesthesia.[4,5,6] A review of available literature on effects of sevoflurane and desflurane on CBF, Vmca, ICP, cerebral blood flow Autoregulation, CO2 reactivity and emergence

characteristics follows. A summary of all relevant studies is given in a tabular form in Table 5, at the end of the section.

Cerebral Blood Flow

Animal studies

In one of the early studies[173], an effect of 0.5 to 2.0 MAC desflurane on CBF was studied in dogs. There was a dose related increase in CBF from 0.5 MAC to 2.0 MAC which was statistically significant, after eliminating the effects of concomitant hypertension. There was a concomitant reduction in cerebral vascular resistance. Lutz et al. showed a dose dependant decrease in canine cerebral metabolic rate for oxygen (CMRO2) during desflurane anaesthesia whereas Scheller et al. documented similar changes with rabbits, using sevoflurane.[173-174] In a study on pigs, Desflurane, sevoflurane and isoflurane were administered in a randomized order to six pigs at 0.5 and 1.0 MAC. The intra-arterial xenon clearance technique was used to measure CBF. Desflurane at 1.0 MAC was associated with 16% higher CBF (P=0.027) at hypocapnia than isoflurane, and with 24% higher CBF (P=0.020) than sevoflurane.[175]

Clinical studies

In a comparative study by Artu et al., Vmca decreased compared with baseline values at 0.5, 1.0, and 1.5 MAC sevoflurane or isoflurane. CPP decreased at 0.5 MAC sevoflurane and at 0.5, 1.0, and 1.5 MAC isoflurane. CVRe increased compared with baseline values at 1 .0 and 1.5 MAC sevoflurane.[176]Bundgaard et al.[177] compared the effects of sevoflurane on CBF, ICP , CMRO2 and CO2 reactivity at 0.7 MAC and 1.3 MAC. An increase in

sevoflurane from 1.5% to 2.5% resulted in an increase in CBF from 29+/-10 to 34+/-12 ml per 100g per min and a decrease in CVR from 2.7+/-0.9 to 2.3+/-1.2 mmHg ml^{-1} min 100g (P<0.05), while ICP and CMRO, were unchanged. CO2-reactivity was maintained at 1.5% and 2.5% sevoflurane.

In children under going urological surgery with sevoflurane and caudal block, Vmca did not vary significantly at 0.5, 1.0 and 1.5 MAC sevoflurane.[178] There was a significant decrease in MAP between 0.5 MAC and 1.0 MAC sevoflurane (P<0.005) and also between 1.0 MAC and 1.5 MAC (P<0.01). There was no significant change in Vmca over 90min at 1.0 MAC sevoflurane.

Bedforthet al[179] compared the effects of rapid introduction of Desflurane and sevoflurane. After the induction of anaesthesia with propofol, either desflurane or sevoflurane (n = 10 per group) was introduced at 7.2% or 2.2%, respectively, and increased to 10.8% or 3.3%, respectively, 2 min later. Middle cerebral artery blood flow velocity was measured continuously. Those patients receiving desflurane had significantly greater middle cerebral artery blood flow velocities, heart rates, and blood pressures than those receiving sevoflurane (P < 0.01). The increase in CBFV recorded after the introduction of desflurane is marked; the maximum mean change of 32 cm/s occurred four minutes after its introduction and represents a 65% increase from baseline. In comparison, the maximum increase in CBFV after the introduction of sevoflurane was 4.4 cm/s, representing a 7% increase from baseline. But ICP measurements were not carried out in this study.

In another study, children undergoing non neurosurgical procedures under propofol anaesthesia were administered desflurane for last 30 mins of procedure, substituting propofol, to achieve faster emergence.[180] In these patients Vmca increased from 37.2 ± 3.1 cm·sec–1 to 57.7 ± 4.1 cm·sec–1 when propofol was changed to desflurane (P < 0.01).Upon emergence of

anaesthesia, Vmca decreased from 57.8 ± 4.2 cm·sec–1 to 37.8 ± 3.2 cm·sec–1 in the desflurane group ($P < 0.01$) but remained unchanged in the propofol group.

Karsliet al.[181] studied the effect of nitrous oxide on cerebral blood flow velocity in children anaesthetised with desflurane. Neither the addition nor removal of nitrous oxide caused any significant changes in middle cerebral artery blood flow velocity, heart rate or blood pressure. This may be due to a more potent cerebral vasodilatory effect of desflurane in children. Nitrous oxide alone has been shown to increase Vmca in children.[182] As such; its effects may be overshadowed by the potent cerebral vasodilatation caused by desflurane.

Mielcket al.[183] investigated the cerebral haemodynamic effects of 1 MAC desflurane, CBF was measured using modified Kety-Schmidt saturation Technique. In comparison with the awake state under normocapnic conditions, desflurane reduced mean cerebral metabolic rate of oxygen (CMRO2) by 51% and mean cerebral metabolic rate of glucose (CMRglc) by 35%. Concomitantly, CBF was significantly reduced by 22%; jugular venous oxygen saturation increased from 58 to 74%. Hypo- and hypercapnia caused a 22% decrease and a 178% increase in CBF, respectively. These findings may be interpreted as the result of two opposing mechanisms: cerebral vasoconstriction induced by a reduction of cerebral metabolism and a direct vasodilator effect of desflurane. CBF alterations under variation of Pa CO2 indicate that cerebrovascular carbon dioxide reactivity is not impaired by application of 1 MAC desflurane.

Fang Luoet al.[184]studied the effects of Desflurane on jugular bulb gases and pressure in neurosurgical patients. Jugular bulb oxygen saturation (SJO2) significantly increased and cerebral arterio jugular difference of oxygen content (AJDO2) and oxygen extraction ratio (O2ER) significantly decreased from 0.7 MAC to 1.0 MAC of desflurane, but there was no

further increase in SJO2 or further decreases in AJDO2 and O2ER at 1.3 MAC compared with 1.0 MAC desflurane.

Intra Cranial Pressure

Animal studies

A Holmstrom et al [185] compared the effects of desflurane or sevoflurane with isoflurane on cerebral blood flow in pigs using intra arterialXe injection technique. In this study at normocapnia, these agents did not seem to differ much in their cerebral vasodilating effects at lower doses (0.5 MAC). At higher doses, (1.0 MAC) however, desflurane, in contrast to sevoflurane, was found to induce more cerebral vasodilation than isoflurane. In another study by the same authors [186], effects of isoflurane, sevoflurane and desflurane on cerebral flow of pigs subjected to raised ICP artificially was studied. This study showed that desflurane increased ICP more and sevoflurane less than isoflurane during normoventilation, but the differences disappeared with hyperventilation.

Artuet al.[187] studied the effects of desflurane on CSF pressure. Desflurane causes greater increases in ventricular CSF pressure than Isoflurane at normocapnia, but not at hypocapnia in dogs.

Clinical studies

Yildiz et al[188] randomised 70 patients to receive either 1 MAC Desflurane or 1 MAC Isoflurane for maintenance of anaesthesia in patients undergoing surgery for supratentorial tumours. There were no statistically significant differences in the incidence of brain relaxation scores between patients who received 1 MAC of desflurane and those who received 1 MAC of isoflurane. Severe brain swelling that typically requires intervention did not occur in any patient in either group. Ornstein et al[70]demonstrated desflurane and

isoflurane cause similar minimal amounts of cerebral vasodilatation at 1 MAC and 1.5 MAC in patients undergoing craniotomy. Cerebral blood flow velocities determined by trans cranial doppler was nearly identical during sevoflurane and isoflurane anaesthesia over a range of concentrations up to 1.5 MAC. Sevoflurane maintains cerebral perfusion pressure slightly better than equipotent doses of isoflurane .[189]In patients with brain tumours, Muzzi et al [190, 191] have demonstrated no difference in lumbar CSF pressure during isoflurane or desflurane at 0.5 MAC with N2O, but showed an increase during anaesthesia with 1 MAC desflurane.

Talkeet al.[6] compared the effects of desflurane, isoflurane and propofol on lumbar CSF pressure, in patients undergoing transphenoidalhypophysectomy. Lumbar CSF pressure increased significantly and remained increased throughout the study with both 0.5 and 1.0 MAC desflurane and isoflurane, compared with propofol. There was no difference between desflurane and isoflurane at either concentration studied for the changes in lumbar CSF pressure, CPP, heart rate and systolic blood pressure. In a comparative study by Artuet al.[176], sevoflurane and isoflurane did not increase ICP significantly at 0.5, 1.0 and 1.5 MAC. Peterson et al. [192] studied the effects of propofol, isoflurane and sevoflurane on ICP and cerebral hemodynamics. Before as well as during hyperventilation, subdural ICP and AVDO2 are lower and CPP higher in propofol-anesthetized patients compared with patients anesthetized with isoflurane or sevoflurane. No significant differences with regard to ICP, CPP, AVDO2, carbon dioxide reactivity, and jugular vein oxygen saturation were found between patients anesthetized with isoflurane and sevoflurane.

In a study in children aged 6 months to 60 months, [193] 0.5 and 1.0 MAC isoflurane, sevoflurane and desflurane in N2O all increased ICP and reduced MAP and CPP in a dose-dependent and clinically similar manner. ICP [mean+/-SD in mmHg] increased statistically significantly in all three groups from baseline to 0.5 MAC ($P<0.001$) and to 1.0 MAC

(P<0.001). From baseline to 1.0 MAC, the increases were +2(2.2), +5 (4.6) and +6 (1.6) with isoflurane, sevoflurane and desflurane respectively. There were no intergroup differences in ICP changes. There were no baseline dependent increases in ICP from 0 to 1.0 MAC with isoflurane or sevoflurane, but ICP increased somewhat more, although statistically insignificant, with higher baseline values in patients given desflurane. The effect of MAP on CPP is 3—4 times higher than the effect of the increases in ICP on CPP and this makes MAP the most important factor in preserving CPP.

Kaye et al.[5] compared the effects of desflurane and isoflurane on cerebral perfusion pressure (CPP), lumbar cerebrospinal fluid pressure (LCSFP), and mean arterial blood pressure (MAP) in patients anesthetized with desflurane or isoflurane undergoing craniotomy for supratentorial mass lesions. At a MAC of 1.2, mean LCSFP was not statistically different between the two study groups either before or after hyperventilation. Additionally, CPP was not significantly different between the two groups.

A recent study by Fraga et al.[4] showed that neither desflurane nor isoflurane changed ICP from baseline at 1 MAC. This study also showed that desflurane did not significantly alter CPP or arteriovenous oxygen content in patients undergoing craniotomy for supratentorial tumours .

Talkeet al.[6] measured the lumbar CSF pressure in normocapnic patients undergoing transphenoidalhypophysectomy. Lumbar CSF pressure increased by 2+/- 2 mmHg(mean +/- SD) with both 0.5 MAC and 1 MAC of sevoflurane.

Cerebral perfusion pressure decreased by 11+/-5 mmHg with 0.5 MAC and by 15 +/- 4 mmHg with 1.0 MAC of sevoflurane. Systolic blood pressure decreased with both concentrations of sevoflurane. The changes produced by 1.0 MAC sevoflurane did not differ

from those observed in a previous study by the same authors with 1.0 MAC isoflurane or desflurane.

CBF autoregulation and CO2 reactivity

Animal studies

Lutz et al.[194] studied the effects of hyperventilation on canine cerebral circulation under desflurane anaesthesia. Measurements were done at 0.5 MAC, 1.0 MAC and 1.5 MAC desflurane before and after hyperventilation. CBF decreased significantly after hyperventilation at all three concentrations of desflurane and cerebral vasculature remained responsive to changes in PaCO2, even in the presence of moderate hypotension.

Clinical studies

Strebel and colleagues[195] showed that desflurane, at concentrations greater than 0.5 MAC, produced a dose-dependent impairment in both static and dynamic cerebral autoregulation. However, in that study, 70% nitrous oxide was used as the background anaesthetic, on the assumption that it had minimal effects on cerebral autoregulation. However nitrous oxide can have profound effects on cerebral autoregulation, therefore, the results of the study by Strebel and colleagues could have been confounded by the presence of nitrous oxide.

Bedforth et al. [196] studied the effects of desflurane, at 1 and 1.5 MAC, on cerebral autoregulation using TCD. Two indices derived from the transient hyperaemic response test (the transient hyperaemic response ratio and the strength of autoregulation) were used to assess cerebral autoregulation. Desflurane resulted in marked and significant impairment in cerebral autoregulation at concentrations 1MAC and above; at concentrations of 1.5 MAC, autoregulation was almost abolished.

In a study by Ornstein[70] et al, cerebrovascular reactivity to CO2 remained intact at 1 MAC and 1.5 MAC desflurane and isoflurane, thus documenting that hyperventilation will decrease cerebral blood flow in each case. Kitaguchi et al demonstrated that blood flow reactivity to blood flow challenge is intact during 0.9 MAC sevoflurane anaesthesia; autoregulation to phenylephrine challenge was also preserved.[197] Gupta et al demonstrated that sevoflurane, at doses as high as 1.5 MAC, is associated with intact autoregulation in normocapnichumans.[198] In another study hypercapnia significantly impaired cerebral autoregulation during general anaesthesia with sevoflurane (1MAC) or propofol. The threshold PaCO2 to significantly impair cerebral autoregulation ranged from 50 to 66 mmHg. The threshold averaged 56 +/- 4 mmHg during sevoflurane anaesthesia and 61 +/- 4 mmHg during propofol anaesthesia.[199]

EEG changes

There was no seizure activity in the EEG with 0.5 MAC and 1.0 MAC isoflurane, sevoflurane and desflurane in pigs.[175]Neither desflurane nor sevoflurane is epileptogenic, even during high dose administration and concomitant hypocapnia.

In a comparative study by Artu et al,[176] EEG was characterized by higher amplitude in the lower frequencies with sevoflurane or isoflurane compared with baseline. At 1.5 MAC, a burst suppression pattern was predominant in two of the eight patients receiving sevoflurane and one of the six patients receiving isoflurane. No instances of epileptiform EEG activity were noted in any of the patients.

Recovery from anaesthesia

Lockhart et al. demonstrated that desflurane leaves rabbit brain faster than isoflurane does, and Eger and Johnson showed that rats given sevoflurane and desflurane recover motor coordination more quickly than those given isoflurane and halothane.[200, 201]

In a study by Yildiz et al,[188] 70 patients received either 1 MAC Desflurane or 1 MAC Isoflurane for maintenance of anaesthesia in patients undergoing surgery for supratentorial tumours. Extubation times, orientation times, and times to eye opening to verbal stimuli were shorter in patients in desflurane group than those in isoflurane group (extubation time, 1.98 vs 5.37 min, *P*= 0.001; orientation times, 7.23 vs 11.62 min, *P*= 0.001; time to eye opening to verbal stimuli, 4.30 vs 8.52 min, *P*= 0.001). Patients in desflurane group also took less time to reach an Aldrete score of 8 than did those in sevoflurane group (9.58 vs 13.86 min; *P*= 0.003)

GiuseppinaMagniet al[202] compared early postoperative recovery and cognitive function in patients undergoing craniotomy for supratentorial expanding lesions and receiving sevoflurane or desflurane anaesthesia. The mean emergence time was similar in the two groups, whereas the mean extubation time and recovery time were longer in Sevoflurane group (15.2 +/- 3.0 min in Sevoflurane group vs. 11.3+/- 3.9 min in Desflurane group and 18.2 +/- 2.3 min in Sevoflurane group vs 12.4+/- 7.7 min in Desflurane group, respectively; *P* = 0.001). No difference between the two groups was found in pain, shivering, nausea, vomiting, and incidence of postoperative hemodynamic events.

Bilotta et al [98] studied the early postoperative cognitive recovery and gas exchange patterns after anaesthesia with sevoflurane or desflurane in overweight and obese Patients undergoing craniotomy. Early postoperative cognitive recovery was more delayed and Short Orientation Memory Concentration Test scores at15 and 30 minutes post anaesthesia were lower in patients receiving sevoflurane based anaesthesia than in those receiving desflurane based anaesthesia (21.5±3.5 vs. 14.9±3.5) (P<0.005) and (26.9±0.7 vs. 21.5±1.4) (P<0.005), respectively.

