"SEVOFLURANE REQUIREMENT TO MAINTAIN BIS GUIDED STEADY STATE LEVEL OF ANAESTHESIA DURING THE REWARMING PHASE OF CARDIOPULMONARY BYPASS WITH MODERATE HYPOTHERMIA"

PROJECT

BY

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CERTIFICATE

This is to certify that this project entitled "**Sevoflurane requirement to maintain BIS guided steady state level of anaesthesia during the rewarming phase of cardiopulmonary bypass with moderate hypothermia**", has been prepared by Dr Divya Amol Chandran-Mahaldar, a DM Cardiothoracic & Vascular Anaesthesia Resident, under the guidance of Dr Shrinivas Gadhinglajkar, Professor, Dept. of Anaesthesiology and under my overall supervision and guidance at Sree Chitra Tirunal Institute for Medical Sciences & Technology, Trivandrum. She has shown keen interest in preparing this project.

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Date: 27/9/2011

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CERTIFICATE

This is to certify that this project entitled "**Sevoflurane requirement to maintain BIS guided steady state level of anaesthesia during the rewarming phase of cardiopulmonary bypass with moderate hypothermia**", is a bonafide work of Dr Divya Amol Chandran-Mahaldar, a DM Cardiothoracic & Vascular Anaesthesia Resident and has been done under my direct guidance and supervision at Sree Chitra Tirunal Institute for Medical Sciences & Technology, Trivandrum. She has shown keen interest in preparing this project.

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DECLARATION

I hereby declare that this project entitled "**Sevoflurane requirement to maintain BIS guided steady state level of anaesthesia during the rewarming phase of cardiopulmonary bypass with moderate hypothermia**", has been prepared by me under the able guidance of Dr Shrinivas Gadhinglajkar, MD Professor, Dept. of Anaesthesiology, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Trivandrum.

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I would be failing in my duty, if I don't thank my patients, without whose consent, this study would have been incomplete.

Date: SCTIMST, TVM
Place: 29.09.2011

Dr Divya Amol Chandran-Mahaldar

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Introduction

INTRODUCTION

Anaesthesia during cardiopulmonary bypass (CPB) is unique in terms of potential for patient awareness. The fact that CPB alters pharmacokinetics and pharmacodynamics of drugs and that virtually all physiological processes of drug absorption, distribution, metabolism, and elimination are affected by unphysiological conditions associated with CPB, including haemodilution, hypotension, hypothermia, and nonpulsatile blood flow, may lead to administration of inappropriately high or low doses of hypnotics and anaesthetics. The oxygenator and tubing may bind large amounts of drugs used in cardiac anaesthesia. Hypothermia and hypothermic CPB especially are associated with a decreased level of consciousness and decreased metabolic rate.

During rewarming phase of CPB, there may be a change in the requirement of anesthetic gases due to altered cerebral metabolic rate and changes in the gas characteristics. It is, therefore, hypothesized that the high-risk periods occur when the patient is rewarmed.

Previous study involving isoflurane concentration monitoring on CPB suggests that the requirement for isoflurane increases during rewarming phase of CPB However; similar studies on sevoflurane are lacking.

We hypothesized that sevoflurane requirement increases during rewarming phase of CPB. We also postulate that sevoflurane provides stable hemodynamic condition during rewarming phase.

During CPB, inhalation anesthetic concentrations can be difficult to quantify in the absence of pulmonary respiration and ventilation. There are currently little data on sevoflurane requirements during hypothermia and cardiopulmonary bypass. Awareness during cardiopulmonary bypass is a major concern and has been cited as an indication for bispectral index (BIS) monitoring of anesthetic depth.

The goal of study would be to assess the extent to which the sevoflurane requirement increases during rewarming phase of CPB. We contemplate the study as limited data is available in the literature on the titration of the dose of inhalational agents during rewarming phase of CPB.

We aimed to assess if there was any increase and the extent of increase in sevoflurane requirements for maintaining hypnosis during hypothermic CPB, with BIS maintained between 40 and 50.

The sevoflurane requirement was quantified by measuring sevoflurane concentrations in the oxygenator expiratory gas. Expiratory gas from the CPB machine oxygenator, having equilibrated with the patient's blood in the oxygenator, could reflect the blood sevoflurane concentrations. This is analogous to measuring end-tidal anesthetic concentrations during general anesthesia. These results could help dosing of sevoflurane during the rewarming phase of hypothermic cardiopulmonary bypass.

Aims & Objectives

AIMS AND OBJECTIVES

1. The purpose of this study was to measure the changes in sevoflurane requirements during the rewarming phase of cardiopulmonary bypass with moderate hypothermia.

2. The influence of sevoflurane on systemic vascular resistance (SVR) when administered during cardiopulmonary bypass (CPB).

3. Predictability and reliability of BIS as a monitor for depth of anesthesia during the conduct of hypothermic CPB based on postoperative patient interview.

4. Utility of end-tidal gas monitoring as an adjunct hypnotic monitor to titrate the anesthetic gas requirement to maintain a constant BIS.

5. Whether, the percentage (%) increase in the requirement for sevoflurane is uniform, and whether it follows a particular pattern which may be predicted.

6. Whether administration of sevoflurane should be discontinued at the time of weaning patient from CPB.

Review of Literature

REVIEW OF LITERATURE

2.1a Cardioprotection with Volatile Anesthetics in Cardiac Surgery

Myocardial ischemia in the perioperative period is a major cause of morbidity and mortality after surgery. Prevention of ischemia has traditionally focused on maintaining the balance between myocardial oxygen supply and demand, using β-adrenergic antagonists, α_2-agonists and/or calcium-channel blockers. New evidence suggests that volatile anesthetics at clinical concentrations may also be useful in protection against perioperative myocardial ischemia, by a mechanism that is independent of effects on myocardial oxygen balance.[1]

It has long been known that all volatile anesthetics decrease myocardial loading conditions and contractility. The new volatile anesthetics, such as desflurane and sevoflurane, demonstrate a similar dose-dependent depression of myocardial function.[2] These depressant effects decrease myocardial oxygen demand and may therefore have a beneficial effect on myocardial oxygen balance during myocardial ischemia. The mechanisms of anesthetic-induced cardioprotection have been the subject of recent reviews.

Ischemic preconditioning represents an adaptive endogenous response to brief sublethal episodes of ischemia, which results in protection against subsequent lethal ischemia. Interestingly, ischemic and anesthetic preconditioning share many common intracellular signaling pathways (Figure 1). These include opening of mitochondrial K_{ATP} channels, increasing mitochondrial reactive oxygen species, activation or translocation of protein kinase C, tyrosine kinases and p38 mitogen-activated protein kinase.[3]. These mechanisms decrease cytosolic and mitochondrial calcium loading.[4] Volatile anesthetics may also protect coronary endothelial cells by mediating nitric oxide release.[5]

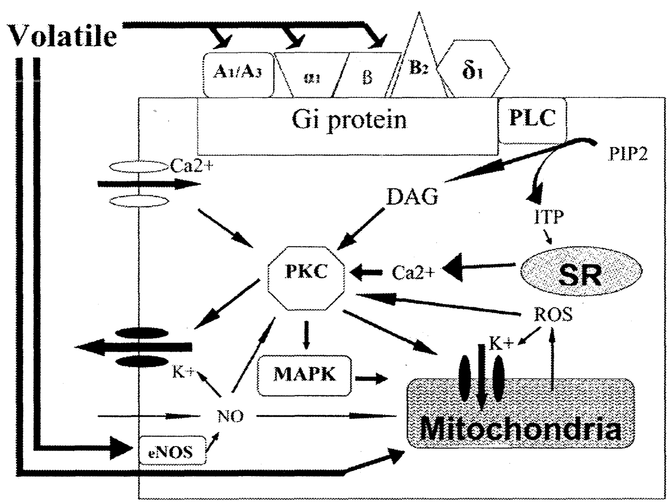


Figure 1. Cellular mechanism of volatile anesthetic preconditioning; volatile anesthetics enhance opening of ATP-sensitive K^+ channels (K_{ATP} channels) by activation of phospholipase C (PLC) via adenosine A_1 and A_3 (A_1/A_3) and adrenergic receptor stimulation, and by nitric oxide synthase (NOS) activation. = B_2 bradykinin$_2$ receptors, Gi protein = inhibitory guanine nucleotide-binding proteins, DAG = diacylglycerol, ITP = inositol 1,4,5-triphosphate, MAPK =

mitogen-activated protein kinases, NO = nitric oxide, PIP_2 = phosphatidyl inositol biphosphate, PKC = protein kinase C, ROS = reactive oxygen species, SR = sarcoplasmic reticulum, α_1 = α_1-adrenergic receptor, β= β-adrenergic receptor, δ_1 = δ_1-opioid receptor

Although ischemic myocardium can only be salvaged by reperfusion, reperfusion itself can lead to additional cellular damage that further augments injury. Volatile anesthetics applied during myocardial ischemia appear to suppress neutrophil activation, neutrophil-endothelial interactions and inflammatory responses that cause myocardial dysfunction.[6] In addition, postischemic administration of volatile anesthetics can also initiate cardioprotection, as evidenced from improved post-ischemic endothelial function, reduced infarct size and less apoptosis.[7] These protective effects against lethal reperfusion injury are recently named anesthetic post-conditioning

There is a large amount of experimental evidence that volatile anesthetics exert beneficial effects on the consequences of myocardial ischemia-reperfusion injury. Research has been focused on the possible implementation of this property in patient care.[8-11]

The implementation of these properties during clinical anaesthesia can provide an additional tool in the treatment or prevention, or both, of ischemic cardiac dysfunction in the perioperative period.