Table 5: Summary of studies comparing effects of volatiles on CBF and autoregulation

S no	Study	n	Anaesthetic	Study population	Parameter	Results
1	Artu et al. 1997	14	Sevo and Iso at 0.5, 1.0, 1.5 MAC	Adults, Supratentorial tumours	Vmca, ICP	Vmca decreased in both groups, no change in ICP
2	Bundgard et al. 1998	20	Sevo 0.7 and 1.3 MAC	Adults, Supratentorial tumours	CBF,ICP,CMRO2, CO2 reactivity	CBF increased and no change in ICP, CMRO2 and CO2 reactivity on increasing sevo from 0.7 to 1.3MAC
3	Fairgrieve et al. 2003	26	Sevo at 0.5. 1.0, 1.5 MAC	Children, non-neurosurgical	Vmca	No significant difference in Vmca, MAP decreased significantly
4	Bedforth et al. 2000	20	Rapid introduction of sevo/des at 1, 1.5 MAC	Adult, non neuro surgical	Vmca	Des increased Vmca by 65%, sevo by 7%
5	Barlow et al. 2004	30	Des at end of surgery	Children, non-neurosurgical	Vmca	Vmca increased significantly
6	Karshi et al. 2003	18	Effect of N2O on patients naesthetised with desflurane	Children, non-neurosurgical	Vmca	No change in Vmca when N2O added to des, because vessels already dilated by des
7	Mielck et al. 1998	9	Desflurane 1 MAC	CABG patients	CBF, CMRO2, CO2 reactivity	CMRO2 decreased 51%, CBF decreased 22%, CO2 reactivity maintained
8	Yildiz et al. 2011	70	Iso or des at 1 MAC	Adults, Supratentorial tumours	Brain relaxation score	No difference in brain relaxation
9	Ornstein et al. 1993	24	Des or iso at 1MAC and 1.5 MAC	Adults, Supratentorial tumours	CBF,CO2 reactivity	No change in CBF and CO2 reactivity intact at 1 and 1.5 MAC des and iso
10	Johson et al. 1995		Sevo and isoupto 1.5 MAC	Adult neurosurgical	CBFV	Similar in both groups
11	Muzzi et al 1991, 1992	20	Iso and des with and without N2O	Adults, Supratentorial Tumours	Lumbar CSF pressure	No difference b/w iso and des at 0.5 MAC with N2O, but LCSF pressure higher in des group at 1.0 MAC volatile without N2O

no	Study	n	Anaesthetic	Study population	Parameter	Results
12	Talke et al. 1996	30	Des, iso, propofol	Trans sphenoidalhypophysectomy	Lumbar CSF pressure	Similar increase in CSF pressure with 0.5 and 1.0 MAC des and iso, no change with propofol
13	Peterson et al 2003	117	Sevo, iso, propofol	Adults, Supratentorial Tumours	ICP, CPP, AVDO2	No differences between iso and sevo
14	Kaye et al. 2004	36	Des, iso up to 1.2 MAC	Adults, Supratentorial Tumours	Lumbar CSF pressure, CPP, MAP	No difference in LCSFP and CPP at 1.2 MAC
15	Fraga et al. 2003	60	Des, iso 1 MAC	Adults, Supratentorial Tumours	ICP, AVDO2,CPP	No change in ICP from baseline, no difference in CPP and AVDO2 with des or iso
16	Talke et al 1999	20	Sevo, 1 MAC	Trans sphenoidalhypophysectomy	Lumbar CSF pressure	LCSFP increased by 2+/- 2 mmhg with sevo 0.5 and 1MAC
17	Strebel et al. 1995	24+18	Des >0.5 with 70%N2O	Non neurosurgical pts	Static and dynamic autoregulation	Both static and dynamic autoregulation impaired, but N2O is confounding
18	Bedforth et al. 2001	8	Des 1 and 1.5 MAC	Non neurosurgical pts	Autoregulation(THRR)	Autoregulation impaired at >1MAC
19	Kitaguchi et al. 1993	10	Sevo 0.9 MAC	Ischemic cerebrovascular disease	Autoregulation	Autoregulation intact at 0.9 MAC sevo
20	Gupta et al 1997	10	Sevo 1.5 MAC	Non neurosurgical pts	Autoregulation	Intact upto 1.5 MAC in normocapnic patients
21	McMulloch et al.2000	8	Sevoupto .5 MAC, propofol	Healthy human volunteers	Autoregulation	Autoregulation impaired at PaCO2>50mmhg
22	Fang Luo et al. 2002	20	Des 0.7 to 1.MAC	Adults, Supratentorial tumours	SJVO2, AJDO2	SJVO2 increased, AJDO2 decreased significantly from 0.7MAC to 1 MAC

Summary

Out of thirteen studies involving effect of desflurane on cerebral hemodynamic parameters shown in table 5, six studies reveal a negative impact of desflurane i.e. increase in cerebral blood flow velocity, direct or indirect evidence of vasodilation more than other volatiles and loss of autoregulation at concentrations more than 1MAC. Eight studies produced evidence to show that the effects of desflurane were similar to that of sevoflurane and isoflurane. CO2 reactivity with desflurane was seen to be maintained up to 1 MAC. Emergence from anaesthesia was faster with desflurane. With the data on effects of desflurane on cerebral hemodynamics being equivocal, the need for a direct comparison of sevoflurane and desflurane in patients undergoing supratentorial surgery was felt and the present study was conceived.

ROLE OF TCD IN NON INVASIVE MEASUREMENT OF CEREBRAL BLOOD FLOW

Introduction

Cerebral blood flow:

Normal aerobic cerebral metabolism requires a plentiful and uninterrupted supply of oxygen. Although the brain constitutes only 2% of the total body mass, it receives 15% of the cardiac output (750 ml/min in adults). Resting CBF is approximately 50 ml/100 g/min. The flow is not evenly distributed. Grey matter, which is metabolically more active, receives approximately 90 ml/100 g/min and in these regions the rate of oxygen consumption, termed the cerebral metabolic rate for oxygen (CMRO2), is about 3 ml/100 g/min. White matter receives about 20 ml/100 g/min and its CMRO2
is approximately 1 ml/100 g/min.

Cerebral perfusion pressure (CPP):

The perfusion pressure (i.e.thearteriovenous pressure gradient) in the brain is more complex than that of other organs because it is confined within an incompressible vault. It is dependent on the pressure difference between the mean arterial pressure (MAP) or the driving pressure (measured at brain level) and the intracranial pressure (ICP) or the pressure that needs to be overcome to supply adequate blood to the brain. This pressure difference is known as the CPP. A normal CPP is 70–80 mm Hg; the threshold for critical ischemia is 30–40 mm Hg.

Control of cerebral blood flow

Various mechanisms exist that allow an adequate basal CBF to supply the substrate demands of the brain.

Flow-metabolism coupling and local chemical regulators:

Local neuronal activity causes an increase in CMRO2 and CMRGl (Cerebral metabolic Rate of Glucose consumption) and is accompanied by an increased regional CBF to match glucose and oxygen use with delivery. The parallel change in CBF with CMRO2 and CMRGl is known as flow-metabolism coupling.

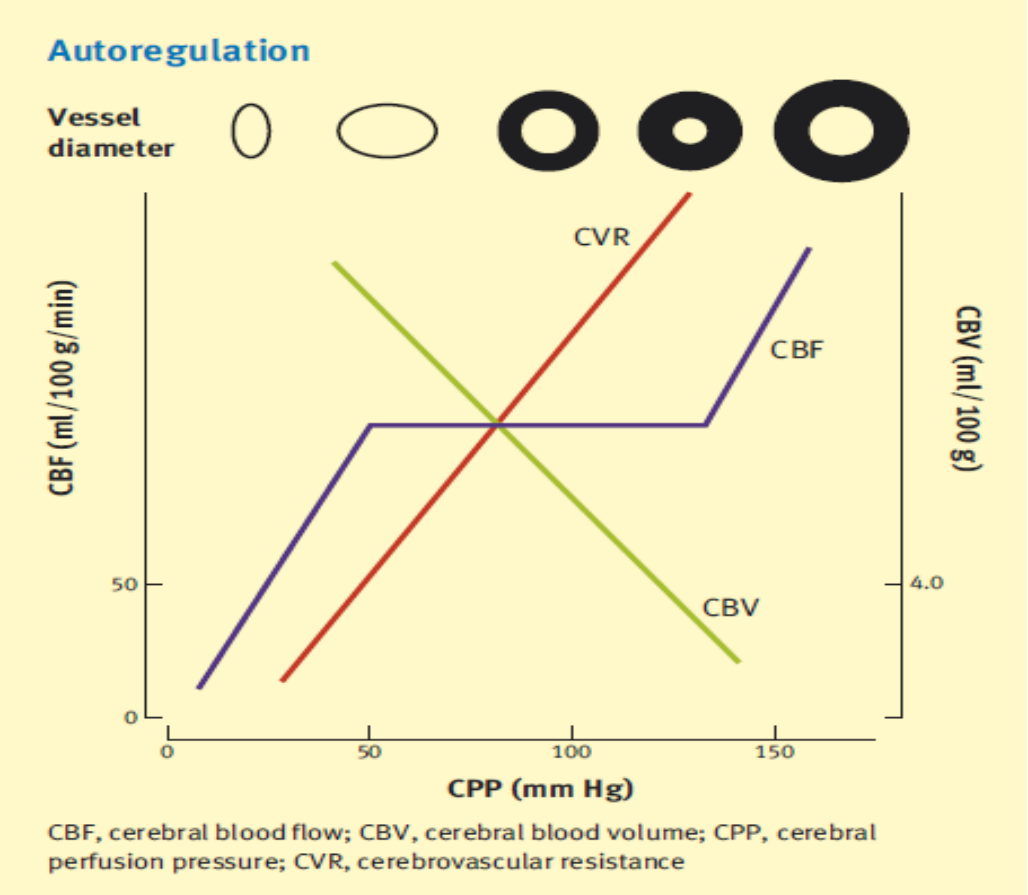
Autoregulation

Autoregulationis the maintenance of a constant CBF despite variations in CPP. Under normal conditions when both ICP and cerebral venous pressure are low, systemic arterial perfusion pressure (i.e. MAP) becomes the primary determinant of CPP. Between a MAP of 50 mm Hg and 150 mm Hg the mean CBF remains constant at 50 ml/100 g/min. However, autoregulation has its physiological limits, above and below which CBF is directly related to perfusion pressure (Figure 5). Autoregulation is achieved by alterations in cerebrovascular resistance (CVR) (occurring over 10–60 seconds) caused by myogenic reflexes to transmural tension in the resistance vessels; thus, as CPP

increases from 50 to 150 mm Hg, cerebral arterioles constrict and therefore restrict increases in CBF.

Autoregulation may be modified by sympathetic nervous system activity. Thus, chronic hypertension or sympathetic stimulation shifts the autoregulatory curve to the right, whilst sympathetic blockade or cervical sympathectomy shifts the curve to the left.

Figure 5: Cerebral blood flow autoregulation



Cerebral venous pressure:

An elevated cerebral venous pressure reduces cerebral venous drainage, expands cerebral blood volume, raises intracranial pressure and therefore reduces CBF.

Arterial carbon dioxide tension:

Carbon dioxide is a potent vasodilator of cerebral blood vessels. As $PaCO_2$ rises between 3.5 kPa (26 mm Hg) and 8 kPa (60 mm Hg) there is a linear increase in CBF.

Arterial oxygen tension and oxygen content:

CBF is directly responsive to changes in oxygen delivery and remains unaltered until a threshold of an arterial oxygen tension (PaO2) of 6.6 kPa
(50 mm Hg) is reached. Below this threshold CBF dramatically rises

Haematocrit

Haematocritis the main determinant of blood viscosity and of oxygen content (and therefore oxygen delivery). CBF changes inversely with whole blood viscosity. Within the normal range of haematocrit, this has a minimal effect on CBF. However, in certain situations when CBF is pathologically decreased (e.g. cerebral vasospasm following subarachnoid haemorrhage), a decrease in haematocrit by haemodilution may improve CBF.

Temperature:

Hypothermia (body temperature of less than 35°C) reduces CMRO2 and CMRGl, and as a result of flow-metabolism coupling CBF decreases. The converse is true for hyperthermia up to a body temperature of 42°C, above which neuronal damage occurs.

Neurogenic regulation:

Cerebrovascular vessels have a rich innervation. Large intracranial and pial vessels have a nerve supply originating from autonomic and sensory ganglia. These contain many vasoactive transmitters, which seem to have a role in the regulation of CBF.

Measurement of cerebral blood flow

A number of techniques for the measurement of CBF have emerged since the pioneering method of Kety and Schmidt in 1945. Many techniques now allow measurement of regional blood flow, giving useful information about changes in blood flow in diseased parts of the brain.

Kety–Schmidt technique:

The Fick principle states that the blood flow through an organ can be measured by determining the amount of an inert substance (Q) removed from the bloodstream by the organ per unit time, and dividing that value by the

difference between the concentration of the substance in arterial blood [A] and the concentration in the venous blood [V] from the organ. Kety and Schmidt used nitrous oxide (N2O) as the inert substance. Patients breathed 15% N2O for 10 minutes whilst serial samples were taken from a peripheral artery and the jugular venous bulb and analysed for N2O content until equilibrium was reached. The total value of N2O taken up was determined by calculating the

N2O content of jugular venous blood at equilibrium.

This technique has a number of disadvantages: the N2O assay is time consuming and tedious and, when low CBF exists, the technique underestimates CBF. Most importantly, it gives a value for global CBF but not regional CBF.

Xenon-133 wash-out:

Regional cortical blood flow can be measured by monitoring the decay of inhaled radioactive isotope Xenon-133 using a battery of scintillation counters positioned over the head. The slope of the wash-out curve of the radioactive

tracer is proportional to the CBF under the detector. The technique provides a two-dimensional analysis of regional CBF but primarily evaluates cortical blood flow. Three-dimensional resolution can be achieved using CT reconstruction in a technique called single-photon emission computed tomography (SPECT).

Other imaging techniques:

Since metabolism is so tightly coupled to blood flow, the uptake of 2-deoxyglucose can be used to estimate regional blood flow. If 2-deoxyglucose is labelled with a positron emitter (e.g. oxygen-15, fluorine-18, carbon-11), its

uptake can be followed using positron emission tomography (PET) scanning and CBF can be estimated

Measurement of cerebral oxygenation

Jugular bulb oximetry:

The jugular bulb is a dilatation of the internal jugular vein just below the base of the skull and may be catheterized using a Seldinger technique. Blood may be sampled for oxygen tension and saturation, giving an indication of CBF

(lower values reflecting greater uptake by the brain and therefore less blood flow, assuming O2 consumption remains constant). The major disadvantage of this technique is that only global CBF can be estimated and not regional changes. In addition, if CBF and oxygen consumption both decrease (e.g. in severe brain injury), jugular venous saturation may be unchanged.

Cerebral microdialysis:

This technique involves the insertion of a fine catheter, containing a dialysis membrane perfused with Ringer's solution, into brain parenchyma. It enables molecules involved in cerebral metabolic pathways to be directly monitored and this can reveal information regarding the adequacy of cerebral oxygenation and blood flow. Metabolites

such as glucose, pyruvate, lactate, glutamate and glycerol or drugs (e.g. phenytoin) diffuse into the solution of the probe from the interstitial fluid (extracellular space) across the membrane andare analysed. The lactate:pyruvate ratio reflects regional cerebral oxygen availability, and has been used clinically in the investigation of head injury and subarachnoid haemorrhage. A rise in the ratio suggests that anaerobic metabolism due to insufficient regional cerebral blood flow is occurring (secondary to hypoxia); treatment may then be taken to correct this impairedphysiology.

Cerebral oxygen partial pressure:

Sensors can be inserted into the brain parenchyma to measure the partial pressure of oxygen in the extracellular fluid of the brain; this reflects the availability of oxygen for oxidative metabolism. Values obtained generally reflect the balance between oxygen delivery and consumption.

Near infra-red spectroscopy:

This monitoring technique is based on the principle that light with wavelengths in the near infra-red region (650–900 mm) transmits through biological tissues. Photons produced by a laser photodiode are directed into the skull, and whilst many are reflected and dispersed, some are transmitted. Certain coloured compounds within the tissues (chromophores), especially oxyhaemoglobin, deoxyhaemoglobin and oxidized cytochrome oxidase, have characteristic absorption spectra. The emergent light intensity is detected and a computer converts the changes in light intensity into changes in chromophore
concentration. Clinical applications of this technique include monitoring of cerebral oxygenation, CBF and volume.

TRANS CRANIAL DOPPLER

Transcranial Doppler ultrasonography (TCD) was introduced in 1982 by Aaslid and colleagues[215] as a non- invasive technique for monitoring blood flow velocity (FV) in the basal cerebral arteries. It is now increasingly being used in anaesthesia and intensive care for research as well as in clinical practice. TCD is based on the use of a range-gated, pulsed-Doppler ultrasonic beam of 2 MHz frequency. The ultrasonic beam crosses the intact skull at points known as 'windows' and is reflected back from the moving erythrocytes in its path. The difference between the transmitted signal and the received signal is called the Doppler shift, and can be expressed by the formula:

Doppler frequency shift=$2 \cdot V \cdot Ft \cdot \cos\theta / C$

where V is the velocity of the reflector (red cells), Ft is the transmitted frequency, C is the speed of sound in soft tissue, and $\cos\theta$ is the correction factor based on the angle of insonation (θ). In TCD, Ft (2 MHz) and C (1540 m/s) remain constant; therefore, frequency shift depends mainly on the blood flow velocity and the angle of insonation of the TCD probe.

Within a vessel, different erythrocytes move at different speeds. The Doppler signal obtained from blood flowing in vessels is therefore, a mixture of different frequency components. Transcranial Doppler machines use spectral analysis and present three-dimensional Doppler data in a two-dimensional format. Time is represented on the horizontal scale, frequency shift (velocity) on the vertical scale, and signal intensity as the relative brightness or colour.

For calculating flow velocity (FV), a 'spectral envelope' corresponding to the maximum FV throughout the cardiac cycle is created. Different parameters are then measured from the 'spectral envelope'

Technique

With TCD, three 'windows' (temporal, orbital and foramen magnum) can be used to insonate different cerebral arteries (Figure 6). The middle cerebral artery (MCA) is most commonly insonated because of the ease of access through the temporal window and the quality of the signal. Also the MCA carries 50–60% of the ipsilateral carotid artery blood flow,[215] and thus can be taken to represent blood flow to the hemisphere.

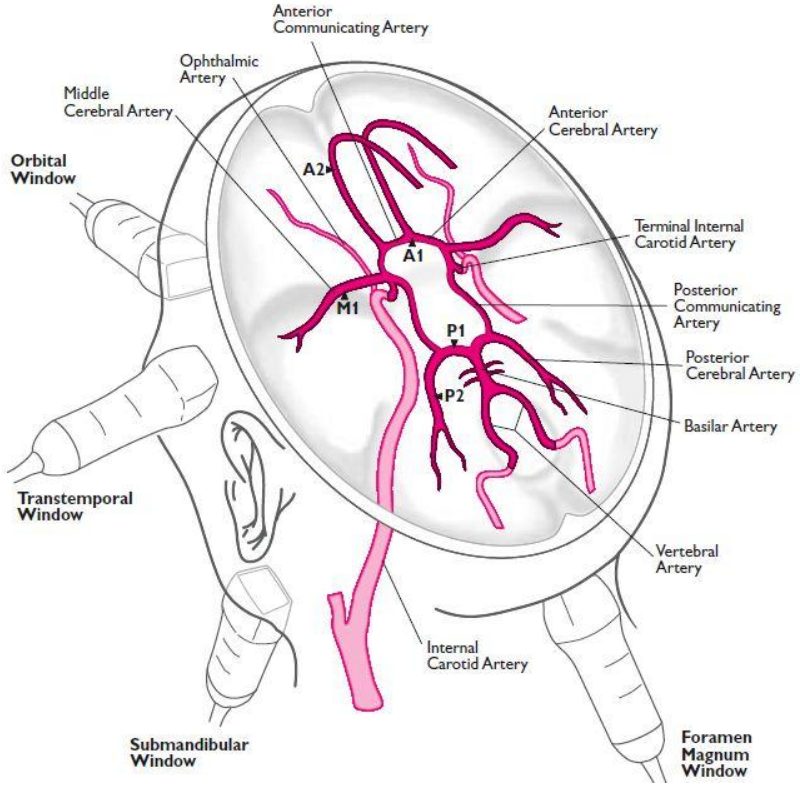


Figure 6 : TCD windows and orientation of basal cerebral vessels

The temporal window is defined as an area delineated by a line drawn from the tragus to the lateral canthus of the eye, and the area 2 cm above this. Moving the probe slowly and systematically over the whole area, the examiner searches for a signal, initially starting at a depth of 50 mm. Having identified the vessel, the examiner should attempt to follow the vessel toward the bifurcation of the internal carotid artery (ICA) into the MCA and anterior cerebral artery. This provides greater confidence that the vessel is indeed the MCA. The

bifurcation of the ICA is usually identified at a depth of 60–65 mm mm following the positive deflection of the MCA FV waveform. The point of maximum deflection is taken for measurements. Insonation of the MCA can be further confirmed by the ability to follow the signal for at least 10mm, and reduction in FV with compression of the ipsilateral carotid artery.[216]

Blood FV

From the FV waveform, systolic, diastolic and time-averaged mean values can be calculated. The mean FV shows least variation and is commonly used. The values for mean MCA FV in healthy adults range from 35 to 90 cm/ s under normal physiological conditions.[217]This variability, despite constant

cerebral blood flow (CBF), is mainly the reflection of variability in the diameter of the MCA or the angle of insonation.

In the short term, MCA FV varies cyclically by around 10%.[218] Side to side variation has been assessed and differences of more than 14% should be considered abnormal.[217] Day to day variation should be less than 10 cm/s in 95% of individuals. Inter-observer variability has been reported as around

7.5% on the same day, and around 13% on different days.[219] Age influences MCA FV. At birth, MCA FV is approximately 24 cm/s increasing to 100 cm/s at 4–6 yr. Thereafter, it decreases steadily to about 40 cm/s in the seventh decade.[220]

Measures of cerebrovascular resistance

Analysis of FV waveform has been performed in a number of ways to allow estimation of the cerebrovascular resistance (CVR). Three indices of CVR have been widely used:

(i) The resistance index (RI) described by Pourcelot[221]

RI= FVs-FVd/ FVs;

(ii) The pulsatility index (PI) of Gosling and King[222]

PI=FVs-FVd/ FVm; and

(iii) The ratio of cerebral perfusion pressure (CPP) to FV: **CPP/FV**. This relies on the assumption that FV and CBF correlate well.

Normal PI ranges from 0.6 to 1.1. The main advantage of PI is that, being a ratio, it is not affected by the angle of insonation. However, both PI and RI may be influenced by a large number of factors including arterial pressure, vascular compliance and PaCO2.[223]

Limitations of TCD

FV vs blood flow

Most importantly, TCD gives information only about blood FV and not blood flow; the two are related as

FV=blood flow volume/blood vessel diameter[224]

Assumptions about the changes in one factor will only hold if the other remains constant. To date there is no widely accepted, reliable method of assessing vessel diameter using TCD. The corollary of the relationship between diameter and flow is such that if flow remains constant while the diameter decreases, the FV will increase. This forms the basis for using TCD to diagnose areas of vessel stenosis or spasm.

Angle of insonation

The TCD velocity spectrum outline represents the blood having the highest velocity in the segment of vessel being studied. The observed velocity is inversely proportional to the cosine of the angle of incidence between the ultrasound beam and the velocity vector. If the angle of incidence is 0^o, the cosine is 1, and at an angle of 15^o, the cosine remains more than 0.96. So within this range, any error caused by change in insonant angle is less than 4%. However, increasing the angle to 30^o results in an error of up to 15%.[214] Because of this,

conclusions based on absolute values of FV measured on different occasions should only be made if the probe has been fixed in position throughout the study period.

Acoustic window

The technical limitation of TCD is the absence of adequate acoustic windows, which occur in around 8% of subjects. Inadequate windows are more common in women and in older subjects.

Comparison of TCD with other techniques of assessing CBF

A number of studies have compared CBF measurement as determined by techniques such as administration of intravenous xenon,[225] the Kety–Schmidt method,[226] Fick principle,[227] and magnetic resonance imaging (MRI),[228] with TCD estimation of FV in order to ascertain whether FV can be used to assess changes in CBF.

Several workers have demonstrated that MCA diameter does not change over a range of arterial pressures and arterial partial pressures of carbon dioxide. TerMinassian and colleagues[227] measured global CBF from changes in AVDO2 and compared this with MCA FV in head injured patients. Their findings suggested that moderate variations in PaCO2 and CPP do not appear to affect the diameter of the MCA in this clinical setting. Giller[229] measured the diameter of basal cerebral arteries directly at craniotomy and found no significant change with changes in arterial carbon dioxide. Valdueza and colleagues[230] found that within the limits of resolution of their magentic resonance imaging matrix, MCA diameter did not change with hypocapnia and reduced CBF. These studies confirm that MCA is resistant to changes in diameter under a wide variety of physiological influences, and therefore changes in FV in these circumstances are more likely to reflect changes in blood flow.

Advantages of TCD over other estimates of CBF

Despite its limitations, TCD has numerous advantages. It can be performed using portable equipment, avoiding the need to move the patient. Once the learning curve has been passed, it is easy to use. It can provide continuous information, and does not involve use of radioactive substances. It can also provide more than just summary measures of flow, with information

available from analysis of the waveform. It is particularly useful for investigation of vasoreactivity because of the rapid response and continuous online beat-to-beat information. Non-flow related measurements such as microemboli could also be monitored.

Cerebral vascular reactivity

The ability of the cerebral vascular bed to undergo constriction or dilatation in response to various stimuli is termed vascular reactivity. It has long been known that CBF remains constant over a range of mean arterial pressures, approximately 60–160 mmHg.[231]This is believed to be a protective mechanism to ameliorate the effects of surges in arterial pressure caused by movement and changes in posture. Outside this range, flow becomes proportional to pressure, with the consequent risks of hypoperfusion at low arterial pressure (<60 mm Hg) and oedema/haemorrhage at high arterial pressure (>160 mm Hg). Although the exact mechanism of autoregulation is unclear, the underlying effect is vasodilation and vasoconstriction of the resistance vessels distal to the feeding arteries. This process is rapid being complete within seconds.[232] It is not instantaneous however, which allows assessment of Autoregulation using dynamic tests.

As TCD provides continuous information about changes in CBFV during changes in arterial pressure or PaCO2 , it has been used to create a dynamic assessment of the cerebrovascular system that is relevant to normal physiology.

Measurement of cerebral autoregulation using TCD

All the methods of assessing cerebral autoregulation assess the changes in FV secondary to the changes in CPP. The autoregulatory phenomenon has different properties, which form the basis of these tests; these properties are speed of autoregulation, the degree to which FV remains constant despite changes in perfusion pressure between the limits of autoregulation (i.e. the gradient of the autoregulatory plateau), and the limits of autoregulation.[233]

Static autoregulation

This refers to the assessment of the autoregulatory plateau over a small range of arterial pressure change. Using TCD, MCAFV is measured under normal physiological conditions and then repeated, once a steady state has been reached, following a 20–30 mm Hg increase in mean arterial pressure induced by a phenylephrine infusion. The index of autoregulation is calculated as the per cent change in the CVR (calculated as mean arterial pressure/FV) per per centchange in the mean arterial pressure. If autoregulation is intact, FV change should be negligible and the value of the index should be 1. A value of autoregulatory index less than 0.4 suggests impaired autoregulation.[233]

Dynamic autoregulation

These tests describe the FV response to sudden changes in perfusion pressure, induced by a number of methods. The thigh-cuff method, first described by Aaslid in 1989,[232] has been extensively used in anaesthesia and intensive care research. In the thigh-cuff method, the MCA FV is measured continuously whilst the arterial pressure is lowered transiently, in a step-wise manner, by rapidly deflating bilateral thigh tourniquets.[235] Normally, both FV and mean arterial pressure decrease initially, but because of intact autoregulation, FV recovers quicker than the mean arterial pressure . If autoregulation is impaired, FV recovery follows passively the recovery in mean arterial pressure. An

autoregulation index (ARI) is calculated based on the goodness of fit between the observed changes in FV and those predicted if autoregulation were as fast as possible (ARI=9) or absent (ARI=0).Anormalvalue has been quoted as 5 (SD 1).[206] The method essentially assesses the speed of autoregulation. The method, however, is cumbersome and the variability is much higher than other methods.

TRANSIENT HYPERAEMIC RESPONSE TEST

This technique of autoregulatory assessment was first described by Giller, has been extensively used in research and clinical arena.

Physiology

This test involves continuous record of middle cerebral artery flow velocities (MCA FV). A brief (3 to 10 seconds) compression of ipsilateral common carotid artery is commenced, which results in a sudden reduction in the MCA FV and presumably perfusion pressure. If autoregulation is intact this provokes vasodilatation in the vascular bed distal to MCA. This vasodilatation causes decreased cerebral vascular resistance and transient increase in MCA FV on release of compression.

Factors analysed:

Standard criteria should be used to identify the MCA with TCD. After a good recording of waveform is obtained, ipsilateral common carotid artery is compressed for 3 to 10 seconds and then suddenly released. Flow velocity waveforms are continuously recorded throughout the study.

The THR test is accepted when it fulfils the following criteria:

- Onset of compression results in sudden decrease of flow velocity
- Heart rate and Blood pressure remains stable during the procedure
- Flow transits after the compression are absent
- The power of the reflected Doppler signal is constant (It indicates that the MCA diameter remains constant)

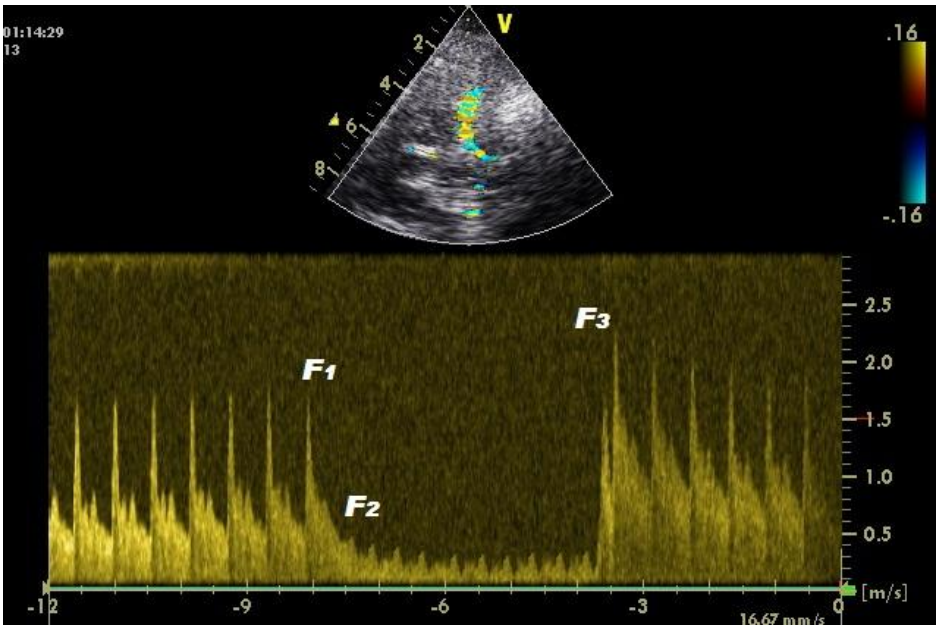


Figure 7 : THRR analysis

For analysis time-averaged mean of the outer envelope of the flow velocity profile preceding the compression (F_1), immediately after compression (F_2), and immediately after the release of compression (F_3) are selected.

As a measure of magnitude of decrease in blood flow velocity during common carotid artery compression the Compression ratio (CR) is calculated.

$$CR = \frac{(F_1 - F_2) \times 100}{F_1}$$

Studies have shown that compression ratio around 40% is ideal for getting a valid THRR and SA values.[235]

The following two autoregulatory indices have been described.

Transient hyperaemic response ratio (THRR): The THR ratio is the ratio between the flow velocity after release of compression and flow velocity before the onset of compression.

$$\mathbf{THRR} = \frac{\mathbf{F_3}}{\mathbf{F_1}}$$

Validation studies and clinical studies have shown that the normal value for THRR is around 1.36±0.09. More than 2 standard deviation change signifies clinically altered autoregulatory response.[233,235]

Strength of Autoregulation (SA): The strength of autoregulation is calculated by normalizing the THRR for changes in mean arterial pressure of the MCA at the onset of compression.

$$\mathbf{SA} = \frac{\mathbf{F_3 \times P_2}}{\mathbf{MAP \times F_1}}$$

Where $\mathbf{P_2 = MAP \times F_2/F_1}$ or 60mmHg whichever is greater (assumed lower limit of autoregulation).

Normal value for strength of autoregulation is around 0.8 – 1.1. Decrease in SA index denotes impaired autoregulation.[233,235]

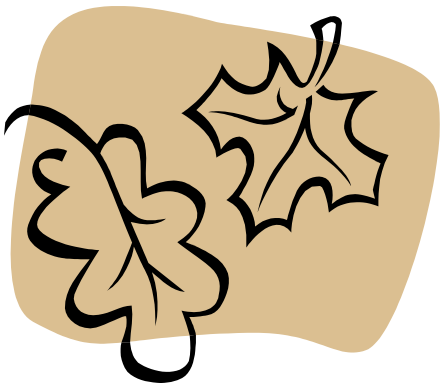
Validity of THRR based autoregulation assessment

This test has been validated against measurement of static and dynamic autoregulation.[206,236]Smielewsky and colleagues have shown that the Transient hyperaemic response ratio is valid index and has similar sensitivity to leg-cuff method, as described by Aaslid*et al* in detecting the changes in cerebral autoregulation produced by different systemic carbon dioxide concentrations.[236] In theory the THR test assess both the gradient as well as the limits of autoregulatory plateau without differentiating between the two. The variability (coefficient of variation<10%) is much lower than the other tests, making it suitable for comparisons. The advantages of THRR based autoregultory assessment are reproducibility, simplicity and lack of pharmacological intervention. The main disadvantage is risk of embolisation of carotid artery atheroma.

Experimental factors like duration of carotid artery compression and magnitude of decrease in blood flow velocity during compression can affect THR ratio. Various studies have applied 5 seconds to 15 seconds of compression. Study conducted by Cavill*et al* in healthy volunteers suggested that at least 10 seconds of compression should be used to get an ideal response as the inherent autoregulatory delay can be 6 to 10 seconds.[235]

Values of compression ratio (CR) in the modelling study for THRR by Smielewski*et al* were 36 to 57 %. Assuming normal blood pressure in all volunteers the CR of 36-57% could reduce the MCA perfusion pressure approximately 40 to 64 mmHg which is well below the lower limit of autoregulation (~ 60mmHg).[236] Study conducted by Cavill*et al* demonstrated that relationship between CR and THRR starts to plateau when CR exceeds 40%, and the authors suggested that a CR of 40% or more approximates to the point at which the autoregulatory capacity is tested to the maximum in normotensive healthy volunteers.[235]

Methodology



METHODOLOGY

The study was approved by the Institutional ethics committee. 40 patients with unilateral supra tentorial tumours were selected for the study. The patients were randomised to two groups of 20 each using a computer generated randomisation program.