2.1b ***Protective effects of sevoflurane on cardiopulmonary bypass***

Sevoflurane attenuates the pulmonary sequestration of neutrophil and leukocytes and also preserves the pulmonary consumption of cytokines at the time of early pulmonary reperfusion[6]. Sevoflurane before or after ischaemia improves contractile and metabolic function while reducing myoplasmic Ca^{2+} loading in intact hearts[4]. Also it has suppressive effects on cytokine release in human peripheral blood mononuclear cells.[13] Sevoflurane applied during myocardial ischemia appear to suppress the inflammatory responses that cause myocardial dysfunction.[12-15] Sevoflurane thus attenuates the systemic inflammatory response induced by cardiopulmonary bypass.[16]

Several studies have indicated that sevoflurane has a cytoprotective effect in various organs during cardiac surgery, and the effect is associated with the suppression of inflammatory cytokines.[17,18]

2.1c ***Volatile anesthetics and improved outcomes after cardiac surgery***

A recent meta-analysis showed that desflurane and sevoflurane reduce postoperative mortality and the incidence of myocardial infarction (MI) after cardiac surgery with significant advantages in terms of postoperative cardiac troponin (cTn) release, need for inotropic support, time on mechanical ventilation, intensive care unit (ICU) stay, overall hospital stay, and survival.[19,20]

Jakobsen et al,[21] in a retrospective, nonrandomized study including more than 10,000 cardiac surgical patients, confirmed that patients without preoperative unstable angina or recent myocardial infarction have lower postoperative mortality after sevoflurane anesthesia than after total intravenous anesthesia (TIVA).

Bignami et al conducted a survey among 64 Italian cardiac surgical centers and showed that 30-day risk-adjusted mortality was significantly reduced when volatile agents were used during cardiac surgery, *especially when there was prolonged use of these agents*.[22] In particular, the risk-adjusted mortality ratio was lowest in those centers that used volatile anesthetics for the majority of their cardiac surgical interventions and highest in those that only used intravenous anesthetics. [23]

2.1d Volatile anesthetics for fast tracking in cardiac anesthesia

Fast-tracking was first introduced in an attempt to decrease the time to tracheal extubation and reduce expensive time in intensive care unit areas. Fast track cardiac anesthesia (FTCA) is a key component to successful conduction of fast-track cardiac surgery. An effective FTCA program requires the appropriate selection of suitable patients, a low-dose opioid anesthetic technique, early tracheal extubation, a short stay in the ICU, and coordinated perioperative care. High dose opioid anesthesia has been replaced by balanced anesthesia technique utilising short acting agents to facilitate shorter times to recovery and extubation[24,25].

Maintenance of anesthesia with the newer inhaled anesthetics (ie, desflurane and sevoflurane) provide for a rapid early recovery as compared with infusion of propofol (ie, TIVA), while allowing easy titratability of anesthetic depth.[26]

Intraoperative awareness is a feared complication in fast tracking due to the use of short acting hypnotics and anesthetics. Using a fast-track technique, Dowd et al[27] reported a low incidence of intraoperative awareness (0.3%) in their prospective investigation, and attributed this low rate to the continuous administration of volatile anesthetics. In addition to providing rapid recovery of ventilatory function, the inhaled anesthetics are useful in producing unconsciousness, muscle relaxation, and suppression of responses to noxious stimulation. By virtue of their anmestic properties, inhalation anesthetic techniques are likely to markedly decrease the incidence of awareness.[28]

Sevoflurane has gained popularity in cardiac surgery because of its rapid elimination thus allowing fast tracking anesthesia. Titration of sevoflurane dosing during CPB is important to avoid awareness and provide hemodynamic stability.[29]

2.2 Awareness in cardiac surgical patients

During cardiac surgery, haemodynamic signs are less reliable guides to anaesthetic depth, as most patients are heavily treated with b-adrenergic blocking drugs and antihypertensive medication. Determining anaesthetic depth during cardiopulmonary bypass with variable degrees of cooling presents an even more complex situation, as even ordinary clinical signs are not available.

Intraoperative awareness (ie, recall), usually defined as explicit recall of intraoperative events, is an infrequent but well recognized adverse outcome after surgery under general anesthesia. Because awareness often is associated with long-term psychologic sequelae, including anxiety[30] and posttraumatic stress disorder,[31-33] it is of significant concern to patients and anesthesiologists alike.

The incidence of intraoperative awareness during general surgery reported in the literature varies between 0.1% and 0.9%.[34] In contrast, the published incidence of awareness in patients undergoing cardiac surgery is significantly higher with older reports of up to 23%.[35,36] Phillips et al. found that over 1% of cardiac surgical patients recalled intra-operative events.[36]

Cardiac surgery represents a sub-group of patients at significantly increased risk of intraoperative awareness. Traditionally, patients undergoing cardiac surgery have always been considered to be at an increased risk for intraoperative awareness because of anesthetic regimens that are intentionally devoid of cardiodepressant inhalation anesthetics and conventional anesthetic agents other than high-dose opioids. Additionally, periods of light anesthesia in the presence of hemodynamic instability, a not infrequent event during cardiac surgery, increase the risk of intraoperative recall.

Cardiopulmonary bypass (CPB) alters the pharmacokinetics and pharmacodynamics of drugs. Virtually all the physiologic processes involved in drug absorption, distribution, metabolism, and elimination are affected because of abnormal physiologic conditions, including hemodilution, hypotension, hypothermia, and nonpulsatile blood flow. [28]

In addition, the oxygenator and tubing may bind large amounts of some drugs.Also, the almost unpredictable pharmacodynamics of anaesthetics under the extracorporeal circulation especially in the rewarming period and at the time of cessation of bypass, haemodilution, and binding on foreign surface areas.[28]

Because hypothermia is associated with a decreased level of consciousness and decreased metabolic rate,[36] it is possible that the high-risk periods occur when the patient is warm. As the initial warm CPB period is usually short, this period rarely is associated with awareness. However, during rewarming, the brain and body core warm much faster than the body shell. Restoration of brain normothermia with decreased anesthetic concentrations may result in an inadequate depth of anesthesia and the potential for awareness[28].

However, the recognition that inhalation agents are useful in preconditioning the heart before CPB and the introduction of fast-track anesthetic techniques have led to significant changes in anesthetic regimens for cardiac surgery over time. The reported incidence of awareness has decreased continuously in the literature, presumably as a result of some of these changes in anesthetic management. The reported incidence of awareness has decreased continuously in the literature, presumably as a result of some of these changes in anesthetic management. Examining a variety of anesthetic regimes, Ranta et al[37] found an incidence of awareness of 0.5% in patients undergoing cardiac surgery.

2.2b Monitoring Awareness during Cardiac Surgery

The widely used clinical parameters such as pressure, rate, sweating and tears (PRST Score) within the course of anaesthesia, cannot predict episodes of intraoperative awareness.

The EEG can be considered to measure the depth of anaesthesia for several reasons. It represents cortical electrical activity derived from summated excitatory and inhibitory postsynaptic activity, which are controlled and paced by subcortical thalamic nuclei. Cerebral blood flow and cerebral metabolism are related to the degree of EEG activity. Awareness during cardiopulmonary bypass has been cited as an indication for bispectral index (BIS) monitoring of anesthetic depth.[38,39,40]

BIS is a dimensionless index from 100 (awake) to 0 (electrical silence). BIS values between 40 and 60 purportedly indicating adequate general anesthesia for surgery.

The BIS is the weighted sum of three descriptors (Fig. 2):

1. Relative BetaRatio, a frequency-domain feature, is the EEG spectral power log (P30–47 Hz/P11–20 Hz),
2. SynchFastSlow, a bispectral-domain feature, is the bispectral power wave band log (B0.5–47 Hz/B40–47 Hz),
3. Burst Suppression is a time-domain feature that quantifies the extent of isoelectrical silence.

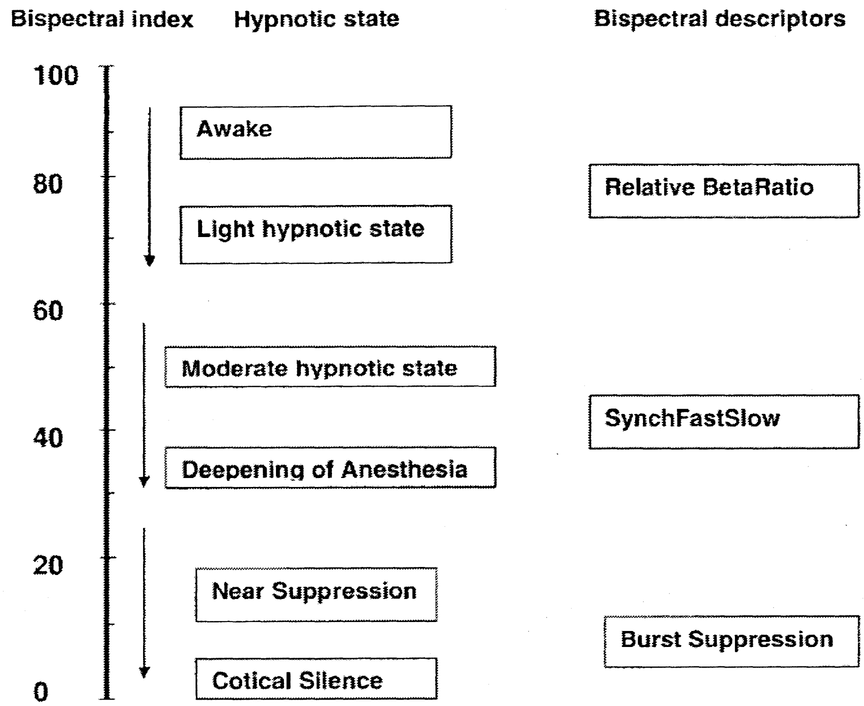


Figure 2. Bispectral Index depth of anesthesia monitoring.