1. Desflurane group (n=20) - received desflurane as volatile anaesthetic agent.

2. Sevoflurane group (n=20)-received sevoflurane as the volatile anaesthetic agent.

The following were the inclusion criteria for both the groups.

1. Patients with unilateral intra axial tumours of size more than 4 cm in MCA territorywithout any clinical features suggestive of raised intra cranial pressure
2. American society of Anesthesiology (ASA) class 1 and 2
3. Age 18-60 years
4. Preoperative Glasgow coma scale (GCS) 15.

Exclusion criteria in both groups were

1. Patient refusal for participation in study
2. American society of Anesthesiology (ASA) class 3 and above
3. Age less than 18 years and more than 60 years
4. Preoperative Glasgow coma scale (GCS) <15
5. Intracranial vascular abnormalities including aneurysm and AV malformations,
6. Documented cases of carotid stenosis, atherosclerosis
7. Infra tentorial or posterior fossa tumours,
8. Midline tumours or bilateral tumours,
9. Emergency surgery,
10. Systemic hypertension stage III & above

11. History of malignant hyperthermia in close relatives
12. Coronary artery disease, Left ventricular dysfunction
13. Pregnant or Nursing woman.
14. Screening ultrasound (Grey-scale and Doppler) examination revealed carotid artery plaque or stenosis in preoperative period the day before surgery.

Patients who met the inclusion criteria were explained about the study drugs and study protocol. Informed consent was obtained from patients who were willing to participate in this study.

Literature review shows that that the mean (SD) value for the THRR is 1.36 (0.09), and that for the SA is 0.98 (0.09) under normal physiological conditions. A change of more than 2 SD is considered statistically significant. We calculated that 20 subjects would be required to reject the null hypothesis for a more than 2 SD change in the value of SA or THRR at a significance level of 90% power and α=0.05. Recruitment of participants was done till 20 subjects completed the whole study protocol in each group.

Patients were kept fasting for 8 hours before the proposed study time. No premedication was used in patients who were enrolled in this study.

Patients were shifted to the operating room. Patients were kept comfortably in supine position with head resting on a head pillow. Patient monitoring was initiated using Electro cardiogram (ECG), and pulse oximeter (SpO2). (PHILIPS intellivue MX700)

After local anaesthesia (0.5 to 1 cc of 2% Lignocaine) infiltration, intravenous access with 18G cannula was obtained and 0.9% saline was started at the flow rate of approximately 100ml/hour. For blood pressure measurements invasive BP was used. Under local anaesthesia infiltration, radial artery was cannulated with 20G cannula. For end tidal CO_2 estimation

($EtCO_2$) sample was obtained from mouth piece and analysed in side stream monitor (S/5 monitor, GE healthcare, UK). Baseline Heart rate, SpO2, EtCO2 and invasive blood pressure were recorded. Temperature was monitored using a nasopharyngeal probe and forced air warming blankets were used to prevent hypothermia.

For TCD examination 2MHz transducer probe (Vivid-i, GE health care, UK) was placed in the temporal window and M_1 segment of MCA was identified according to anatomical location, colour scale imaging, and depth of insonation and direction of flow. For calculating flow velocities(FV), the 'spectral envelope' corresponding to the maximum FV throughout the cardiac cycle was recorded and time averaged mean flow velocity calculated by the software was taken as the Vmca reading. After a steady state of flow velocity recording, angle correction was applied so that the angle between linear segment of M1 and angle of insonation was less than 15°. Base line Vmca was recorded for 10 seconds. After informing the patient, gentle compression of common carotid artery was done with continuous monitoring of FV. Compression was maintained for 10 seconds and then abruptly released. Flow Velocities were monitored continuously for 10 seconds following release of compression. Throughout the procedure the obtained FV data were stored in the hardware. For analysis time-averaged mean of the outer envelope of the flow velocity profile (Vmca) preceding the compression (F_1), immediately after compression (F_2) and immediately after the release of compression (F_3) were selected.

The THR ratio was calculated as the ratio between the peak flow velocity after release of compression (F_3) and peak flow velocity before the onset of compression (F_1).

The Transient hyperaemic response test (THR test) was accepted when it fulfilled the following criteria:

- Onset of compression resulted in sudden decrease in FV

- Heart rate and Blood pressure remained stable during the procedure
- Flow transits after the compression were absent
- The power of the reflected Doppler signal was constant (as it indicates that the MCA diameter remains constant)

Transient hyperaemic response testing was done on right side MCA followed by left side MCA. After 90 seconds THR testing was repeated on both sides. The average value from two samples was recorded as baseline values.

The strength of autoregulation was calculated by normalizing the THRR for changes in mean arterial pressure of the MCA at the onset of compression.

$$SA=F_3xP_2/MAPxF_1$$

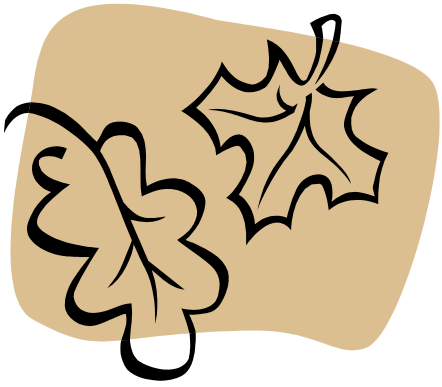
Where P_2 =MAP x F_2/F_1.

All the parameters measured were recorded separately as “tumour side measurements” and “normal side” measurements for all patients for further analysis.

After obtaining baseline recordings, anaesthesia was induced with propofol (2 mg/kg of IBW) and fentanyl (2 mcg/kg of IBW). Neuromuscular block was induced with Vecuronium (0.1 mg/kg) and was monitored throughout anaesthesia using train-of-four monitoring. After anaesthesia induction the trachea was intubated, and mechanical ventilation with intermittent positive pressure ventilation (IPPV) was started at a tidal volume of 7 mL/kg of IBW and with respiratory frequency adjusted to maintain end-tidal CO2 at pre induction levels (+/- 2mmhg), through a semi closed circuit with 2.0 L/min of fresh gas flow. The patient was ventilated with air/O2 mixture (50:50).

After mechanical ventilation was started, fluorinated inhalational anaesthesia (sevoflurane or desflurane, according to the group assignment) was introduced. The volatile agent was titrated to maintain a minimum alveolar concentration (MAC) of 0.5 (end tidal concentration of 3% for desflurane, 1% for sevoflurane). An equilibration period of 15 minutes was allowed for the volatile anaesthetic concentration to stabilize between blood and brain. TCD was done as described above and the FV was recorded twice for averaging. Hemodynamic parameters, ETCO2, TCD measurements (Vmca, THRR, SA from tumour side and normal side) and Arterial Blood Gas measurements were recorded. After recording TCD parameters, volatile anaesthetic concentration was increased to achieve a MAC of 1.0 (end tidal concentration of 6% for desflurane and 2% for sevoflurane) and after a further equilibration period of 15 minutes, second set of measurements – hemodynamic parameters, ETCO2, TCD measurements (Vmca, THRR, SA from tumour side and normal side) – were be recorded. MAP was maintained within 10% of baseline using Mephentermine intravenous boluses. The study ended at this point and the surgical team proceeded with positioning and surgery. Patient was reversed and extubated at the end of the procedure as per established institutional protocols. Intra operative and postoperative adverse events were recorded.

Statistics



DATA ANALYSIS

Demographic data of the two groups of patients were collected and tabulated. Vital parameters [HR, IBP (Systolic, Diastolic, Mean), SpO2, EtCO2] were continuously monitored and mean values were recorded at baseline and during administration of desflurane and sevoflurane at 0.5 MAC and 1 MAC. Complications if any were monitored and recorded- episodes of bradycardia, tachycardia, hypotension and hypertension were documented.

Flow velocities (TCCD) recorded during autoregulatory assessment were collected from two groups (desflurane group and sevoflurane group) of patients at baseline and during administration of desflurane and sevoflurane at 0.5 MAC and 1 MAC, separately for tumour side and normal side. In all groups following parameters were recorded.

- **Mean flow velocity from MCA (Vmca)**
- **THRR – Transient hyperaemic response ratio = F_3/F_1**
- **SA – Strength of autoregulation - $(F_3*P_2)/(MAP*F_1)$**
- **Compression ratio (%) = $(F_1-F_2)* 100/F_1$**

**Where F_1 represents peak flow velocity before compression, F_2 represents peak flow velocity after compression; F_3 represents peak flow velocity after release of compression. MAP –is average mean arterial pressure during the study period, and P2 estimated perfusion* pressure in MCA at the onset of compression calculated as P2= MAP*(F2/F1)

STATISTICS

SPSS version 16 was used for statistical analysis. Student t-test was used to analyse parametric demographic data like age and weight between two groups. Chi-square test was used to assess the difference between gender distributions among two groups. The haemodynamic parameters, Vmca, THRR, and SA were analysed using Analysis of Variance (ANOVA). To assess the statistical difference between repeated measurements within a group, one way repeated measure ANOVA and for differences between two groups mixed repeated measure ANOVA were used. Significance was assessed at 95% confidence interval and p value less than 0.05 was considered statistically significant.

Results

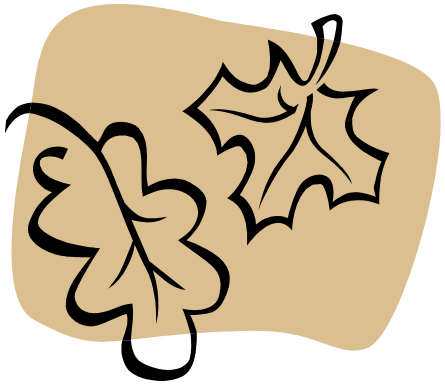


TABLE –6: Comparison of the Demographic factors between the groups

	DESFLURANE (n-20)	SEVOFLURANE (n-20)	**P**
AGE years Mean (SD)	41.7 (12.1)	40.5 (14.6)	**0.779**
GENDER (M:F)	8:12	8:12	**1.000**
WEIGHT in Kg Mean (SD)	64.1 (9.8)	60.3 (10.3)	**0.234**
TUMOUR volume(mm^3)	90.8	115.5	**0.555**

Figure 8: Comparison of Age between groups

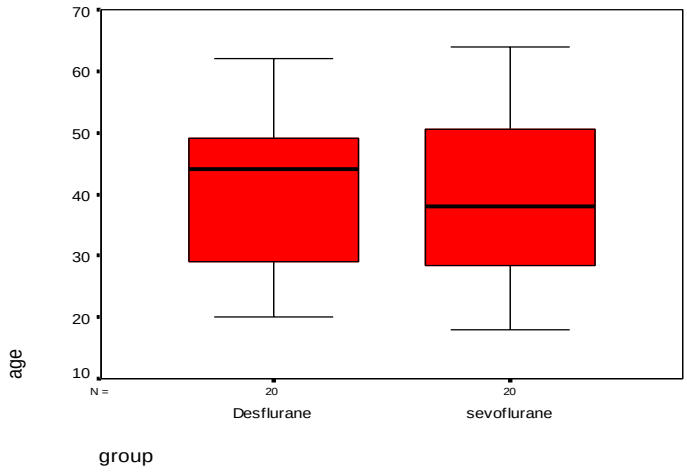
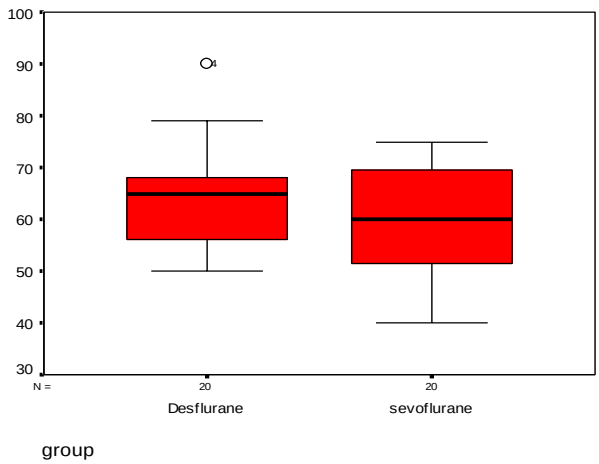


Figure9: Comparison of weight between groups



RESULTS

Twenty five patients were recruited in sevoflurane group to achieve a target study group of 20 patients; five patients had poor temporal bone window and difficulty in insonation. Twenty four patients were recruited in desflurane group, four patients had poor temporal bone window. Measurements of cerebrovascular haemodynamic indices were carried out in each patient on the tumour hemisphere and normal hemisphere, thus generating four sets of data i.e. Desflurane tumour side (DT) and normal side (DN) and Sevoflurane tumour side (ST) and normal side (SN). There were no complications related to the study.The observations and analysis of demographic factors, autoregulatory and cerebral hemodynamic parameters are as follows.

Mean age in Desflurane group was 41.6 ±12.1years. The mean age in Sevoflurane group was 40.4 with SD of 14.6 years. Analysis with student t test showed p value of 0.779 which was not statistically significant.

Gender distribution (Male: Female) was 8:12 among both groups; using Chi-Square test the p value obtained was 1.00, which was not statistically significant.

Mean weight in Desflurane group was 64.1± 9.8 Kg. The mean weight in Sevoflurane group was 60.25± 10.2 kg. Student-t test was used and the p value obtained was 0.234 which indicated no statistical significance (Table 6).The mean tumour volumes in each group, calculated from MRI images were similar (P -0.555).

TABLE-7: showing the changes in the hemodynamic parameters and EtCO2 at baseline, 0.5 MAC and 1.0MAC

	DESFLURANE (n-20)				SEVOFLURANE (n-20)			
	Baseline	0.5 MAC	1 MAC	**p**	baseline	0.5 MAC	1 MAC	p
Heart rate(bpm) (mean± SD)	83.6 (7.7)	81.7 (5.9)	82.3 (6.4)	**0.645**	79.5 (7.9)	77.2 (7.9)	77.6 (7.8)	**0.612**
Mean BP (mmHg) (mean± SD)	98.7 (11.5)	95.4 (11.6)	95.8 (10.8)	**0.607**	95.4 (5.3)	92.6 (4.8)	91.7 (6.2)	**0.090**
ETCO2(mmHg) (mean± SD)	35.3 (1.8)	34.3 (1.7)	34.1 (1.5)	**0.065**	34 (1.8)	33.3 (1.6)	33.7 (1.5)	**0.348**

Table -8: Cerebral haemodynamic indices (Desflurane group)

Desflurane	Tumour			Normal		
	F1	F2	F3	F1	F2	F3
Baseline	72.88	37.74	84.53	68.52	33.68	88.60
0.5MAC	63.06	31.73	31.86	65.44	31.77	31.76
1 MAC	62.73	74.08	73.65	63.76	81.77	73.87

Table 9: Cerebral haemodynamic indices (Sevoflurane group)

sevoflurane	Tumour			Normal		
	F1	F2	F3	F1	F2	F3
Baseline	77.2	42.25	97.19	71.77	39.26	90.06
0.5 MAC	67.18	34.99	79.61	66.1	36	82.64
1 MAC	60.99	35.39	72.36	56.81	30.33	68.84

Table 7 shows that blood pressure and heart rate were maintained within the 10% range of baseline before and after administration of Desflurane and Sevoflurane at 0.5 and 1.0 MAC. This was achieved by administration of intermittent boluses of intravenous mephentermine. Eight patients in the sevoflurane group required mephentermine to keep blood pressure within 10% of baseline whereas five patients in the desflurane group required mephentermine. ETCO2 was maintained within 2 mmHg from baseline at 0.5 and 1.0MAC in both the groups. There was no significant difference in MAP, HR and ETCO2 from baseline in both the study groups (P>0.05).None of the patients had other significant hemodynamic change requiring intervention.

Table 8 & 9 shows the cerebral haemodynamic parameters of desflurane and sevoflurane respectively. F1 is the systolic flow velocity of MCA before compression, F2 is the systolic velocity during compression and F3 is the systolic velocity after release.

Table-10: showing Comparison of mean flow velocity and dynamic autoregulation indices from baseline to 0.5 MAC and 1 MAC in the desflurane group

	Side	Baseline (A)	0.5MAC (B)	1MAC(C)	p	p (A&B)	p (A&C)	p (B&C)
Compression ratio (CR)	Tumour	36.2 (17.49)	42.08 (19.93)	40 (19.23)	0.611	0.989	1.000	1.000
	Normal	44.16 (15.01)	45.33 (16.94)	38.0 (19.02)	0.352	1.000	.776	.540
mFV	Tumour	43.35 (13.04)	36.76 (13.23)	36.65 (12.32)	**0.017**	**0.001**	**0.080**	1.000
	Normal	40.8 (10.07)	38.0 (13.84)	37.87 (13.61)	0.302	0.583	0.675	1.000
THRR	Tumour	1.16 (0.18)	1.19 (0.27)	1.19 (0.19)	0.873	1.00	1.00	1.00
	Normal	1.32 (0.26)	1.25 (0.16)	1.18 (0.27)	**0.049**	0.631	0.101	0.483
SA	Tumour	0.61 (0.16)	0.61 (0.16)	0.61 (0.18)	0.976	1.00	1.00	1.00
	Normal	0.67 (0.19)	0.63 (0.17)	0.59 (0.21)	0.327	0.902	0.407	1.00

P (A, B, C) = p values with Bonferroni correction

The compression ratio (CR) did not show any statistically significant difference from baseline to 0.5 MAC and 1 MAC in the DT and DN groups. The table (Table 10) shows that in the desflurane group there were decreases in the mean flow velocity at 0.5 and 1 MAC in both tumour as well as normal hemisphere from baseline. Overall the decrease in mFV was statistically significant (p.01) in the tumour hemisphere whereas in the normal hemisphere it was found not to be statistically significant. The decrease in mFv was seen significant at 0.5 MAC on the DT side; however between 0.5 and 1 MAC there was no change in both tumour as well as normal hemisphere.

With regard to indices of dynamic autoregulation, the THRR test showed maintenance of dynamic autoregulation on the (DT) tumour side from baseline at 0.5 and 1.0 MAC. In contrast there was a trend towards decrease in THRR values in the normal side (DN) at 0.5 and 1.0 MAC. The decrease was found to be statistically significant. (p - .049) However a post hoc analysis did not show a significant difference at 0.5 as well as 1 MAC. Similarly the strength of autoregulation was better maintained in the DT group at 0.5 and 1.0 MAC, whereas it was reduced in the DN group. However the decrease is not statistically significant (Table 10).

Table 11: showing Comparison of mean flow velocity and dynamic autoregulation indices from baseline to 0.5 MAC and 1 MAC in the sevoflurane group

		Baseline (A)	0.5MAC (B)	1MAC (C)	p	p (A&B)	p (A&C)	p (B&C)
CR	Tumour	34.4 (17.5)	34.48 (17.54)	36.48 (17.41)	0.909	1.0	1.0	1.0
	Normal	40.24 (13.86)	40.74 (15.13)	37.43 (15.89)	0.743	.304	0.06	0.68
mFV	Tumour	47.52 (19.15	39.4 (14.3)	35.72 (10.8)	**0.018**	**0.05**	0.067	0.857
	Normal	42.9 (11.8)	38.9 (11.3)	32.85 (9.6)	**0.005**	0.707	**0.004**	**0.014**
THRR	Tumour	1.25 (0.20)	1.22 (0.17)	1.18 (0.11)	**0.282**	1.00	0.246	1.00
	Normal	1.26 (0.11)	1.25 (0.10)	1.21 (0.07	**0.211**	1.000	0.212	0.511
SA	Tumour	0.68 (0.09)	0.63 (0.11)	0.63 (0.11)	**0.143**	0.445	0.118	1.00
	Normal	0.65 (0.10)	0.64 (0.11)	0.65 (0.08)	**0.291**	0.599	0.519	1.00

P (A,B,C)= p values with Bonferroni correction

The compression ratio (CR) did not show any statistically significant difference from baseline to 0.5 MAC and 1 MAC in the ST and SN groups. In the Sevoflurane group, mean flow velocity decreased from base line to 1.0 MAC both on the tumour side and normal side significantly (p values 0.05 and 0.018 respectively). The THRR was maintained on both the tumour as well as the normal hemisphere in the sevoflurane group at 0.5 and 1.0 MAC compared to baseline value. Similarly the strength of autoregulation was also maintained in both hemispheres at 0.5 and 1.0 MAC with sevoflurane (Table 11).

Table 12: Comparison between tumour side and normal side - Desflurane

		Normal (mean+/-SD)	Tumour (mean+/-SD)	P
Vmca (Desflurane)	Baseline	40.8(10.1)	43.3(13.0)	0.493
	0.5MAC	38.0(13.8)	36.8(13.2)	0.774
	1.0MAC	37.9(13.6)	36.6(12.3)	0.768
THRR (Desflurane)	Baseline	1.32(0.26)	1.16(0.18)	0.034*
	0.5 MAC	1.25(0.17)	1.20(0.27)	0.459
	1 MAC	1.18(0.27)	1.19(0.19)	0.918
SA (Desflurane)	Baseline	0.67(0.19)	0.61(0.16)	0.270
	0.5MAC	0.63(0.17)	0.61(0.18)	0.686
	1 MAC	0.59(0.21)	0.61(0.18)	0.779

Table 13: Comparison between tumour side and normal side - Sevoflurane

		Normal (mean+/-SD)	Tumour (mean+/-SD)	P
Vmca (Sevoflurane)	Baseline	42.9(11.8)	47.5(19.1)	0.365
	0.5MAC	38.9(11.3)	39.4(14.3)	0.912
	1.0MAC	32.8(9.6)	35.7(10.8)	0.378
THRR (Sevoflurane)	Baseline	1.26(0.12)	1.26(0.20)	0.953
	0.5MAC	1.25(0.10)	1.22(0.17)	0.530
	1 MAC	1.21(0.08)	1.18(0.12)	0.394
SA (Sevoflurane)	Baseline	0.65(0.11)	0.68(0.11)	0.800
	0.5MAC	0.64(0.11)	0.63(0.11)	0.854
	1 MAC	0.65(0.08)	0.63(0.08)	0.363

Comparison between tumour side and normal side

A comparison of mFV between the tumour side and normal side showed no significant differences at baseline, 0.5 MAC and 1 MAC in both desflurane and sevoflurane groups. The THRR was significantly higher on the normal side, compared to tumour side in the desflurane group at baseline (P-0.034), but there was no difference at 0.5 MAC and 1.0MAC. There was no difference in THRR in the sevoflurane group between tumour side and normal side. Strength of autoregulation was not significantly different between tumour side and normal side in desflurane and sevoflurane groups (Tables 12&13).

Table 14:-Comparison of desflurane and sevoflurane groups (normal side)

		Desflurane (Normal side)	Sevoflurane (Normal side)	P
Vmca	Baseline	40.8 (10.1)	42.9 (11.8)	0.548
	0.5 MAC	38.0 (13.8)	38.9 (11.3)	0.820
	1 MAC	37.9 (13.6)	32.8 (9.6)	0.185
THRR	Baseline	1.32 (0.26)	1.26 (0.12)	0.367
	0.5 MAC	1.25 (0.17)	1.25 (0.10)	0.980
	1 MAC	1.18 (0.27)	1.21 (0.08)	0.692
SA	Baseline	0.67 (0.19)	0.65 (0.11)	0.782
	0.5 MAC	0.63 (0.17)	0.64 (0.11)	0.803
	1 MAC	0.59 (0.21)	0.65 (0.08)	0.364

Table 15:-Comparison of desflurane and sevoflurane groups (Tumour side)

		Desflurane (Tumour side)	Sevoflurane (Tumour side)	P
Vmca	Baseline	43.3 (13.0)	47.5 (19.1)	0.425
	0.5 MAC	36.8 (13.2)	39.4 (14.3)	0.554
	1 MAC	36.6 (12.3)	35.7 (10.8)	0.802
THRR	Baseline	1.16 (0.18)	1.26 (0.20)	0.125
	0.5 MAC	1.20 (0.27)	1.22 (0.17)	0.742
	1 MAC	1.19 (0.19)	1.18 (0.12)	0.850
SA	Baseline	0.61 (0.16)	0.68 (0.10)	0.113
	0.5 MAC	0.61 (0.18)	0.63 (0.12)	0.568
	1 MAC	0.61 (0.18)	0.63 (0.11)	0.993

Comparison between the desflurane group and sevoflurane group

A comparison between the cerebral haemodynamic parameters between the desflurane group and sevoflurane group was done to look for differences in the pattern and degree of change in parameters. The MCA mean flow velocities, THRR and SA were not significantly different between desflurane group and sevoflurane group on tumour side as well as normal side. (Table 14&15)

Comparison of cerebrovascular indices

Figure 10: Comparison of mean flow velocity of desflurane group

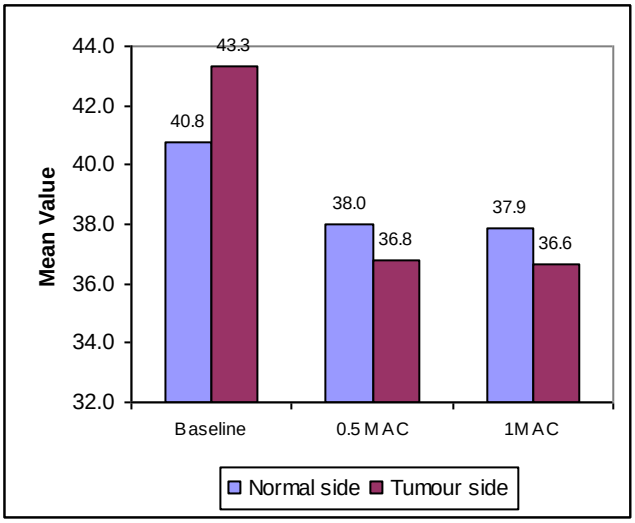


Fig 11: Comparison of mean flow velocity of sevoflurane group

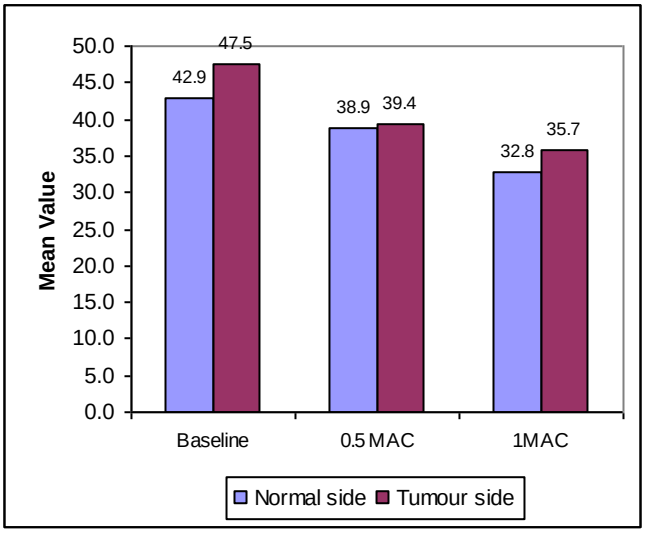


Fig 12: Comparison of transient hyperemic response ratio of desflurane group

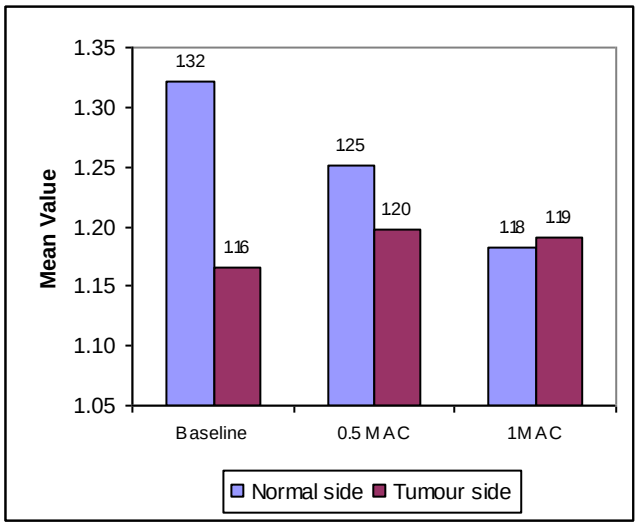
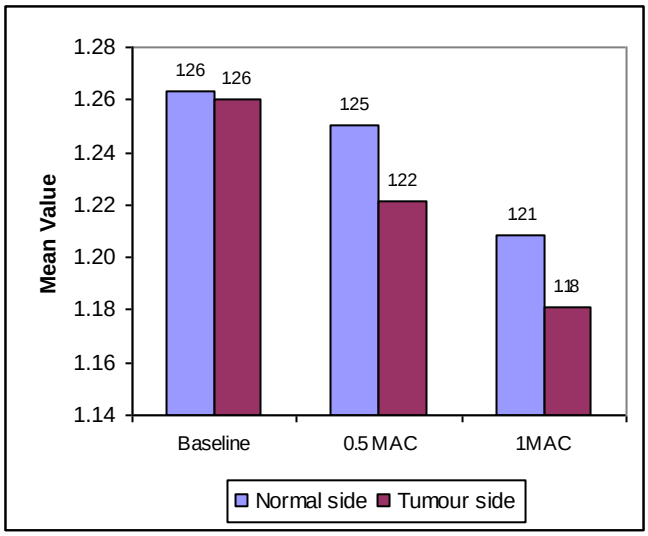


Fig 13: Comparison of transient hyperemic response ratio of sevoflurane group



Comparison of cerebrovascular indices between the tumor side and normal side

Fig 14: Comparison of mean flow velocity between the tumor side and normal side of desflurane group

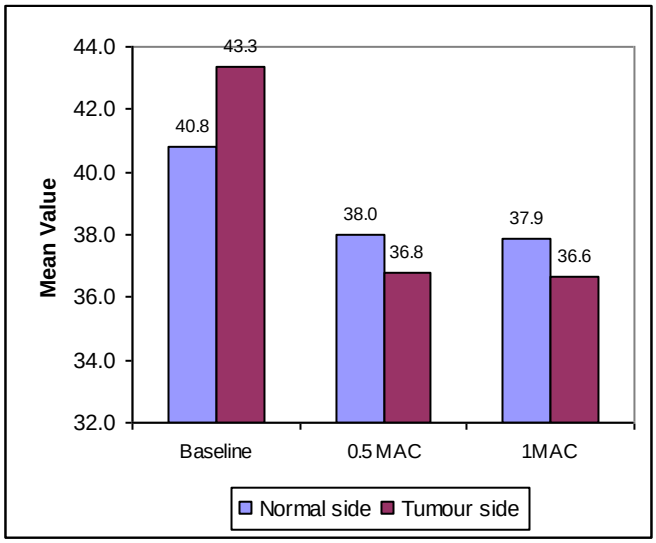


Fig 15: Comparison of mean flow velocity between the tumor side and normal side of sevoflurane group

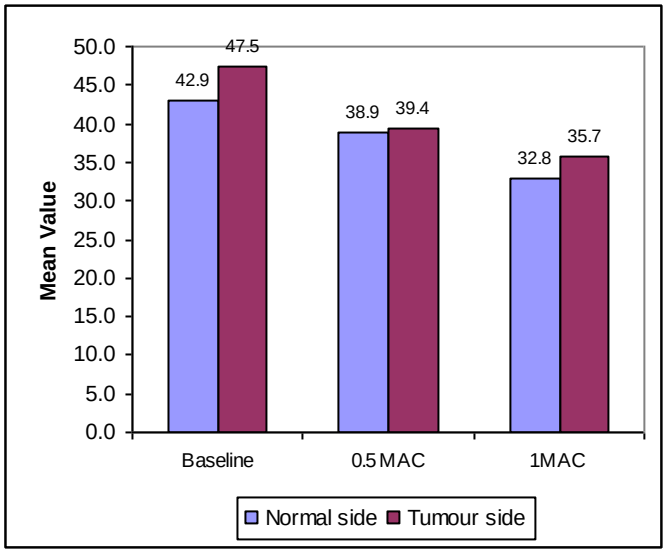


Fig 16: Comparison of transient hyperemic response ratio between the tumor side and normal side of desflurane group

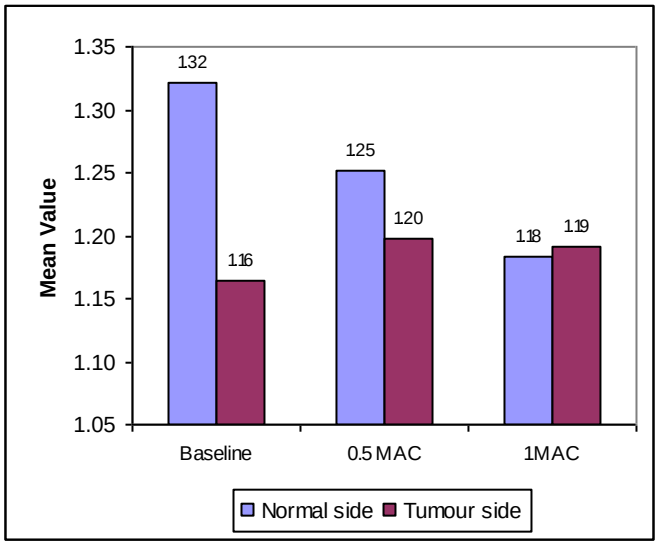
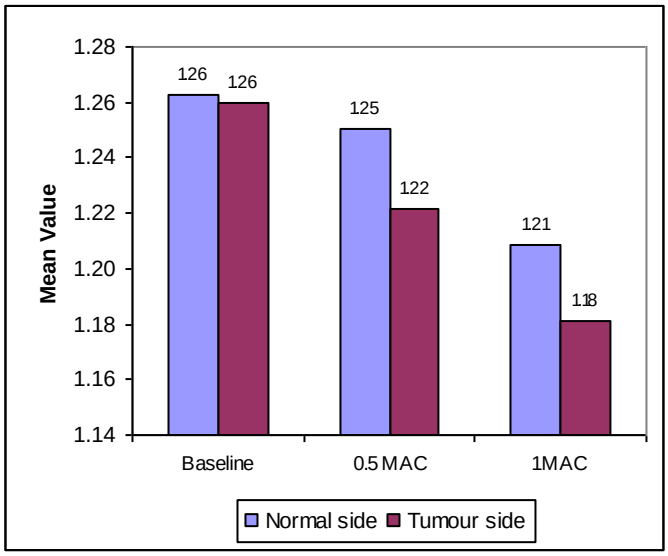