Monitoring the depth of anaesthesia by the bispectral index facilitates the titration of anaesthetic drugs during operation as well as assisting in early recovery. Puri et al have used this index to control the administration of anaesthetic agents in order to stabilize haemodynamics and promote recovery from anaesthesia in patients undergoing cardiac surgery with cardiopulmonary bypass.[41]hypothermia

2.2b.1 *BIS during CPB*

BIS values always do not coincide with the clinically judged sedative-hypnotic state.

This could arise from an underlying pathophysiology of EEG cerebral function or because of shortcomings in the performance and design of the BIS monitor.[42] Although BIS monitoring has been advocated for guiding anesthetic requirements during cardiopulmonary bypass, BIS algorithms are based primarily on normothermic patients. It is unclear if BIS has the same relationship to hypnosis during hypothermic conditions. Literature has contradictory evidence to the above.

Chakravarthy[43] et al assessed the interchangeability of bispectral index during normotension, hypotension and during pulseless state in patients undergoing coronary artery bypass graft surgery.They concluded that the bispectral index and index of consciousness values may be interchangeable. The interchangeability is better appreciated during normotension and hypotension but not during non pulsatile state of cardiopulmonary bypass.

Dewandre [44]et al studied BIS in patients undergoing CABG under mild hypothermic (30'C) CPB. BIS was neither affected by surgical stimulation nor by CPB and mild hypothermia. They concluded that BIS was a reliable monitor to assess the hypnotic effects of anaesthetics during normothermic or mild hypothermic CPB.

2.2b.2 *BIS and hypothermia*

Dahaba noted the following in his review article during hypothermic CPB under constant isoflurane anesthesia, BIS was estimated to decrease by

1.12 BIS units for each degree Celsius decrease in body temperature. Hypothermia produces a linear decrease in inhaled anesthetic requirements.[42]

In fact, hypothermia itself serves as a complete anesthetic at 20°C.This is attributed to the increase in the solubility of inhaled anesthetics in the lipid membrane with lower temperature, resulting in larger concentrations of anesthetics being available at a cellular level, which would result in a BIS decrease.[45]

2.2b.3 *Evaluation of awareness*

A structured interview according to Brice is the most accepted tool for awareness detection, minimizing the risk of pseudo-memory generation, but with a certain diagnostic capacity.[46]

Brice interview has been used by various studies to evaluate standard anesthetic technique regarding awareness. The interviews are performed within the first 24 hours, on day 3 or 4, and on day 6 or 7 after anesthesia. This approach was chosen based on previous findings that approximately one third of the cases of awareness are detected only during a later interview.[32,38]

Occasionally in too lightly anesthetized patients the interview did not become positive The diagnostic power, the timing of the Brice interview, or the number of interviews performed may be questioned.[47] In this context, Nordstrom et al[48] were able to show that patients under propofol anesthesia may respond to commands and display consciousness without having explicit postoperative recall.

However, the optimal method of detecting awareness without postoperative memory is unknown. Additionally, nearly all anesthetic agents produce at least some retrograde amnesia, thus possibly reducing the occurrence of explicit memory.

2.3 a) Volatile anesthesthetics during cardiopulmonary bypass

During cardiac surgery volatile agents are administered to maintain anesthesia and prevent intraoperative awareness. During cardiopulmonary bypass (CPB), volatile anaesthetics can be added to the oxygenator to provide anaesthesia,[49,50] regulate systemic vascular resistance[51,52] and reduce hormonal responses to CPB.[53,54] These agents are continued on CPB in order to prevent inadequate anesthesia and resultant awareness.

But inhalation anesthetic concentrations can be difficult to quantify during CPB in the absence of pulmonary respiration and ventilation. The rate of washin and wash out of volatile anaesthetics via oxygenators depends on their solubility in blood.55.

Two important factors affect the solubility of volatile anaesthetics are hypothermia and crystalloid haemodilution. During CPB, hypothermia will increase anaesthetic blood solubility and haemodilution will reduce it.

Nussmeier and colleagues found that wash in of isoflurane appeared to occur more slowly during CPB than during administration via the lungs in normothermic patients, presumably because hypothermia increases tissue capacity, compensating for the effect of hemodilution that otherwise would decrease the blood/gas partition coefficient.

During rewarming, washout appeared to occur as rapidly as from the lungs of normothermic patients. This may have resulted from the declining blood/gas partition coefficient (due to rewarming) and relatively limited tissue stores of the volatile agent. The relationship between exhaust and arterial partial pressures was reasonably consistent. Hence the authors concluded for clinical purposes, measurement of gas exhausted from the oxygenator can be used to estimate partial pressure in arterial blood.[56]

Uptake and elimination of the volatile agent are dependent on the composition of the oxygenator.

To define the limitations imposed by oxygenators, washin and washout curves for volatile anesthetic agents administered to bubble oxygenators primed with diluted blood (without connection to a patient) were defined. There was rapid equilibration of anesthetic partial pressure between delivered gas and blood (85-90% within 16 minutes). Increasing the gas inflow to the oxygenator from 3 to 12 L/min hastened washin and washout slightly, while increasing the pump blood flow from 3 to 5 L/min had no effect. Rates of washin and washout of anesthetics differed as a function of their blood/gas solubilities: enflurane greater than isoflurane greater than halothane during washin; isoflurane greater than enflurane greater than halothane during washout. However, these differences were small. Oxygenator exhaust partial pressures of anesthetic correlated with simultaneously obtained blood partial pressures, suggesting that monitoring exhaust gas may be useful clinically.[57]

2.3b) *Sevoflurane on* CPB

Rodig et al[58] in their study comparing wash-in of isoflurane versus sevoflurane on CPB in a cold phase with arterial blood and bladder temperatures maintained at 32–33^{0}C found that. *F*E/*F*I increased more rapidly with sevoflurane relative to isoflurane.

The partition coefficient in undiluted normothermic blood is 0.65 for sevoflurane and 1.4 for isoflurane [59]. Similar differences may be assumed during hypothermic CPB because of the counterbalancing effects of haemodilution and hypothermia on blood-gas partition coefficients.

Sevoflurane reached a relatively steady state for both agents from the 10th to the 20th min.

The elimination of sevoflurane, expressed as the relative blood concentration, was significantly increased in polypropylene membrane oxygenators compared to poly-(4-methyl-1-pentene) membrane oxygenators. This resulted in an approximately threefold higher sevoflurane blood concentration in the poly-(4-methyl-1-pentene) group over the course of cardiopulmonary bypass.[60]

2.4 a) Hypothermia and anaesthetic requirements

Hypothermia decreases anaesthetic requirements in a rectilinear fashion, such that a 10^0C decrease from 38^0C results in an approximately 50% decrease in halothane and isoflurane requirements. Antogini [45]et al determined anesthetising temperature as 20^0C. This is attributed to the increase in the solubility of inhaled anesthetics in the lipid membrane with lower temperature, resulting in larger concentrations of anesthetics being available at a cellular level. Although hypothermia can decrease anaesthetic requirements, most work was carried out in animal studies, and few studies have quantified the magnitude of its effect in humans. Sevoflurane solubility increased by 5.4% of the solubility at 37^0C for each degree that equilibration temperature was reduced.[61]

2.4 b) Anaesthesia requirements during rewarming phase of CPB

Hypothermia is associated with a decreased level of consciousness and decreased metabolic rate, it is possible that the high-risk periods for increased anesthetic requirement occur when the patient is warm. During rewarming, the brain and body core warm much faster than the body shell. Restoration of brain normothermia with decreased anesthetic concentrations may result in an inadequate depth of anesthesia and the potential for awareness.[28]

2.5 Effects of sevoflurane on systemic vascular resistance during CPB

Volatile anaesthetics are known to induce hypotension because of effects on the central and autonomic nervous system, on the myocardium and because of a direct action on vascular smooth muscle.

The decrease in arterial pressure caused by sevoflurane may result from depression of myocardial contractility and decreased peripheral vascular resistance.

SVRI can be calculated from MAP, assuming a fixed pump flow rate for a given body surface area. If venous drainage is adequate at all times, central venous pressure can be assumed as zero. The venous reservoir volume does not reflect changes in capacitance vessels when a venous reservoir with an integral cardiotomy reservoir is used.

Rodig and colleagues did not find significant changes in SVRI from baseline over the 20-min period with 1.0 and 2.0 vol % sevoflurane. Vasodilatation capacity was evident by the decrease in SVRI with higher concentrations of sevoflurane.[58] 1.5 MAC of sevoflurane caused arteriolar vasodilatation as evidenced by reduction in SVRI and, thus, perfusion pressure.

Materials & Methods

MATERIALS AND METHODS

Approval was obtained from the institutional ethics committee. All patients were given information brochure regarding the surgery and anesthesia and written informed consent was obtained from the patients before the study.

INCLUSION CRITERIA

Fifty adult patients undergoing elective coronary artery bypass surgery requiring cardiopulmonary bypass were recruited.

EXCLUSION CRITERIA

The Patients with the following conditions were excluded

1. Preexisting neurologic disease
2. Chronic treatment with sedative drugs
3. Alcoholism
4. Left ventricular ejection fraction < 50%
5. Significant renal disease (creatinine > 2 mg/ dl or BUN > 20 mg/ dl)
6. Hepatic disease (SGPT > 150 IU and total bilirubin > 3 mg/ dl)
7. Age over 70 years
8. Patients at risk of malignant hyperthermia.