Fig 17: Comparison of transient hyperemic response ratio between the tumor side and normal side of sevoflurane group



Comparison of cerebrovascular indices between groups

Fig18: Comparison of mean flow velocity between desflurane and sevoflurane for normal side

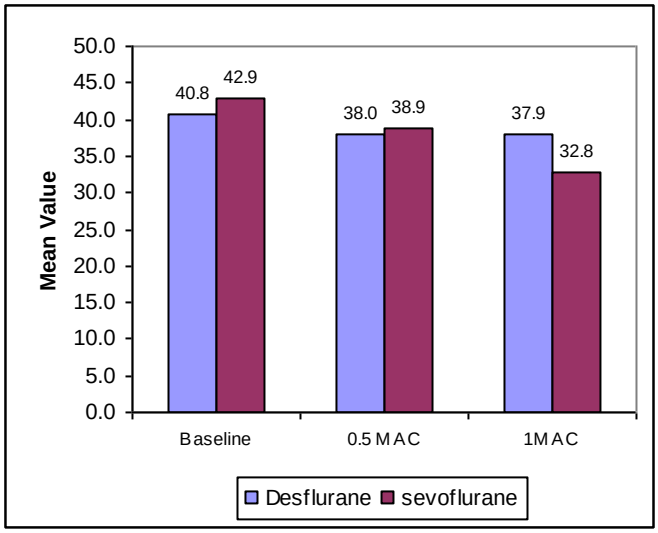


Fig19: Comparison of mean flow velocity between desflurane and sevoflurane for tumour side

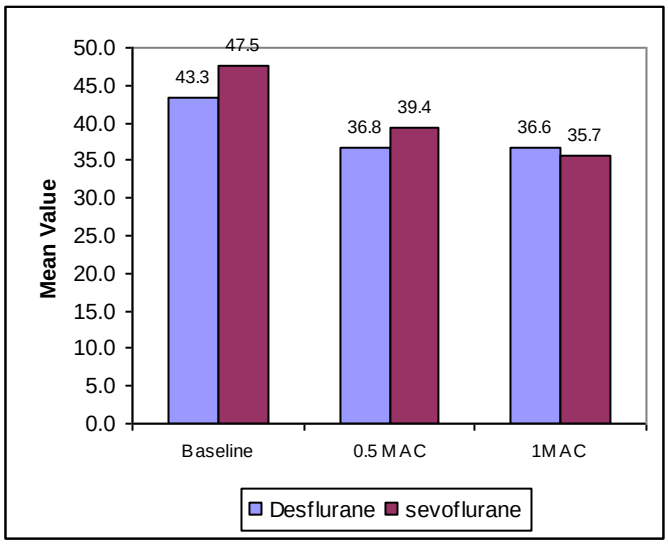


Fig 20: Comparison of transient hyperemic response ratio between desflurane and sevoflurane for normal side

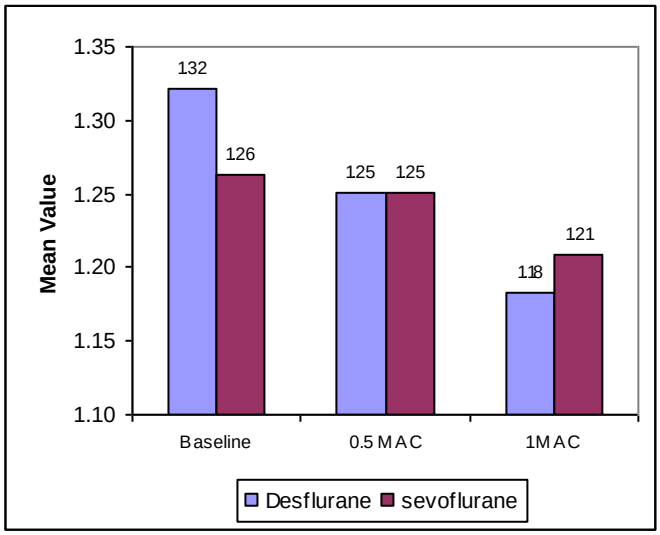
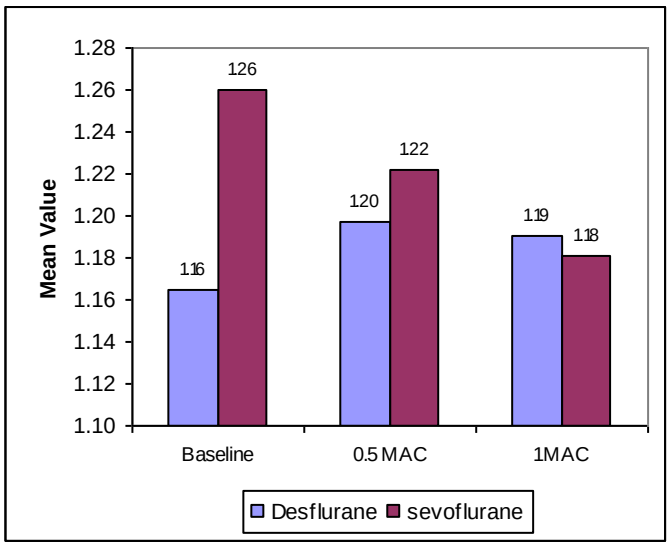
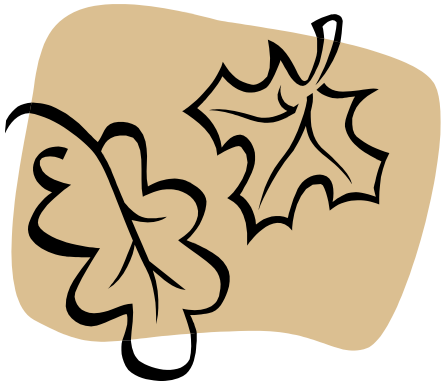


Fig 21: Comparison of transient hyperemic response ratio between desflurane and sevoflurane for tumour side



Discussion



DISCUSSION

Our study compared the dynamic autoregulation of desflurane Vs sevoflurane in patients with brain tumours in the MCA territory at clinically useful concentrations of 0.5 and 1 MAC. We found that overall, there were no significant differences in cerebral haemodynamic effects of desflurane and sevoflurane at 0.5MAC and 1 MAC in patients with supratentorial tumours, without features of raised ICP at normocapnia.

Sevoflurane and Desflurane are both fluorinated inhalational anaesthetics characterized by a low blood/gas partition coefficient that favours rapid emergence. Sevoflurane is widely used in neuroanaesthesia, whereas desflurane raises concern because it induces cerebral vasodilation, and in patients with expanding cerebral lesions could lead to suboptimal surgical conditions. But others have found that changes caused by desflurane in ICP and cerebral blood flow are similar to that of isoflurane and hence desflurane continues to be used in neuroanaesthesia[4,5,6]. Few published studies have investigated how balanced anaesthesia with sevoflurane or desflurane affects perioperative systemic and cerebral hemodynamics, but none have carried out a direct comparison of cerebrovascular effects of these drugs in patients with intracranial pathology.

TCD has been used to measure cerebral blood flow velocity changes with use of various anaesthetic agents and to assess phenomenon of autoregulation of cerebral blood flow. TCD has major advantage over other methods because of the simplicity, low cost, repeatability, and it does not have any radiation hazards. The new improvements in transcranial Doppler like colour duplex imaging have improved the sensitivity and accuracy.

This study was designed to assess the effect of clinically useful concentrations of Sevoflurane and Desflurane on cerebral blood flow parameters in patients with supratentorial mass lesions. TCD was used to assess middle cerebral artery flow parameters (Vmca), and indices of autoregulation -transient hyperaemic response ratio (THRR) and strength of autoregulation (SA)- at baseline and at two different concentrations of volatile anaesthetics, 0.5 MAC and 1 MAC. The possibility of differences in cerebral blood flow and autoregulation due to the presence of a tumour was also investigated.Pre-procedure USG screening was done in our study to rule out any vascular pathology in common carotid arteries, that might cause abnormal intracranial flow velocities and to ensure that the patient has no risk of atheroma embolisation during carotid compression.

Transcranial colour Doppler imaging modality with angle correction option was used to ensure that same segment of artery was insonated in the same angle before and after the volatile agent was introduced. Factors that can cause abnormality in flow velocity and autoregulatory assessment like uncontrolled hypertension and Pregnancy were excluded. Patients diagnosed with unilateral supratentorial tumours, scheduled to undergo surgery were included in the study. Age, gender and body weight distribution was comparable between two groups (Table-6).

During the study, the systemic factors that can possibly affect cerebral blood flow velocity were maintained within the acceptable range (<10% of baseline). Thus, we can postulate that the autoregulatory and cerebral hemodynamic parameters obtained were mainly due to the drug's effect on cerebral circulation and not due to the alteration in systemic hemodynamics.

MCA flow velocities

Comparison of mean MCA flow velocities (Vmca) showed that there was no significant difference in Vmca from baseline to 0.5 MAC and 1 MAC in Desflurane group on the non-tumour hemisphere. The Vmca decreased significantly from baseline to 0.5 MAC on the tumour side, but did not decrease significantly further, when desflurane concentration was increased to 1MAC. On the other hand, there was a statistically significant decrease in Vmca from baseline to 0.5 MAC and 1 MAC in sevoflurane group on tumour hemisphere and non-tumour hemispheres. The possible reason for the decrease in the mean flow velocity is the reduction in the cerebral metabolism caused by the inhalational anaesthetic agents.

The concern for use of desflurane in neuroanaesthesia was due to early studies demonstrating a vasodilatory effect of desflurane on cerebral vasculature. In animal studies, desflurane is reported to produce a dose dependant increase in CBF. Lutz et al. studied[173] effects of 0.5 to 2.0 MAC desflurane on CBF in dogs. There was a dose related increase in CBF from 0.5 MAC to 2.0 MAC, which was statistically significant, after eliminating the effects of concomitant hypertension. There was a concomitant reduction in cerebral vascular resistance. In a study in pigs, desflurane at 1.0 MAC was associated with 16% higher CBF (P=0.027) at hypocapnia than isoflurane, and with 24% higher CBF (P=0.020) than sevoflurane.[186]

On the other hand, some animal studies were encouraging; Lenz et al.[211] demonstrated that effects of desflurane on CMRO2 were similar to that of isoflurane in rats and Lutz et al.[194] showed that cerebrovascular reactivity to CO2 was preserved in Dogs anaesthetised with desflurane.

In our study there was no increase in Vmca at 0.5 and 1 MAC concentrations of desflurane, in fact a modest, decrease in Vmca was observed. This finding is similar to some earlier studies on effect of desflurane on CBF.

In an elegant study Ornstein et al.[70] measured CBF using intravenous Xenon technique in neurosurgical patients anaesthetised with 1 and 1.5 MAC desflurane and isoflurane. The reduction in CBF and preservation of CO2 reactivity was comparable in desflurane and isoflurane groups.

Fraga et al.[4] demonstrated that AVDO2 decrease was similar at1 MAC of desflurane and isoflurane and there was no change in ICP from baseline in both groups. These findings were also reflected in a study by Fang Luo et al.[184] in which SJVO2 increased and AVDO2 decreased from 0.7 MAC to 1 MAC desflurane, but there was no further change from 1 MAC to 1.3 MAC, suggesting that maximum reduction in CMRO2 took place at 1 MAC desflurane. Further increase in desflurane concentrations resulted only in fall in MAP, indicating more vasodilation than reduction in CMRO2 at higher concentrations. Mielck et al.[183] investigated the cerebral haemodynamic effects of 1 MAC desflurane. Desflurane reduced mean cerebral metabolic rate of oxygen (CMRO2) by 51% and, CBF was significantly reduced by 22%; jugular venous oxygen saturation increased from 58 to 74. These findings may be interpreted as the result of two opposing mechanisms: cerebral vasoconstriction induced by a reduction of cerebral metabolism and a direct vasodilator effect of desflurane.

When the findings of the above-mentioned studies are interpreted, it evolves that at low concentration, desflurane has similar effects as sevoflurane and isoflurane- i.e. reduction in CBF and ICP, but as concentration increases vasodilation predominates. Up to

1 MAC desflurane does not cause an increase in CBF and above 1 MAC, vasodilation leads to an increase in CBF.[4, 183,184]

The findings in our study also reflect the findings in the above- mentioned studies, especially when the result of the change in Vmca with sevoflurane is interpreted alongside that of desflurane. The decrease in Vmca with sevoflurane was greater and was shown to be statistically significant there by suggesting a lesser degree of vasodilation at 1 MAC sevoflurane, as compared to that of desflurane.

Some of the published evidence citing increased Vmca with desflurane needs further consideration. Bedforth et al.[179] demonstrated that rapid introduction of 1.5 MAC desflurane increased CBFV by 65% while sevoflurane introduction increased CBFV by 7 %. The cardiovascular stimulatory effects of rapid introduction of desflurane has been reported[45,46] and could have contributed to this rise in CBFV. Addition of N2O to children anaesthetised with 1 MAC desflurane did not lead to an expected rise in CBFV [181] there by suggesting that desflurane had already caused maximal cerebral vasodilation. This finding cannot be generalised to adult population since it has been observed that children demonstrate an increased sensitivity to the cerebral vasodilatory effects of the inhalational anaesthetic agents.[204]

The significant decrease in Vmca in the sevoflurane group in our study compares well with existing literature on cerebrovascular effects of sevoflurane. Studies using PET have shown a decrease[212] or no change[213] in CBF with sevoflurane. Several studies measuring Vmca with sevoflurane have shown that Vmca decreases with sevoflurane and decrease in Vmca was comparable to that with equal MAC concentrations of isoflurane [176,177,178,189].

Since there were some differences between cerebral haemodynamic parameters from baseline to 0.5 MAC and 1 MAC in the four groups (desflurane tumour, normal and sevoflurane tumour, normal) statistical testing was carried out between the tumour side and normal side of each volatile agent group. The presumption was that the tumour itself might have some effect on blood flow, i.e. increase in blood flow, which may affect the cerebral blood flow with the introduction of volatile agents. There was no statistically significant difference between the mean flow velocities of tumour and normal side in desflurane and sevoflurane groups ($P>0.05$).

Very few studies have studied the effect of tumours on regional cerebral blood flow distribution. Vajramuni et al [202] studied the effect of halothane nitrous oxide anaesthesia on cerebral blood flow in patients with fronto parietal gliomas and found no difference in Vmca, PI and RI between tumour and normal side.

There were some concerns about the blood supply to gliomas . A study conducted by Hardebo et al. showed that blood vessels in malignant gliomas exhibit regressive changes in all layers of the vascular wall[205]. Those blood vessels were not innervated by nerve endings sensitive to vasoactive agents and totally lost vascular reactivity to vasoactive agents.

At the outset, this study was planned to detect the differences of the effects of desflurane and sevoflurane on cerebral blood flow and autoregulation. The Vmca values were tested for significance in changes between the desflurane and sevoflurane groups (desflurane tumour side v/s sevoflurane tumour side and desflurane normal side v/s sevoflurane normal side). The Vmca was not significantly different between desflurane group and sevoflurane group on tumour side as well as normal side ($P>.05$) (please refer tables 14&15). Thus, the small (but statistically significant) changes in Vmca within the

group (from baseline to 0.5 and 1 MAC) were not significant when direct comparison between groups was carried out. This finding suggests that desflurane and sevoflurane have similar effects on cerebral flow changes at 0.5 MAC and 1.0 MAC in normocapnic patients i.e. the degree of change of Vmca was same with both agents. This finding is similar to that of previous studies. [4,183,184]

The rational for using Trans Cranial Doppler (TCD) for measuring cerebral blood flow velocity as a surrogate for cerebral blood flow and its validity needs further elaboration. The cerebral blood flow is directly proportional to the cerebral blood flow velocity and inversely proportional to the diameter of the vessel. Thus, flow is not same as velocity (as measured by TCD), but blood flow velocity measurements can be used for quantification of cerebral blood flow, provided the vessel diameter remains constant.

In this study, due care was taken to minimise the factors that may change the diameter of cerebral blood vessels. Changes in Pa CO2 was minimised to avoid reflex vasoconstriction or vasodilatation caused by cerebrovascular reactivity to carbon dioxide. This was achieved by continuous ETCO2 measurement and adjustment of minute ventilation to maintain ETCO2 within 2 mmHg from awake values. The mean arterial pressure was maintained within 10% of baseline values using Mephentermine intravenous boluses, to avoid any reflex vasoconstriction due to myogenic vasoconstriction and to maintain a stable baseline for the THRR measurements. Temperature was monitored using a nasopharyngeal probe and forced air warming blankets were used to prevent hypothermia. By minimising chances of a change in diameter of MCA, the measurement of cerebral blood flow velocities would closely reflect the changes in cerebral blood flow. This method of using TCD measurements for quantifying cerebral flow has been used in several studies and validated.

Fodale et al [203], in a review article analysed more than fifty studies using TCD to measure flow velocities in patients anaesthetised with volatile agents, nitrous oxide and IV agents. The article also reports studies using TCD to measure autoregulation and cerebrovascular reactivity to CO2.

Effect of Desflurane and Sevoflurane on Cerebral Autoregulation

Our study also compared the effects of desflurane and sevoflurane on cerebral autoregulation. Autoregulation was assessed using Transient Hyperaemic Response Ratio (THRR) and Strength of Autoregulation (SA).

When data was compared within the groups, THRR showed a statistically significant reduction on the normal side of the desflurane group (P-0.49) from baseline to 0.5 and 1.0 MAC, however post hoc analysis showed that it was not significant. On the tumour side there was no significant change in THRR. In the sevoflurane group, THRR was not significantly different on tumour side and normal side between baseline, 0.5 MAC and 1.0 MAC.

There were no statistically significant differences in SA between baseline, 0.5 and 1MAC in all groups. The quoted value of SA in literature is 0.93 (+/-0.06). The values of SA obtained in our study were lower (mean values ranging from 0.59 to 0.68 in different groups). The reason for these observed lower values of SA, even in baseline measurements could not be explained.

The data was also analysed for differences in autoregulatory parameters between tumour side and non-tumour side. The THRR was significantly higher on the normal side, as compared to tumour side in the desflurane group at baseline (mean THRR 1.32(0.26) v/s

1.16(0.18), P-0.034), but there was no difference at 0.5 MAC and 1.0MAC. There was no difference in THRR in the sevoflurane group between tumour side and normal side. Strength of autoregulation was not significantly different between tumour side and normal side in desflurane and sevoflurane groups.

Since there were differences between THRR values within the group, the data was analysed for differences between the desflurane and sevoflurane groups. The differences in THRR and SA were not statistically significant between desflurane group and sevoflurane group when compared directly, implying that the pattern of change (increase or decrease) and degree of change in parameters were similar in both groups.

Thus, this study showed that there were no significant differences between sevoflurane and desflurane in cerebral autoregulation, assessed using THRR and SA at 0.5 MAC and 1.0 MAC at normocapnia, in patients with supratentorial tumours without features of raised ICP. The tendency towards a marginally significant decrease (P-0.049) in THRR on the normal side of desflurane group from baseline to 1MAC points to the potential of desflurane to cause cerebral vasodilation at higher concentrations. However the effects of desflurane >1 MAC was not assessed in this study.

The finding that sevoflurane maintains autoregulation is similar to findings of previous studies and some studies have reported that sevoflurane maintains autoregulation even up to 1.5 MAC[197,198]. But the studies on autoregulation with desflurane have reported varying results.

Strebel and colleagues[195] showed that desflurane, at concentrations greater than 0.5 MAC with 70% N2O, produced a dose-dependent impairment in both static and dynamic cerebral autoregulation. However, nitrous oxide itself can have profound effects on

cerebral autoregulation, therefore, the results of the study by Strebel and colleagues could have been confounded by the presence of nitrous oxide.

Bedforth et al.[196] studied the effects of desflurane, at 1 and 1.5 MAC, on cerebral autoregulation using THRR and SA in non-neurological patients. Desflurane resulted in marked and significant impairment in cerebral autoregulation at concentrations 1MAC and above; at concentrations of 1.5 MAC, autoregulation was almost abolished. The difference between results of our study and the study by Bedforth and colleagues could be due to the difference in the study subjects - we included patients with supratentorial tumours whereas Bedforth et al included non – neurosurgical patients. Whereas there was a trend towards derangement of autoregulation in the desflurane group of our study, the degree of decrease in autoregulation was not as marked in the study by Bedforth and colleagues.

Tibble et al[206] demonstrated impaired autoregulation at 0.5 and 1.5 MAC desflurane, but N2O was used in this study, and the study was powered to compare THRR and SA, not to assess autoregulation with desflurane.

Autoregulatory assessment was carried out with Transient hyperaemic response induced by carotid compression. THR ratio is widely used in evaluation of anaesthetic agents and their effect on cerebral autoregulation, because of simplicity, reproducibility and lack of major complications [209]. This has been validated against standard dynamic autoregulatory assessment technique like 'Thigh cuff method' and static autoregulatory assessment technique using Phenylephrine infusion[206,207]. These indices also correlate with CO2 induced vasodilatory changes[210].

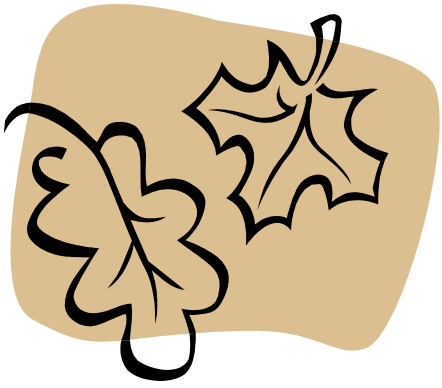
LIMITATIONS

This study was carried out in patients with neurological disease like supratentorial tumours, but without clinical features of raised ICP. Hence the results of our study cannot be extrapolated to the patients with raised ICP. Similarly, this study was limited to clinically used concentrations of 0.5 and 1.0 MAC of desflurane and sevoflurane. The vasodilatory effects of desflurane are more marked at concentrations more than 1 MAC, with derangement of autoregulation reported at 1.5 MAC. It will not be ethically possible to test high concentration of inhalational agents (>1.0 MAC) in patients with raised ICP.

The cerebrovascular haemodynamic effects of the induction agent used could interfere with the effects of volatile agents. Adequate time was allowed for effects of propofol to wane, and after starting volatile agents a further equilibration time of 15 minutes was allowed for FA/FI to stabilise.Desflurane is reported to have some effects on CSF formation and reabsorption, the most important being the increase in resistance to reabsorption which could lead to an increase in ICP. This aspect was not studied; it was thought that the time from introduction of desflurane to opening of dura was too short to have a significant impact on ICP due to impairment of CSF reabsorption.

Errors in TCD estimation of flow velocities is a concern, especially when accurate measurements of flow velocities are required for calculating autoregulatory indices. The changes in diameter of MCA was minimised by keeping the ETCO2 within 2 mmHg from pre induction values and keeping MAP within 10% of normal limits. We did not use a stabilising device for the TCD probe to fix it at the same recording site and minimise changes in angle of insonation and to insonate the same segment of MCA for all measurements. However, we used the angle correction method to minimise these errors.

Conclusion



CONCLUSION

In our study we compared the effects of desflurane and sevoflurane on the cerebral blood flow and autoregulation using TCD measurements of mean MCA blood flow velocities, transient hyperaemic response test and strength of autoregulation. On direct comparison of both agents, there were no significant differences between desflurane and sevoflurane groups in maintaining dynamic indices of autoregulation at 0.5 MAC and 1 MAC at normocapnia, when MAP is maintained within 10% of baseline values.

The findings suggest that desflurane causes cerebral vasodilation at higher concentrations, but at 1 MAC the changes are not significantly different from that of sevoflurane. This study was carried out at normocapnia in order to maintain the ETCO2 values within narrow limits for maintaining the MCA diameter constant. In clinical practice, mild hypocapnia is routinely used in neuroanaesthesia procedures. This adds another layer of safety to safe use of volatiles and the Vmca and CBF would be lower than the observations in this study in actual clinical practice.

Other properties of desflurane and sevoflurane should also be considered while choosing a volatile agent for neuroanaesthesia. Desflurane provides faster emergence and recovery than sevoflurane. Desflurane can be used at very low flows without danger of carbon monoxide formation, whereas sevoflurane needs to be used with higher flow rates, if used for long durations, thus driving up the cost.

Overall, our study shows that desflurane and sevoflurane have comparable effects on cerebral haemodynamics up to 1 MAC. Both the agents can be safely used in neurosurgical patients with supratentorial tumours without features of raised ICP.

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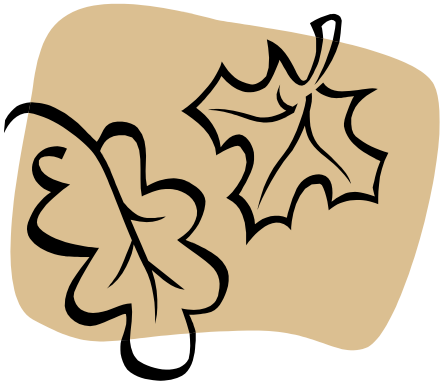

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The comparative effects of 0.5 MAC and 1.0 MAC concentrations of Sevoflurane and Desflurane on middle cerebral artery flow parameters in patients undergoing surgery for supratentorial masses using Trans Cranial Doppler

PROFORMA : **serial number :** **/ 40**

Group Sevoflurane/ Desflurane

Name : Diagnosis :

Age : Proposed surgery :

Sex: Date of surgery :

I.P number : Wt :

Check list :

Fators	**Include**	**Exclude**	**Factors**	**Include**	**Exclude**
Patient consent	Yes	No	H/O malignant hyperthermia	No	Yes
ASA	I & II	III & IV			
Age	19-50	< 18, >50	Included in any other study in preceeding one month.	No	Yes
GCS	15	<15			
Tumor location	Supra tentorial	Infra tentorial			
Nature of procedure	Elective	Emergency			
			TCCDI – Bone window	Normal	Abnormal
H/O CAD, LV dysfunction	No	Yes			
Systemic HT stage III & above	No	Yes			
Heart block	No	Yes			
Pregnancy , Nursing	No	Yes			
			TCCDI – localisation of MCA	Possible	difficult

Intraoperative Hemodynamic parameters :

		Entropy	HR	SpO2	BP sys/Dia MAP	RR	ETCO2
Before induction							
After steady state with volatile	0.5 MAC						
	1.0 MAC						

	BASELINE					COMPRESSION					RELEASE				
	V Max (F1)	V Min	V Mean mFV	PI	RI	V Max F2	V Min	V Mean	PI	RI	V Max F3	V Min	V Mean	PI	RI
Pre induction Rt															
Pre induction Lt															
0.5 MAC RT															
0.5 MAC LT															
1.0 MAC RT															
1.0 MAC LT															

Mephentermine – yes/no Dose:-- Complications if any:-----

MASTER CHART-DESFLURANE GROUP

HAEMODYNAMIC PARAMETERS

Pt No.	Age	Sex	Wt	Side	B HR	.5 HR	1 HR	B MAP	.5 MAP	1 MAP	B CO2	.5 CO2	1 CO2
1	45	M	68	Lt	**71**	**69**	**70**	93	95	98	**35**	**35**	**35**
2	42	M	65	Rt	**86**	**84**	**88**	113.33	110	109	**36**	**35**	**36**
3	48	F	58	Rt	**78**	**79**	**82**	108.66	100	103	**34**	**33**	**34**
4	48	M	90	Lt	**86**	**80**	**83**	114	111	109	**32**	**31**	**31**
5	58	F	60	Rt	**72**	**77**	**75**	84.66	85	88	**34**	**32**	**33**
6	22	M	56	Rt	**78**	**82**	**84**	86.66	84	85	**35**	**33**	**34**
7	43	F	72	Rt	**90**	**82**	**88**	89.33	82	85.33	**36**	**35**	**35**
8	50	M	65	Rt	**68**	**74**	**73**	99.33	95	93	**34**	**33**	**34**
9	25	M	55	Rt	**88**	**82**	**80**	90	88	86	**34**	**33**	**32**
10	29	F	52	Lt	**100**	**98**	**97**	88.66	92	86	**34**	**34**	**32**
11	29	M	75	Lt	**86**	**84**	**82**	106.66	102.66	101	**38**	**36**	**36**
12	51	M	79	Rt	**84**	**80**	**76**	106.66	105	107	**36**	**35**	**33**
13	62	F	65	Lt	**90**	**88**	**92**	120.66	118	115	**34**	**33**	**33**
14	20	M	56	Lt	**82**	**76**	**78**	83.33	77.33	79.33	**40**	**38**	**36**
15	42	F	68	Rt	**86**	**80**	**82**	95.33	89	92	**38**	**36**	**36**
16	46	M	66	Lt	**86**	**82**	**80**	106.66	101	105	**36**	**35**	**34**
17	47	F	55	Lt	**88**	**84**	**85**	85.33	78	79	**34**	**33**	**33**
18	55	M	67	Rt	**76**	**80**	**81**	103.66	105	102	**36**	**34**	**35**
19	43	F	50	Lt	**88**	**85**	**83**	110	103	105	**36**	**37**	**34**
20	28	M	60	Lt	**90**	**88**	**87**	88	86	90	**34**	**35**	**36**

Pt No *– PATIENT NUMBER****B****-BASELINE****0.5 – 0.5MAC anaesthetic agent concentration*** ***1.0- 1.0 MAC anaesthetic agent concentration volatile***

HR – *HEART RATE* ***MAP –*** *MEAN BLOOD PRESSURE* ***CO2****- EtCO2*

DESFLURANE TUMOUR SIDE – CEREBRAL AUTOREGULATORY AND HEMODYNAMIC INDICES

Pt No.	B-F1	B-mFV	B-F2	B-F3	B-CR	B-THRR	B-SA	.5F1	.5mFV	.5F2	.5F3	.5CR	.5THRR	.5SA	1F1	1 mFV	1 F2	1 F3	1 CR	1 THRR	1 SA
1	45	25.53	25	50	44.44	1.11	0.62	34.87	22.34	21	33.36	39.77	0.96	0.58	35.62	21.08	22	37.12	38.23	1.04	0.64
2	61.88	37.83	35	73.08	43.44	1.18	0.67	48.2	26.64	28	45.71	41.91	0.95	0.55	73	45	33.32	75	54.35	1.02	0.47
3	100.44	64.78	62	88	38.27	0.88	0.54	72.83	42.14	43	74.07	40.96	1.02	0.60	55.14	31.97	33	77.8	40.15	1.41	0.84
4	60.64	36.58	36	65.61	40.63	1.08	0.64	47.98	28.59	14.74	59.61	69.27	1.24	0.38	43.82	24.43	17.24	52.96	60.65	1.21	0.48
5	84.3	54.37	40.1	99.3	52.43	1.18	0.56	81.4	52.07	41.3	103.7	49.26	1.27	0.65	93.1	61.9	50	107	46.29	1.15	0.62
6	56.2	37.26	35	84.3	37.72	1.5	0.93	49.5	24.77	28.1	83.1	43.23	1.68	0.95	47.7	27.63	23.9	86.9	49.89	1.82	0.91
7	77.74	49.65	42.48	101.83	45.35	1.31	0.72	62.26	34.73	38.18	66.56	38.67	1.07	0.65	74.3	43.34	52.8	78	28.93	1.04	0.74
8	51.1	32.5	24.2	72.3	52.64	1.41	0.67	51.4	34.33	28	67.2	45.52	1.31	0.71	63.4	41.93	34.2	76.5	46.05	1.21	0.65
9	50.22	27.28	30	72.58	40.26	1.44	0.86	48.5	26.13	31.3	49.36	35.46	1.02	0.66	31.86	16.82	19.83	37.12	37.76	1.16	0.72
10	65.7	40.47	28.72	73.44	56.28	1.12	0.49	48.5	29	28.72	38.18	40.78	0.79	0.47	47.64	30.43	26	65.7	45.42	1.38	0.75
11	35.38	20.04	22	38	37.81	1.07	0.67	27.85	16.38	12.37	39.88	55.58	1.43	0.64	64.82	33.87	17.55	69.12	72.92	1.06	0.28
12	106.96	62.2	65	144.31	39.23	1.35	0.82	96.27	56.17	51.01	78.01	47.01	0.81	0.43	58.74	39.95	37.91	64.84	35.46	1.10	0.71
13	81.76	48.15	48	92	41.29	1.13	0.66	71.72	39.60	16.67	116.45	76.766	1.62	0.38	52.8	26.99	28.72	58.82	45.60	1.11	0.60
14	104.77	59.21	42.85	137.84	59.10	1.31	0.54	95.74	56.37	28.99	100.87	69.72	1.05	0.32	89.32	48.81	22.57	84.18	74.73	0.94	0.23
15	84.62	48.5	32.61	87.21	61.46	1.03	0.39	97.53	53.95	48.5	81.18	50.27	0.83	0.41	63.12	30.43	40.76	83.76	35.42	1.32	0.85
16	65	39	37	71.35	43.08	1.09	0.62	53.1	32.28	31	81.78	41.62	1.54	0.89	90.49	54.00	58.15	97.15	35.73	1.07	0.68
17	59.68	33.3	20.11	50.22	66.30	0.84	0.28	47.64	24.12	24.61	74.3	48.34	1.56	0.81	52.8	26.42	31.49	60.54	40.35	1.14	0.68
18	76.4	41.53	32.1	94.36	57.98	1.23	0.52	80.42	47.13	33.75	105.14	58.03	1.31	0.55	69.5	39.43	30.2	88.06	56.54	1.26	0.55
19	69.98	43.61	26.13	64.82	62.66	0.92	0.35	44.18	28.71	28.71	53.64	35.02	1.21	0.79	51.06	31	17.53	57.08	65.66	1.11	0.38
20	119.74	65.1	70.48	130	41.14	1.08	0.64	101.4	59.73	56.74	129.41	44.04	1.28	0.71	96.5	57.5	40	115.3	58.54	1.19	0.49