The techniques of anesthesia, surgery, and cardiopulmonary bypass followed existing institutional practice.

Premedication - The patients had oral diazepam 10 mg the night before and the day of surgery. Antihypertensive medication was continued on the day of surgery except angiotensin-converting enzyme inhibitors and calcium channel blockers. All oral hypoglycemic medications were omitted on the morning of surgery.

Anesthesia was induced with fentanyl 5μg/kg, midazolam 0.05 mg/kg and sleep dose of propofol, and pancuronium 0.2 mg/kg, was used for muscle relaxation. All patients had endotracheal intubation and controlled ventilation to maintain the end-tidal carbon dioxide between 35-45 mmHg. All patients were monitored hemodynamically in accordance with the institution's standard cardiac anesthetic protocol.

Anesthesia was maintained with sevoflurane titrated by BIS. Morphine infusion of 20 μg/kg/h of was used for analgesia. Cardiopulmonary bypass was carried out using a **SARNS** 9000 (Terumo corporation, Tokyo, Japan) cardiopulmonary bypass machine and Affinity Adult (Metronics) oxygenator. During cardiopulmonary bypass, anesthesia was maintained with sevoflurane delivered by a Datex Ohmeda Tec 7 vaporizer, which was connected to the fresh gas flow of the cardiopulmonary bypass machine. Expiratory gas was sampled from the oxygenator's sole expiratory port. Patients' temperatures were regulated using the cardiopulmonary bypass machine and warm/cold water-circulating mattress. Both nasopharyngeal and rectal temperatures were monitored in all patients

BIS monitoring (BIS XP forehead electrode; Aspect Medical Systems Inc, Newtown, MA) was commenced before inducing anesthesia, and this was continued throughout anesthesia and surgery. Sevoflurane concentrations were measured using the agent analyzer of the S/5 anesthesia monitor (GE Healthcare, United Kingdom). During CPB, this agent analyzer was connected using separate gas sampling tubes to the expiratory gas flows of the oxygenator. The connections were gas tight to prevent atmospheric gas contaminating the sampled gases. The cardiopulmonary bypass machine fresh gas flow were adjusted to maintain normal acid-base balance using the pH-stat system, guided by arterial blood gas measurements taken every half hour. The anesthesiologist adjusted the vaporizer settings to maintain a moderate depth of anesthesia, with the BIS index between 40 and 50.

During the rewarming phase, the nasopharyngeal rectal temperature gradient was kept to less than 2^0C to aid complete and gradual rewarming. The sevoflurane concentrations were measured at every degree C interval from 29 to 35^0C when BIS variation was minimal as it was institution protocol to cool upto 29^0C and warm upto 35^0C for all CABG. The Pearson correlation coefficient was used to assess if the expiratory sevoflurane requirement increased as the temperature increased.

Linear regression was used to quantify this association. A paired *t* test was used to compare the expiratory sevoflurane at 29^0C and 35^0C. Fifty patients were recruited based on a previous similar study based on isoflurane[55].

The mean perfusion pressure was maintained between 60 and 80 mmHg during CPB using vasoconstrictors (phenylephrine,noradrenaline) or vasodilators (sodium nitroprusside). Systemic arterial pressures, measured via a radial artery cannula, were monitored continuously throughout the procedure and, at the end of degree increase in temperature period; recordings were made of mean arterial pressure (MAP). Systemic vascular resistance (SVR) was calculated from MAP (mm Hg) and pump flow rate, Q (litre/ min) as:

$$SVR = MAP/Q \times 80 \text{ (dynes.sec.cm}^{-5}\text{)}.$$

We calculated systemic vascular resistance index (SVRI) from MAP, a fixed pump flow rate and body surface area (BSA).

$$SVRI = SVR / BSA$$

As venous drainage was adequate at all times, we assumed that central venous pressure was zero. The venous reservoir volume did not reflect changes in capacitance vessels as we used a venous reservoir with an integral cardiotomy reservoir. Hypotension during CPB requiring intervention was defined as MAP <50 mmHg and hypertension as MAP >90 mmHg. All data are presented as median (range). Differences between changes in SVRI from baseline values

At the end of surgery, all patients were transferred to the cardiothoracic intensive care unit. Analgesia, sedation, weaning of artificial ventilation, and extubation followed normal institutional practice.

Each patient was interviewed by the staff with the same structured, modified Brice Interview (Table 1) 3 times postoperatively. Patients were interviewed within the first 24 hours of surgery, and follow-up interviews were performed on day 3 or 4 as well as on day 6 or 7 after surgery. Awareness was defined by the presence of explicit memory of any event from the induction of anesthesia to the recovery of consciousness in the ICU.

Table 1: Modified Brice Interview

1. What is the last thing you remember before you went to sleep?
2. Were you put to sleep gently?
3. Do you remember anything between going t sleep and waking up?
4. Did you have any dreams while you were asleep for surgery?
5. What is the first thing you remember once you woke up?
6. What is the worst thing about your operation?
7. Do you have any problems going to sleep since your operation?
8. Do you have any problems sleeping through the night since your operation?
9. Do you have any newly appeared nightmares since your operation?

Observations & Results

OBSERVATIONS AND RESULTS

Forty four male and six female patients were included in this study. The sex ratio is skewed with a significantly higher percentage of males.

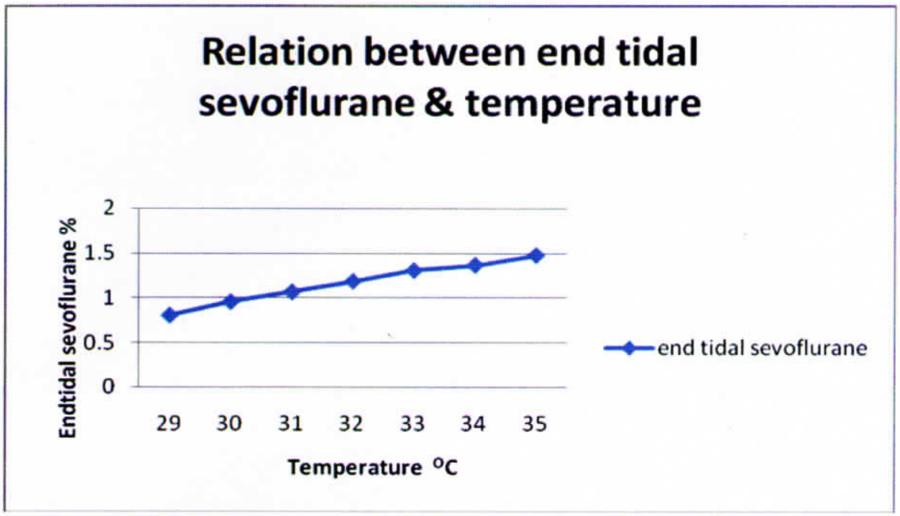
The mean (standard deviation) age in years was 58.5 (7.3) years with a mean body surface area (BSA) of patients in the study group was 1.68 (0.15) m^2.

Table-1 Expiratory Sevoflurane Concentration at Temperatures between 29^0C and 35^0C Maintaining the Bispectral Index between 40-50.

Temperature (^0C)	Expiratory Sevoflurane Mean % (± STDev)	BIS Mean (± STDev)
29	0.81(0.15)	41.9(3.14)
30	0.96(0.15)	42.06(4.06)
31	1.07(0.22)	42.52(3.13)
32	1.19(0.27)	43.44(4.11)
33	1.31(0.29)	44.34(3.85)
34	1.37(0.28)	45.54(4.45)
35	1.48(0.28)	50.10(5.61)

The expiratory sevoflurane concentrations required to maintain the BIS between 40 and 50, over a temperature range from 29°C to 35°C, during the rewarming phase of cardiopulmonary bypass are shown in Table 1.

Figure 1



There was a progressive increase in the sevoflurane requirements as temperature increased. The sevoflurane requirements at 35°C were compared with that at 29°C using a paired t test, and the difference was both clinically substantial (0.45%) and statistically significant ($p < 0.001$).

In relating temperature and sevoflurane requirement, the Pearson correlation coefficient was 0.67 and suggesting a good positive association.

Linear regression using temperature as the independent variable and expiratory sevoflurane as the dependent variable showed a temperature beta coefficient of 0.11 and constant of -2.34.

Hence sevoflurane levels can be predicted with reasonable accuracy by the equation.

End tidal Sevoflurane concentration=0.11x temperature-2.34

Fresh gas flows and pump flows were correlated to find if they affected endtidal sevoflurane levels on CPB.

The results are displayed in table 2.

Table 2

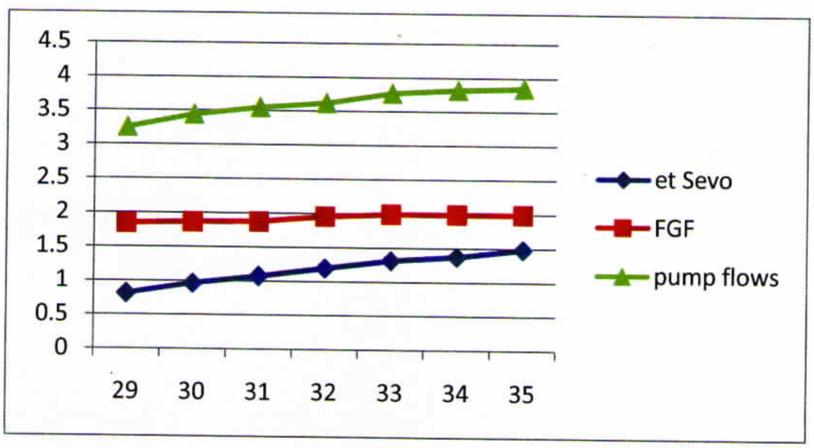
	p value	Significance	Correraltion coefficient	Interpretation
Temperature	p < 0.001	significant	0.67	Good correlation
Fresh gas flows	p=0.17	Not significant	0.01	Poor correlation
Pump flows	p < 0.001	significant	0.06	Poor correlation

When temperature and pump flows were evaluated using multivariate analysis only temperature had a good correlation with statistical significance which is tabulated in table 3.

Table 3

	p value	Significance
Temperature	p < 0.001	significant
Fresh gas flows	p = 0.75	Not significant

Figure 2



A graphical representation of the end tidal sevoflurane, fresh gas flows and pump flows is depicted in figure 2.

Sevoflurane and systemic vascular resistance.

The relationship with increasing sevoflurane concentration during rewarming with SVRI is tabulated in table 4 and graphically represented in figure 3.

Table 4

Temperature (^{0}C)	End tidal sevoflurane Mean % (± STDev)	SVR Mean dynes.sec.cm^{-5} (± STDev)
29	0.81(0.15)	1833.72(391.96)
30	0.96(0.15)	1762.34(299.96)
31	1.07(0.22)	1685.996(279.24)
32	1.19(0.27)	1639.62 (236.12)
33	1.31(0.29)	1611.64(206.41)
34	1.37(0.28)	1567.54(175.81)
35	1.48(0.28)	1518.67(255.19)

Figure 3

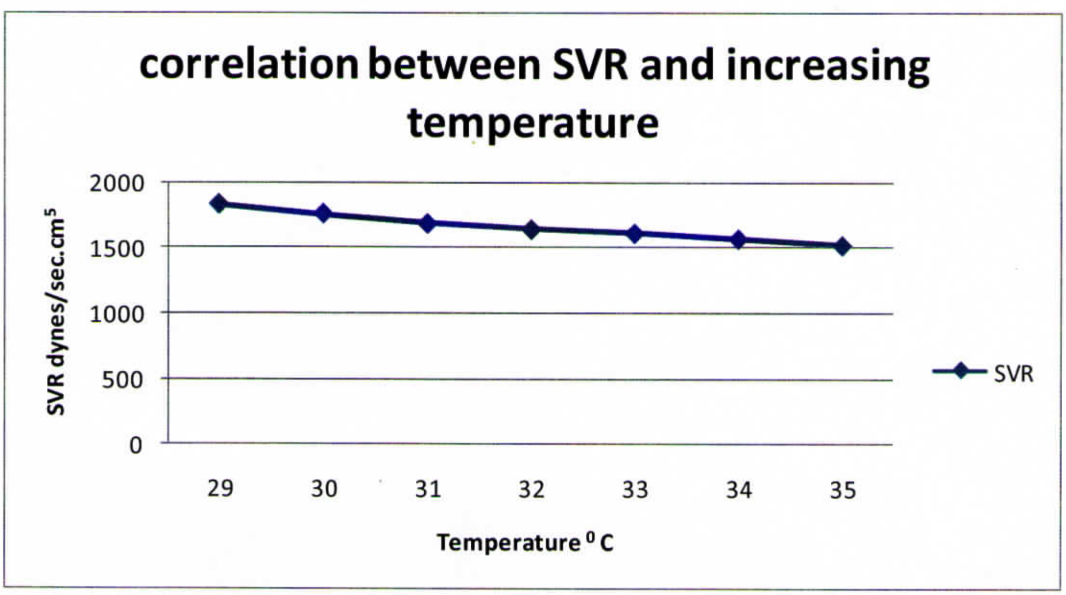
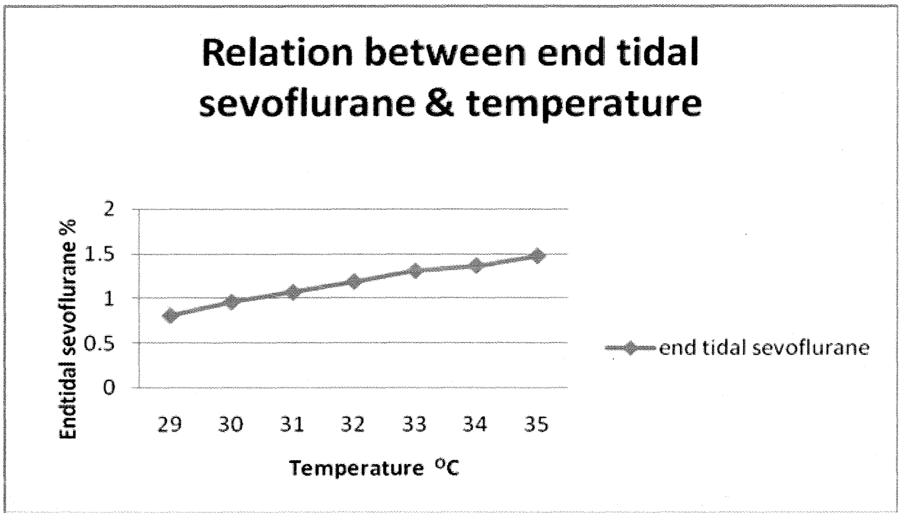


Figure 3 : Correlation between SVR and increasing temperature

Figure 1



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Linear regression using temperature as the independent variable and expiratory sevoflurane as the dependent variable showed a temperature beta coefficient of 0.11 and constant of -2.34.

Hence sevoflurane levels can be predicted with reasonable accuracy by the equation.

End tidal Sevoflurane concentration=0.11x temperature-2.34

Fresh gas flows and pump flows were correlated to find if they affected endtidal sevoflurane levels on CPB.

The results are displayed in table 2.

Table 2

	p value	Significance	Correraltion coefficient	Interpretation
Temperature	p < 0.001	significant	0.67	Good correlation
Fresh gas flows	p=0.17	Not significant	0.01	Poor correlation
Pump flows	p < 0.001	significant	0.06	Poor correlation

When temperature and pump flows were evaluated using multivariate analysis only temperature had a good correlation with statistical significance which is tabulated in table 3.

Table 3

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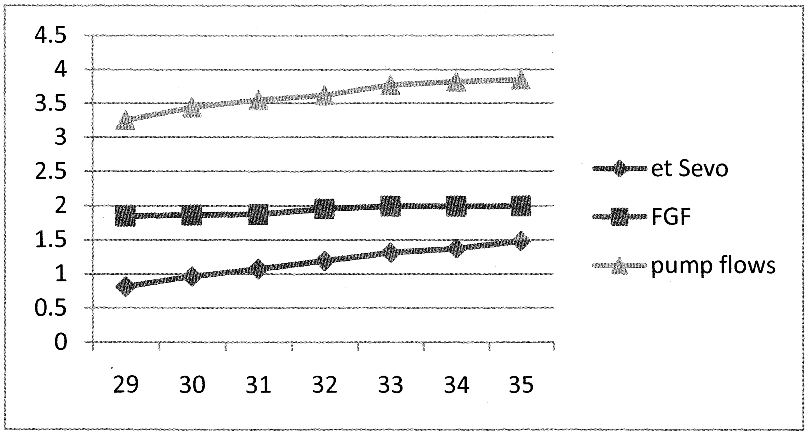
Figure 2



A graphical representation of the end tidal sevoflurane, fresh gas flows and pump flows is depicted in figure 2.

Sevoflurane and systemic vascular resistance.

The relationship with increasing sevoflurane concentration during rewarming with SVRI is tabulated in table 4 and graphically represented in figure 3.

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Figure 3

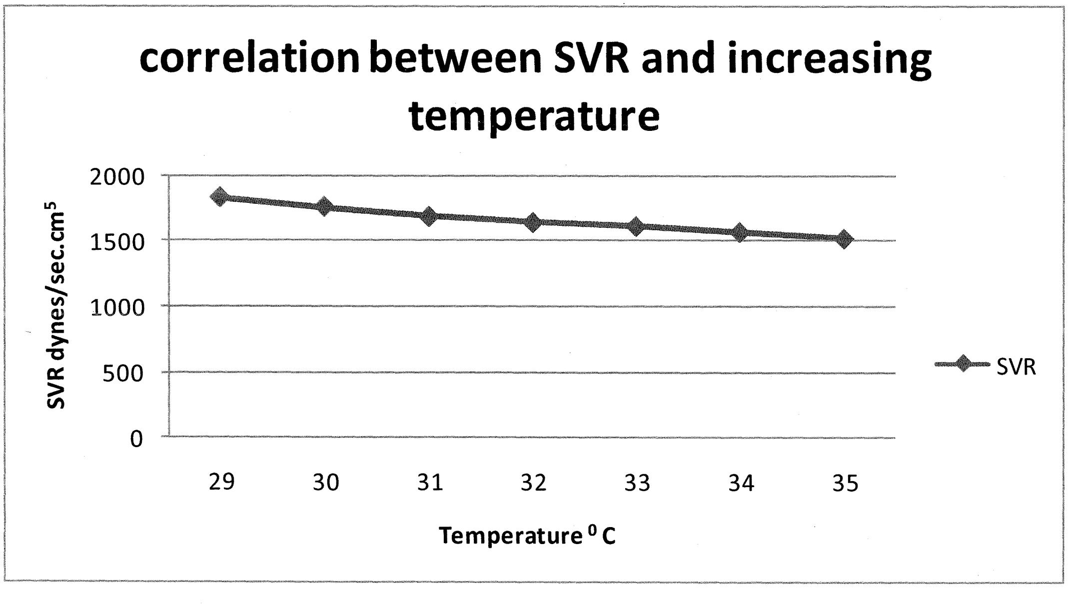

Figure 3 : Correlation between SVR and increasing temperature

As the endtidal sevoflurane concentration increased with increase in temperature the systemic vascular resistance decreased.