***Pt No** – PATIENT NUMBER mFV-MCA mean flow velocity F2- MCA systolic velocity during compression F-3- MCA systolic flow velocity at release of compression **CR**-*

*COMPRESSION RATIO**THRR** – TRANSIENT HYPERREMIC RESPONSE RATIO**SA** – STRENGTH OF AUTOREGULATION*

DESFLURANE NORMAL SIDE – CEREBRAL AUTOREGULATORY AND HEMODYNAMIC INDICES

Pt No.	B-F1	B-mFV	B-F2	B-F3	B-CR	B-THRR	B-SA	.5F1	.5mFV	.5F2	.5F3	.5CR	.5THRR	.5SA	1F1	1 mFV	1 F2	1 F3	1 CR	1 THRR	1 SA
1	65.7	36.56	40	84	39.11	1.27	0.77	52.8	33.3	28	66	0.5 CR	0.5 THRR	0.5 SA	50.65	30.10	30	55	40.76	1.08	0.64
2	80.54	53.17	29.54	100	63.32	1.24	0.45	71.83	43.63	40	80	46.96	1.25	0.66	73.5	44.19	40	82	45.57	1.11	0.60
3	74.32	49.44	40.73	123	45.19	1.65	0.90	67.85	42.97	40	76	44.312	1.11	0.62	66.61	37.58	29.29	72	56.02	1.08	0.47
4	58.15	33.27	33	66	43.25	1.13	0.64	38.84	26.83	33.85	42.99	41.04	1.12	0.66	45.49	24.49	22.22	47	51.15	1.03	0.50
5	80.3	54.36	36.9	94.7	54.04	1.17	0.54	84.3	52.16	40.4	105.5	12.84	1.10	0.96	94.5	66.96	36.5	110.3	61.37	1.16	0.45
6	58.8	38.73	28.7	111.3	51.19	1.89	0.92	49.6	29.06	20.1	86.7	52.07	1.25	0.59	40	23.33	25.2	86.5	37	2.16	1.36
7	61.4	37.88	37.32	112.15	39.21	1.82	1.11	61.4	36.74	40.76	86.35	59.47	1.74	0.70	74.3	46.78	44	83.76	40.78	1.12	0.66
8	54.1	33.5	24.2	72.3	55.26	1.33	0.59	46.7	29.1	26	67.4	33.61	1.40	0.93	64.2	42.6	34.2	78.7	46.72	1.22	0.65
9	72.58	45.06	32.16	84.62	55.69	1.16	0.51	64.84	34.44	32.16	67.42	44.32	1.44	0.80	40.88	23.34	24	47.67	41.29	1.16	0.68
10	54.52	34.44	30.44	65.7	44.16	1.20	0.67	38.18	23.26	22	47.64	50.40	1.03	0.51	37.32	22.40	22	40.76	41.05	1.09	0.64
11	49.34	29.28	25	63.6	49.33	1.28	0.65	45.5	26.85	28	49.34	42.37	1.24	0.71	41.6	26.7	24	40.74	42.30	0.97	0.56
12	97.74	52.92	32.36	73.21	66.89	0.74	0.24	91.15	49.82	24.39	110	38.46	1.08	0.66	79.26	43.08	21.88	75.98	72.39	0.95	0.26
13	87.52	49.11	47	97	46.29	1.10	0.59	81.18	45.1	18.39	93.23	73.24	1.20	0.32	88.93	48.79	47.64	127.45	46.42	1.4	0.76
14	91.63	49.69	42.85	123.72	53.23	1.35	0.63	134.24	81.18	62.36	163.77	77.34	1.14	0.26	104.72	60.22	68.78	102.15	34.32	0.97	0.64
15	76.88	47.06	31.3	110.43	59.28	1.43	0.58	62.26	34.73	32.16	74.3	53.54	1.21	0.56	57.1	29.7	18.39	68.2	67.79	1.194	0.38
16	63.86	37.66	36	78	43.62	1.22	0.68	85.24	44.24	47	103.87	48.34	1.19	0.61	80.75	48.27	49.44	74.32	38.77	0.92	0.56
17	39.9	23.26	20.97	62.26	47.44	1.56	0.82	40.76	22.40	14.09	47.64	44.86	1.21	0.67	32	20.66	16	35	50	1.09	0.54
18	53.6	29.33	32.8	68.72	38.80	1.28	0.78	55.48	31.16	27.7	78.8	65.43	1.16	0.40	58.4	38.86	23.1	84	60.44	1.43	0.56
19	49.34	26.41	28.71	68.26	41.81	1.38	0.80	41.6	23.83	21.83	48.48	50.07	1.42	0.70	47.62	25.84	20.11	65.68	57.76	1.37	0.58
20	100.25	54.75	43.7	113.21	56.40	1.12	0.49	95.06	49.07	36.25	140.12	47.52	1.16	0.61	97.4	53.46	38.7	100.35	60.26	1.03	0.40

***Pt No** – PATIENT NUMBER mFV-MCA mean flow velocity F2- MCA systolic velocity during compression F-3- MCA systolic flow velocity at release of compression **CR-** COMPRESSION RATIO**THRR** – TRANSIENT HYPERREMIC RESPONSE RATIO**SA** – STRENGTH OF AUTOREGULATION*

MASTER CHART-SEVOFLURANE GROUP

HAEMODYNAMIC PARAMETERS

Pt No.	Age	Sex	Wt	Side	B HR	.5 HR	1 HR	B MAP	.5 MAP	1 MAP	B CO2	.5 CO2	1 CO2
1	51	M	65	Lt	78	76	77	98.66	96	94	31	32	32
2	33	M	50	Lt	54	52	55	104.66	101	98	30	31	30
3	33	F	40	Rt	80	76	77	92	90	88	31	30	31
4	47	M	70	Lt	88	79	84	96	94	98	35	34	33
5	33	F	62	Rt	86	82	81	86.33	84.33	108	37	36	36
6	23	F	50	Lt	80	76	78	91.33	87	81.33	32	33	34
7	23	F	57	Lt	80	76	77	98	95	87.33	34	32	34
8	41	M	60	Rt	78	78	80	94.66	93	84	34	31	34
9	26	F	74	Lt	76	74	75	94.66	96	93	35	33	35
10	46	F	59	Rt	86	75	79	86.66	88	85	34	33	34
11	24	M	75	Rt	82	78	76	99.33	95	94	36	35	36
12	18	M	45	Lt	78	84	76	93.33	90	88	34	35	34
13	47	F	53	Rt	76	80	80	101.33	97	94	36	34	35
14	31	M	60	Rt	78	86	86	92.66	90	87	34	33	34
15	60	M	73	Rt	82	76	74	95.33	91	91	34	33	34
16	60	F	60	Lt	80	78	76	97.33	94	94	34	35	33
17	35	M	69	Lt	67	64	62	91.66	89	87	34	34	34
18	50	M	50	Lt	86	88	92	89.66	86	88.66	35	33	34
19	64	M	58	Lt	88	82	85	99	94	95	34	34	33
20	64	M	75	Lt	88	84	83	106.66	103	99	36	35	34

Pt No *– PATIENT NUMBER****B****-BASELINE****0.5 – 0.5MAC anaesthetic agent concentration*** ***1.0- 1.0 MAC anaesthetic agent concentration volatile***

HR – *HEART RATE* ***MAP –*** *MEAN BLOOD PRESSURE* ***CO2****- EtCO2*

SEVOFLURANE TUMOUR SIDE – CEREBRAL AUTOREGULATORY AND HEMODYNAMIC INDICES

Pt No.	B-F1	B-mFV	B-F2	B-F3	B-CR	B-THRR	B-SA	.5F1	.5mFV	.5F2	.5F3	.5CR	.5THRR	.5SA	1F1	1 mFV	1 F2	1 F3	1 CR	1 THRR	1 SA
1	185.29	106.99	104.29	221.75	43.71	1.19	0.67	152.51	84.41	86	168	43.61	1.10	0.62	45.49	25.55	22	52	51.63	1.14	0.55
2	59.6	34.90	33	72	44.63	1.20	0.66	48.49	25.67	27	56	44.31	1.15	0.64	38	22	22	42	42.10	1.10	0.63
3	100.25	61.70	60	120	40.14	1.19	0.71	70.41	41.81	38	77.87	46.03	1.10	0.59	92.79	50.51	52	96.92	43.95	1.04	0.58
4	58.14	33.26	32	72	44.96	1.23	0.68	55.47	37.21	30	58.89	45.91	1.06	0.57	64.88	35.50	38	83.27	41.43	1.28	0.75
5	86.13	51.37	49	104	43.10	1.20	0.68	88.25	57.25	53.3	115.25	39.60	1.30	0.78	66.72	37.60	35.95	80.99	46.11	1.21	0.65
6	80.30	47.05	46	108.67	42.71	1.35	0.77	61.38	35.01	35	80.3	42.97	1.30	0.74	53.64	30.14	30	61	44.07	1.13	0.63
7	93.23	63.41	50	112.15	46.36	1.20	0.64	57.96	38.46	32	61.4	44.78	1.05	0.58	60.54	39.9	41.62	66.56	31.25	1.09	0.75
8	57.41	36.87	30	68	47.74	1.18	0.61	42.1	24.12	25	58.35	40.61	1.38	0.82	40.85	24.81	24	43.55	41.24	1.06	0.62
9	63.55	37.40	35	75	44.92	1.18	0.64	67.91	37.30	40.31	69	40.64	1.01	0.60	51.93	25.78	27	70.87	48.06	1.36	0.70
10	60.54	34.73	29.58	73.44	51.13	1.21	0.59	68.37	40.84	38	74.39	44.42	1.08	0.60	67.51	38.26	39	70	42.23	1.03	0.59
11	57.96	35.02	33	69	43.06	1.19	0.67	51.08	31.58	27	64.84	47.14	1.26	0.67	50.22	30.14	20.11	53	59.95	1.05	0.42
12	67.4	38.46	35.58	87.52	47.21	1.29	0.68	43.32	26.7	25	55.44	42.28	1.27	0.73	64.82	35.01	29.57	72.56	54.38	1.11	0.51
13	55.41	33.88	24.32	73.51	56.10	1.32	0.58	54.12	32.86	22.41	71.42	58.59	1.31	0.54	52.78	33.29	30	65.68	43.16	1.24	0.70
14	45.04	28.99	17.53	86.32	61.07	1.91	0.74	57.08	32.39	20.11	60.52	64.76	1.06	0.37	56.24	29.60	22	68.9	60.88	1.22	0.47
15	62.26	35.42	35	69.14	43.78	1.11	0.62	107.03	59.11	40.28	120	62.36	1.12	0.42	116.02	69.80	55.69	148.11	51.99	1.27	0.61
16	95.18	51.76	49.27	108.32	48.29	1.13	0.58	86.49	45.41	40.28	101.9	53.42	1.17	0.54	68.52	38.17	33.87	74	50.56	1.07	0.53
17	52.8	33.3	28	49.36	46.96	0.93	0.49	38.18	21.54	22	42	42.37	1.10	0.63	39.9	26.13	20	45	49.87	1.12	0.56
18	75.2	45.33	45.1	116.41	40.02	1.54	0.92	57.94	38.45	30.2	88.9	47.87	1.53	0.79	57.88	37.09	32.4	78.5	44.02	1.35	0.75
19	111.01	65.65	66	160	40.54	1.4	0.85	68.3	41.96	33.1	88.2	51.53	1.29	0.62	70	41.93	40.2	102	42.57	1.45	0.83
20	113.45	74.94	68	126	40.06	1.11	0.66	63.39	35.15	27.45	107.03	56.69	1.68	0.73	68.87	43.19	23.94	81.71	65.23	1.18	0.41

***Pt No** – PATIENT NUMBER mFV-MCA mean flow velocity F2- MCA systolic velocity during compression F-3- MCA systolic flow velocity at release of compression **CR-** COMPRESSION RATIO**THRR –** TRANSIENT HYPERREMIC RESPONSE RATIO**SA –** STRENGTH OF AUTOREGULATION*

SEVOFLURANE NORMAL SIDE – CEREBRAL AUTOREGULATORY AND HEMODYNAMIC INDICES

Pt No.	B-F1	B-mFV	B-F2	B-F3	B-CR	B-THRR	B-SA	.5F1	.5mFV	.5F2	.5F3	.5CR	.5THRR	.5SA	1F1	1 mFV	1 F2	1 F3	1 CR	1 THRR	1 SA
1	53.62	29.99	31	65	42.18	1.21	0.70	76.69	46.09	42.34	90	44.79	1.17	0.64	35.52	20.50	20	42	43.69	1.18	0.66
2	43.36	23.28	23	53	46.95	1.22	0.64	42.29	22.22	24	50	43.24	1.18	0.67	36	20.66	21	44	41.66	1.22	0.71
3	76.6	50.08	40	90	47.78	1.17	0.61	74.27	54.09	40.56	92	45.38	1.23	0.67	66.77	36.88	40	76	40.09	1.13	0.68
4	65.68	39.31	36.42	78	44.54	1.18	0.65	65.35	36.80	36	75	44.91	1.14	0.63	53.33	33.94	32	60.17	39.99	1.12	0.67
5	81.28	47.31	43.22	100	46.82	1.23	0.65	71.58	43.86	34.5	101.32	51.80	1.41	0.68	60.66	32.56	32.76	80.99	45.99	1.33	0.72
6	78.18	46.92	44.09	86.7	43.60	1.10	0.62	64.82	35.01	38	83.74	41.37	1.29	0.75	49.34	29.85	28	66.54	43.25	1.34	0.76
7	87.21	58.40	51	112.15	41.52	1.28	0.75	84.62	51.94	50	100	40.91	1.18	0.69	56.24	35.02	32.16	62.26	42.81	1.10	0.63
8	64.93	37.87	39	78	39.93	1.20	0.72	42.1	26.12	24	57.5	42.99	1.36	0.77	39.25	22.49	21.06	43.53	46.34	1.10	0.59
9	92.79	59.21	55	108	40.72	1.16	0.68	78.08	38.37	24.33	104.23	68.83	1.33	0.41	78.08	40.30	43.22	90	44.64	1.15	0.63
10	60.54	33.01	33.96	79.55	43.90	1.31	0.73	49.44	29.37	28	59.77	43.36	1.20	0.68	41.7	23.35	21.49	51.65	48.46	1.23	0.63
11	51.08	28.14	32.16	74.3	37.03	1.45	0.91	57.1	35.30	31.3	85.49	45.18	1.49	0.82	43.34	25.56	23	51.1	46.93	1.17	0.62
12	55.36	32.02	26.81	83.42	51.57	1.50	0.72	97.5	61.36	52.9	106.09	45.74	1.08	0.59	82.88	47.91	44.18	112.97	46.69	1.36	0.72
13	56.81	33.75	22.41	71.42	60.55	1.25	0.49	59.66	36.73	27.85	67.46	53.31	1.13	0.52	73.42	40.74	43.32	86	40.99	1.17	0.69
14	74.28	45.62	40.74	105.26	45.15	1.41	0.77	45.42	25.50	14.32	56.71	68.47	1.24	0.39	41.31	22.49	15.64	52	62.13	1.25	0.47
15	70	40.18	26.13	82.9	62.67	1.18	0.44	103.18	59.54	51.84	141.69	49.75	1.37	0.68	92.91	55.25	35.15	110.88	62.16	1.19	0.45
16	95.48	51.84	60.8	101.9	36.32	1.06	0.67	82.64	43.28	40	99.33	51.59	1.20	0.58	62.11	28.73	35	76	43.64	1.22	0.68
17	48.5	31.29	27	67.42	44.32	1.39	0.77	39.04	24.12	20.97	48.56	46.28	1.24	0.66	39.9	26.13	23	45	42.35	1.12	0.65
18	94.9	55.35	48.5	116.41	48.89	1.22	0.62	57.8	34.93	32.1	72	44.46	1.24	0.69	63.96	39.65	32.4	78.5	49.34	1.2	0.62
19	108.32	66.38	64	151.96	40.91	1.40	0.82	65.79	35.39	27.9	76.11	57.59	1.15	0.49	70.1	42.56	41.7	87.3	40.51	1.24	0.74
20	76.62	48.12	40	95.8	47.79	1.25	0.65	64.67	38.14	36	82.64	44.33	1.27	0.71	49.4	32.29	21.6	60	56.28	1.21	0.53

***Pt No** – PATIENT NUMBER mFV-MCA mean flow velocity F2- MCA systolic velocity during compression F-3- MCA systolic flow velocity at release of compression **CR**-COMPRESSION RATIO**THRR** – TRANSIENT HYPERREMIC RESPONSE RATIO**SA** – STRENGTH OF AUTOREGULATION*