The change in SVR, expressed as a percentage change from baseline values at temperature of 29°C and end tidal sevoflurane concentration at 29°C are expressed in table 5.

Table 5

Temperature (°C)	Endtidal sevoflurane Mean % (±STDev)	% decrease in SVR
29	0.81(0.15)	-
30	0.96(0.15)	3.89
31	1.07(0.22)	8.00
32	1.19(0.27)	10.58
33	1.31(0.29)	12..11
34	1.37(0.28)	14.52
35	1.48(0.28)	17.18

29 of 50 patients required the use of phenyephrine 1-2μg/kg boluses to maintain blood pressure >50 mmHg. Of these, 2 patients required nor adrenaline infusion in the dose of 0.05μg/kg/min dose infusion to maintain mean arterial pressure.

Only 1 of the 50 patients received sodium nitroprusside infusion on CPB to maintain mean arterial pressure.

None of the patient indicated an explicit memory of intraoperative events during any of the 3 interviews. None had sweating, tearing, or hypertension, and the BIS did not exceed 60 at any time during cardiopulmonary bypass.

Summary of results

1. Sevoflurane requirement increases during rewarming phase of hypothermic cardiopulmonary bypass
2. End tidal sevoflurane can be predictably estimated at a known temperature using the equation

   End tidal Sevoflurane concentration = 0.11 x temperature-2.34
3. Marginal increase in fresh gas flows do not affect sevoflurane levels on CPB.
4. Pump flows increased to maintain flows for temperature does not affect sevoflurane levels on CPB.
5. Sevoflurane administration decreases systemic vascular resistance on CPB.
6. Administering sevoflurane on CPB titrated by BIS prevents the occurrence of intraoperative awareness.

Discussion

DISCUSSION

Inhalational agents form an integral part of anesthesia for cardiac surgery. New evidence suggests that volatile anesthetics at clinical concentrations may also be useful in protection against perioperative myocardial ischemia, by a mechanism that is independent of effects on myocardial oxygen balance.[1] Volatile anesthetics applied during myocardial ischemia appear to suppress neutrophil activation, neutrophil-endothelial interactions and inflammatory responses that cause myocardial dysfunction.[6]In addition, postischemic administration of volatile anesthetics can also initiate cardioprotection, as evidenced from improved post-ischemic endothelial function, reduced infarct size and less apoptosis.[7] There is a large amount of experimental evidence that volatile anesthetics exert beneficial effects on the consequences of myocardial ischemia-reperfusion injury.[8-11] A recent meta-analysis showed that desflurane and sevoflurane reduce postoperative mortality and the incidence of myocardial infarction (MI) after cardiac surgery with significant advantages in terms of postoperative cardiac troponin (cTn) release, need for inotropic support, time on mechanical ventilation, intensive care unit (ICU) stay, overall hospital stay, and survival.[19,20]

Intraoperative awareness remains one of the major concerns during cardiac surgery. By virtue of their anmestic properties, inhalation anesthetic techniques are likely to markedly decrease the incidence of awareness, while allowing easy titratability of anesthetic depth.[26-28]Although, we did not evaluate patient awareness in the intraoperative period, we ruled out its possibility based upon the findings of Brice interview conducted in the postoperative period. The Brice interview has been used in several prior investigations and is thought to be the most appropriate way to elicit awareness in postoperative patients.[34-36] Although the interview used in the present study was a modification of the Brice questionnaire, the primary questions that Brice used to elicit recall remained unchanged.[46-48]. We performed the same interview 3 times in the postoperative period because of the known association between timing of the interview and detection of awareness. This approach was chosen based on previous findings that approximately one third of the cases of awareness are detected only during a later interview. None of our patients had explicit awareness which reinforces that fact that titrated continuous administration of sevoflurane based on BIS during CPB and surgery helps prevent intraoperative awareness.

This study showed that sevoflurane requirements for hypnosis are increased during the rewarming phase of hypothermic cardiopulmonary bypass when guided by BIS monitoring. The increased sevoflurane requirement was statistically significant in the multivariate analysis with a strong positive correlation. Our findings were similar to the previous study by Eugene et al[55] on isoflurane requirement during the rewarming phase of hypothermic CPB.

As R squared, measure of goodness of fit is 0.67 the agreement between observed and modelled values is good. We can estimate the sevoflurane concentration based on the temperature which is expressed in the form of an equation.

$$\text{Endtidal Sevoflurane concentration} = 0.11 \times \text{temperature} - 2.34$$

This implies that the % increase in the requirement for sevoflurane is uniform, and follows a particular pattern which may be predicted using the above formula. This pattern may be valuable to adjust the concentration of inhaled sevoflurane during rewarming phase of CPB in the absence of BIS monitoring.

Although the oxygenator expiratory gas concentration is not routinely measured, no expensive equipment was required to convey the expiratory gas to the anesthetic agent analyzer. Nussmeier et al in their study of inhalational agents used during CPB concluded that oxygenator exhaust partial pressures of anesthetic correlated with simultaneously obtained blood partial pressures, suggesting that monitoring exhaust gas may be useful clinically.[57]

Measured sevoflurane concentrations may be affected by pressure fluctuations, but we aimed to minimize variations by keeping the fresh gas flows relatively constant and by using the air-break sampling system. In a study by Nussmeier, increasing the gas inflow to the oxygenator from 3 to 12 L/min hastened wash in and washout slightly. Our fresh gas flows varied very little from 1.6-1.99 L/min. The increase in sevoflurane concentration correlated weakly with increasing marginal fresh gas flows and did not show statistical significance in our study. Hence fresh gas flow could not have had much effect on sevoflurane concentrations.[57]

In the same study by Nussmeier found that increasing the pump blood flow from 3 to 5 L/min had no effect on the washin and washout of the inhalational agent[57]. We found similar results in our study. Although pump flow was significant in linear regression with significant p values ($p < 0.001$), in the multivariate analysis it failed to show any statistical significance.

We used BIS as hemodynamic monitor as sympathetic signs have poor specificity and sensitivity for monitoring adequacy of hypnosis. Moreover BIS is routinely used for all patients undergoing general anaesthesia in our institute. BIS monitoring enabled continuous, scaled, and more objective measurements of hypnosis. BIS monitoring has been shown to reduce recovery times, reduce drug usage and costs, and improve the consistency of anesthetic depth[38-40].

Although BIS monitoring has been advocated for guiding anesthetic requirements during cardiopulmonary bypass, BIS algorithms are based primarily on normothermic patients. It is unclear if BIS has the same relationship to hypnosis during hypothermic conditions. Severe hypothermia itself can cause slowing of the electroencephalogram (EEG) and loss of consciousness. Dewandre et al studied BIS in patients undergoing CABG under mild hypothermic (30°C) CPB. BIS was neither affected by surgical stimulation nor by CPB and mild hypothermia. They concluded that BIS was a reliable monitor to assess the hypnotic effects of anaesthetics during normothermic or mild hypothermic CPB[44]. Since most of our study period had temperature between 29-35^{0}C. We presume that BIS accurately measured the hypnotic effects of sevoflurane on CPB. As none of our patients had intraoperative awareness in the post operative interview we conclude that BIS is a reliable hypnotic monitor during hypothermic CPB conditions.

Sevoflurane is a fluoridated derivative of methyl isopropyl ether with MAC of 2% at 37^{0}C in adults. The endtidal sevoflurane in our study at 35^{0}C was 1.48+/-0.28%. This is less than the expected MAC at normothermia. This finding could be explained due to the following.

We used morphine infusions rather than intermittent boluses to prevent sudden changes in anesthetic depth and the BIS and had continued these during CPB. However, it is possible that decreased metabolism during hypothermia may have increased the plasma levels of morphine and of the diazepam used in premedication, and these may have contributed to reduced sevoflurane requirements. Another problem is that opioids may cause low-frequency EEG activity and render the BIS less sensitive to changes in hypnotic level.

We found that SVR decreased with increasing end tidal sevoflurane concentrations. As sevoflurane was being administered to the patient throughout bypass the effect site equilibrium for sevoflurane would have been achieved during the study period. Hence wash in of sevoflurane on CPB as a confounding factor was eliminated.

Rodig et al concluded that sevoflurane had vasodilator properties on mild hypothermic (32-34° C) CPB significant at higher doses (3%). However we found that sevoflurane reduced SVR at lower concentrations during the rewarming phase[58]. This could be due to the steady state already achieved for sevoflurane on CPB along with the increase in temperature which itself causes vasodilatation.

During cardiopulmonary bypass (CPB), complex neuroendocrine responses occur and result in haemodynamic changes. Systemic vascular resistance (SVR) before, during, and after CPB was documented in patients undergoing coronary artery bypass surgery were studied by Kam et al[64].

Whilst the overall effect was an increased SVR, transient profound decreases in SVR at the commencement of CPB, during the rewarming phase, and immediately on weaning off CPB were demonstrated.[64]

Use of sevoflurane on CPB ensures homogenous rewarming due to its vasodilatory properties. Decrease in SVR enhances cardiac output in the immediate post CPB phase which may be an additional beneficial effect of using sevoflurane on CPB[65].

Mean arterial pressure was maintained between 60-80mmHg throughout CPB. This is in accordance with the various studies that showed better outcomes with better hemodynamic control. A large number of prospective observational studies have examined the association between hypotension on CPB (typically defined as a MAP < 50 mm Hg) and adverse outcomes postoperatively. The primary outcome variable assessed in many of these clinical trials was neurologic dysfunction (variably defined). This value is likely based on data supporting a MAP of 50 mm Hg as the lower limit of cerebral autoregulation. Early investigations have suggested that cerebral blood flow (CBF) remains relatively constant at MAPs between 50–150 mm Hg.

The autoregulatory curve may be shifted to the right in the older, hypertensive, and patients with pre-existing cerebral vascular disease patient.

Theoretically, perfusion pressures of >70 mm Hg may reduce the risk of hypoperfusion in the high-risk patient population and enhance collateral blood flow[67,68].

Inhalational agents are traditionally discontinued 10-15 min prior to weaning off CPB for the fear of the myocardial depressant effects of these drugs[57]. BIS at 35^{0}C was 50.10(±5.61). Hence discontinuation of anesthetic agent predisposes the patients to the risk of awareness during the warming phase of CPB. Adequate anesthesia should be ensured as longer acting agents are supplanted by shorter acting agents to facilitate fast track recovery.

Sevoflurane was not found to alter heart rate or cardiac index at all concentrations compared with awake values. Shortening fraction and rate-corrected velocity of circumferential fiber shortening decreased at 1.5 but not at 1 MAC of sevoflurane[63]. Thus sevoflurane required to maintain anesthesia during CPB should not be discontinued during weaning of CPB.

We weaned patients off bypass at 35 ^{0}C, as per institutional policy. Grigore et al concluded that a slower rewarming rate with lower peak temperatures during CPB may be an important factor in the prevention of neurocognitive decline after hypothermic CPB[68-70]. Sahu et al found that Weaning from CPB at 33 degrees C may be used to lower the postoperative impairment of neurocognitive function[69]. Potential mechanisms for this neuroprotection include an improvement in the CBF/$CMRO_2$ balance and a decreased incidence of central nervous system hyperthermia. As rapid rewarming is inevitably associated with overshoot of targeted temperatures, failure to minimize the temperature gradient will result in increased exposure to hyperthermic temperatures and thus an increased potential for neurocognitive decline.

Sevoflurane being a vasodilator assists in homogenous rewarming before weaning the patient from CPB. Studies have shown that rewarming during CPB falls short of restoring the heat loss during cooling by almost 33% despite a normal core temperature at the end of CPB. Because the core receives a high proportion of cardiac output relative to its weight, it rewarms faster than the rest of the body. Consequently, severely constricted peripheral vasculature may not adequately dilate and is not rewarmed enough, despite some minutes spent with core temperatures at normothermia on bypass. As these vascular beds dilate during the early postbypass period, possibly because of resumption of pulsatile flow, heat is transferred from the warm core to peripheral beds, especially to muscle and subcutaneous fat tissue, resulting in decreased core temperatures. Low core temperatures in the postoperative period may be associated with shivering, resulting in higher oxygen consumption and venous desaturation, which ultimately lead to hemodynamic instability.

Noback and Tinker used SNP to permit high pump flows during rewarming and showed better peripheral rewarming and much smaller afterdrop in the postbypass period[72]. Arteriolar vasodilation was proposed to be the effective mechanism in that study. M.Tugrul et al investigated the potential beneficial effects of isoflurane, in particular its arterial vasodilating properties, in the rewarming period of CPB. They summarised that isoflurane is as effective as SNP infusion in improving the uniformity of rewarming; with stable hemodynamics[73].

These properties could be extrapolated to sevoflurane during the rewarming period of CPB because of its anesthetic and vasodilating properties.

The objectives of a cardiac anaesthetic technique are to maintain haemodynamic stability and myocardial oxygen balance, minimize the incidence and severity of ischaemic episodes, and facilitate early tracheal extubation if appropriate. Inhalational agents have a role to play in each of the above mentioned characteristics.

LIMITATIONS

A limitation of the study is that sevoflurane requirements were only assessed during the rewarming phase. Requirements may be different during the cooling phase, but these were difficult to assess because of the considerable fall in temperature even before active cooling on cardiopulmonary bypass.

Although rewarming was carried out gradually to ensure complete rewarming and a minimal core-peripheral temperature gradient, it was not always possible to hold the nasopharyngeal temperatures absolutely steady for BIS and sevoflurane measurement.

The expiratory gas sevoflurane concentration may also not be equal to the blood sevoflurane concentration. This is a similar problem to that encountered during normal anesthesia when end-tidal concentrations are often used to guide anesthetic dosage and depth.

These limitations all reduce the applicability of the measurements to other anesthetic drug combinations.

We attempted to standardize anesthesia as far as possible, but the unprediacability of pharmacokinetics and pharmacodynamics of anesthetics on extracorporeal circulation and variations in patient resposes could have introduced confounding factors in our study.

Nevertheless, it may be possible that the patients perceived intraoperative events without having explicit postoperative memory. In this context, Nordstrom et al[48] were able to show that patients under propofol anesthesia may respond to commands and display consciousness without having explicit postoperative recall. As our standard anesthesia protocol includes propofol as one of the main hypnotic agents, we cannot exclude an underestimation of such awareness in the current study. However, the optimal method of detecting awareness without postoperative memory is unknown. Additionally, nearly all anesthetic agents produce at least some retrograde amnesia, thus possibly reducing the occurrence of explicit memory.

In our study we found that sevoflurane requirement increases during rewarming phase of CPB. However larger studies are required to translate our result in to a higher level of evidence.

Larger patient groups are required to achieve a definitive incidence of awareness. This represents a difficult task because of the low incidence rate in modern anesthesia and because of the number of interfering factors.

Conclusions

CONCLUSIONS

1. Sevoflurane requirements increase during rewarming phase of hypothermic CPB to maintain constant BIS levels.

2. Higher concentrations of sevoflurane results in decrease in SVRI.

3. Monitoring anesthetic concentrations in the oxygenator expiratory gas may be a useful and reliable adjunct to monitoring the depth of anesthesia.

4. The percentage increase in the requirement for sevoflurane is uniform, and follows a particular pattern which may be predicted.

5. Administration of sevoflurane should not be discontinued at the time of weaning patient from CPB in order to prevent inadvertent intraoperative awareness.

6. BIS is a reliable hypnotic monitor to prevent intraoperative awareness, when used during hypothermic bypass.

7. End-tidal gas monitoring may be a valuable adjunct to titrate the anesthetic gas requirement to maintain constant BIS during hypothermic bypass.

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Age	BSA	Patient	29	Dial	Exp sevo	BIS	MAP	Hb	HCT	SVR	CPB	TEMP	FGF		30	Dial	Exp sevo	BIS	MAP	SVR	CPB	TEMP	FGF	Rewarm		31	Dial	Exp sevo	BIS	MAP	SVR	CPB	TEMP	FGF	Rewarm
68	1.44	1		1	1	40	71	8.9	26.1	2641.86	2.15	29	1.5			1	1.2	41	72	2314	2.42	32.8	1.5	5			1	1.2	40	72	1920	3	33	1.5	5
64	1.51	2		1	0.78	49	78	7.7	22.9	2400	2.6	29.8	2			1	0.98	40	78	2039.2	3.06	32.5	2	10			1.5	1.2	46	70	1733.74	3.23	33.6	2	3
66	1.59	3		1	0.86	40	70	8	24.1	1733.74	3.23	29.9	1.9			1	0.92	41	68	1684.2	3.23	32.7	1.9	5			1	1	40	68	1595.3	3.41	32.9	1.9	6
55	1.95	4		2	1.1	48	74	8.4	25.6	1720.93	3.44	30.2	1.5			2	1.4	55	80	1860.5	3.44	33.2	1.5	8			2	1.8	49	78	1520.83	3.84	34	1.5	3
67	1.69	5		1	0.86	41	68	7.7	23.6	1749.19	3.11	29.7	1.5			1	0.98	40	78	1608.2	3.88	33.1	1.5	6			1.5	1.4	44	73	1486	3.93	33.5	2	4
63	1.64	6		1	0.68	40	72	10.4	32.1	1756.09	3.28	29.9	2			1	0.7	40	84	1882.4	3.57	33	2	9			1	0.73	41	80	1904.76	3.36	34.2	2	5
53	1.75	7		1	0.75	40	68	9.9	30.8	1581.4	3.44	30	2			1.5	1.12	54	71	1539.3	3.69	32	2	5			1.5	1.2	45	75	1626.01	3.69	33	2	6
50	1.53	8		1	0.9	40	76	9.1	28	1905.95	3.19	30.3	2			1	1	44	76	1684.2	3.61	32.3	2	5			1	1.2	40	70	1551.24	3.61	33.3	2	5
67	1.5	9		1	0.88	46	74	8.8	27	1915.85	3.09	29.8	1.5			1	0.91	40	70	1702.1	3.29	32.6	1.5	5			1.5	1.2	43	70	1702.12	3.29	33.1	1.5	5
49	1.58	10		0.75	0.9	40	70	8.1	24.7	2533.93	2.21	30.6	1.9			1	0.98	40	70	2222.2	2.52	32.9	1.9	4			1	1.1	41	70	2089.55	2.68	33	2	3
51	1.67	11		1	0.87	40	71	9.1	27.9	1737	3.27	29.3	1.9			1	0.96	41	72	1740.2	3.31	32.2	1.9	3			1	1	40	72	1694.11	3.4	33	1.9	4
63	1.67	12		0.5	0.32	40	68	7.7	24	1482.28	3.67	29.9	1.8			1	0.86	41	70	1548.4	3.72	32	1.8	5			1	0.92	40	70	1465.96	3.82	32.8	1.8	5
65	1.81	13		0.5	0.29	44	70	8	24.8	1393.03	4.02	30.1	1.9			1	0.82	42	80	1557.2	4.11	31	1.9	4			1	0.98	41	76	1479.31	4.11	32.4	1.9	4
47	1.82	14		1	0.76	40	70	10	28	1400	4	30	1.9			1	0.86	42	68	1360	4	32	1.9	7			1	0.92	42	70	1333.33	4.2	33	1.9	5
68	1.93	15		0.8	0.76	40	68	7.9	23.7	1600	3.4	30	2			1	0.82	41	68	1478.3	3.86	32.3	2	5			1	1	40	72	1488.37	3.87	33	2	6
54	1.57	16		1	0.85	40	70	8.2	25	2522.52	2.22	30.2	1.9			1	0.92	41	72	2285.7	2.52	32.9	1.9	4			1	0.98	42	74	2208.95	2.68	33	2	3
69	1.89	17		1	0.92	44	68	9.9	30.1	1280	4.25	30.6	2			1	0.97	40	71	1302.8	4.36	32.6	2	7			1	1	43	68	1192.98	4.56	32.4	2	3
57	1.55	18		1	0.86	40	70	7.8	23.6	1744.54	3.21	29.5	2			1	0.93	41	70	1728.4	3.24	31.1	2	5			1	0.95	42	71	1731.7	3.28	32.4	2	4
58	1.81	19		1	0.85	44	68	8.4	25.5	1314	4.14	29.7	2			1	0.95	40	69	1314.3	4.2	32.7	2	8			1	0.98	42	69	1314.28	4.2	32.7	2	5
64	1.52	20		1	0.8	40	72	8.2	25	1858.06	3.1	29.8	1.5			1	0.9	42	78	2006.4	3.11	31.1	1.5	5			1.5	1.2	48	78	1902.43	3.28	32.7	1.5	5
61	1.65	21		1	0.66	45	71	7.3	23	1775	3.2	30	1.5			1	0.96	40	80	1876.8	3.41	32.8	1.5	7			1.5	1.1	40	74	1691.42	3.5	32.7	1.5	3
52	1.62	22		1	0.73	40	78	7.8	24.1	2337.07	2.67	30.6	2			1	0.81	40	78	2189.5	2.85	31.7	2	6			1	0.86	41	80	2214.53	2.89	32	2	5
66	1.77	23		1	0.8	45	70	8.5	26.3	1333.33	4.2	30.9	2			1	0.93	41	70	1323.9	4.23	31.4	2	4			1	0.94	41	70	1314.55	4.26	32.1	2	5
57	1.97	24		1	0.66	44	72	8.7	27.7	1440	4	30	2			1	0.77	40	75	1408.5	4.26	31.6	2	8			1	0.77	45	75	1408.45	4.26	31.6	2	8
49	1.77	25		1	0.98	40	77	8.1	25.2	2176.67	2.83	29.6	2			1.5	1.4	56	75	1904.5	3.15	32.9	2	8			1.5	1.5	50	78	1968.45	3.17	32.3	2	3
65	1.74	26		1	0.8	50	80	9.1	28.1	1679.79	3.81	30.5	2			1	0.98	40	78	1620.8	3.85	32.1	2	5			1	1.1	40	78	1521.95	4.1	32.1	2	3
59	1.72	27		1	0.66	40	70	7.8	24.3	1555.55	3.6	30.5	2			1	0.72	40	77	1621.1	3.8	32.2	2	5			1	0.92	40	78	1642.1	3.8	32.2	2	5
43	1.51	28		1	0.9	40	74	7.8	23.6	2276.92	2.6	30.6	1.5			1	0.95	42	76	2171.4	2.8	32	2	7			1	1	45	80	2277.58	2.81	32.5	1.5	7
65	1.8	29		1	0.98	40	68	8.1	25.2	1370.27	3.97	30.7	2			1	0.99	45	72	1443.6	3.99	32.5	2	4			1	1	41	73	1327.27	4.4	33	2	6
49	1.58	30		0.75	0.9	40	70	8.1	24.7	2533.93	2.21	30.6	1.9			1	0.98	40	70	2222.2	2.52	32.9	1.9	4			1	1.1	41	70	2089.55	2.68	33	2	3
64	1.44	31		1	1	40	71	8.9	26.1	2641.86	2.15	29	1.5			1	1.2	40	72	2314	2.42	32.8	1.5	5			1	1.2	40	72	1920	3	33	1.5	5
64	1.52	32		1	0.8	40	72	8.2	25	1858.06	3.1	29.8	1.5			1	0.9	42	78	2006.4	3.11	31.1	1.5	5			1.5	1.2	47	78	1902.43	3.28	32.7	1.5	5
43	1.51	33		1	0.9	40	74	7.8	23.6	2276.92	2.6	30.6	1.5			1	0.95	42	76	2171.4	2.8	32	2	7			1	1	40	80	2277.58	2.81	32.5	1.5	7
69	1.93	34		0.8	0.76	40	68	7.9	23.7	1600	3.4	30	2			1	0.82	41	68	1478.3	3.86	32.3	2	5			1	1	40	72	1488.37	3.87	33	2	6
67	1.5	35		1	0.88	46	74	8.8	27	1915.85	3.09	29.8	1.5			1	0.91	40	70	1702.1	3.29	32.6	1.5	5			1.5	1.2	43	70	1702.12	3.29	33.1	1.5	5
55	1.95	36		2	1.1	48	74	8.4	25.6	1720.93	3.44	30.2	1.5			2	1.4	40	80	1860.5	3.44	33.2	1.5	8			2	1.8	45	78	1520.83	3.84	34	1.5	3
53	1.75	37		1	0.75	40	68	9.9	30.8	1581.4	3.44	30	2			1.5	1.12	54	71	1539.3	3.69	32	2	5			1.5	1.2	45	75	1626.01	3.69	33	2	6
51	1.67	38		1	0.87	40	71	9.1	27.9	1737	3.27	29.3	1.9			1	0.96	40	72	1740.2	3.31	32.2	1.9	3			1	1	40	72	1689.15	3.41	33	1.9	4
47	1.82	39		1	0.76	40	70	10	28	1400	4	30	1.9			1	0.86	42	68	1353.2	4.02	32	1.9	7			1	0.92	42	70	1330.17	4.21	33	1.9	5
64	1.51	40		1	0.78	41	78	7.7	22.9	2400	2.6	29.8	2			1	0.98	40	78	2039.2	3.06	32.5	2	10			1.5	1.2	43	70	1733.74	3.23	33.6	2	3
51	1.67	41		1	0.87	40	71	9.1	27.9	1737	3.27	29.3	1.9			1	0.96	41	72	1740.2	3.31	32.2	1.9	3			1	1	50	72	1694.11	3.4	33	1.9	4
54	1.57	42		1	0.85	40	70	8.2	25	2522.52	2.22	30.2	1.9			1	0.92	41	72	2285.7	2.52	32.9	1.9	4			1	0.98	40	74	2208.95	2.68	33	2	3
67	1.69	43		1	0.86	41	68	7.7	23.6	1749.19	3.11	29.7	1.5			1	0.98	40	78	1608.2	3.88	33.1	1.5	6			1.5	1.4	48	73	1486	3.93	33.5	2	4
63	1.64	44		1	0.68	40	72	10.4	32.1	1756.09	3.28	29.9	2			1	0.7	40	84	1882.4	3.57	33	2	9			1	0.73	40	80	1904.76	3.36	34.2	2	5
52	1.65	45		1	0.9	40	70	7.8	23	1559.89	3.59	30.8	2			1	1	40	70	1517.6	3.69	32.8	2	3			1	1	40	72	1560.97	3.69	34.2	2	5
67.00	2.05	46		1	0.69	48.00	75.00	8.40	26.20	1285.79	4.67	30.00	2.00			1	1.00	48.00	78.00	1324.8	4.71	32.80	2.00	7.00			1.00	1.00	40.00	76.00	1256.2	4.84	33.50	2.00	4.00
49	1.65	47		1	0.86	50	80	8.6	26.6	1933.53	3.31	30.8	2			1	1	40	78	1846.2	3.38	32.6	2	3			1	1.1	50	68	1600	3.4	33.5	2	4
50.00	1.54	48		1	0.69	40.00	76.00	8.50	26.4	2040.26	2.98	30.8	2			1	0.89	40.00	74	1873.4	3.16	32.5	2	5			1	0.90	40.00	72	1756.1	3.28	33.5	2	5
63	1.66	49		1	0.8	40	70	8.1	24.8	1681.68	3.33	29.8	2			1	0.88	42	71	1680.5	3.38	32.8	2	5			1	0.90	40.00	73	1722.71	3.39	33	2	6
60	1.68	50		1	0.78	41.00	71.00	7.90	24	1539.3	3.69	30	2			1	0.90	40.00	70	1513.5	3.7	33	2	4			1	0.78	40.00	71.00	1522.79	3.73	33.8	2	5

Patient	32	Dial	Exp sevo	BIS	MAP	SVR	CPB	TEMP	FGF	Rewarm	33	Dial	Exp sevo	BIS	MAP	SVR	CPB	TEMP	FGF	Rewarm
1		1.5	1.6	48	70	1842.11	3.04	34.2	1.5	4		1.5	1.4	41	76	2000	3	34	2	8
2		1.5	1.3	46	70	1733.75	3.23	33.8	2	7		1.5	1.3	45	77	1907.1	3.2	34	2	5
3		1	1.1	45	68	1549.86	3.51	33.1	1.9	3		1	1.2	48	68	1506.9	3.6	33	2	3
4		2	2	50	78	1548.39	4.03	34.2	2	7		2	2.1	46	77	1524.8	4	35	2	6
5		1	1.1	42	70	1609.2	3.48	35.1	2	6		1.5	1.3	42	70	1564.2	3.6	35	2	4
6		1	0.92	41	79	1880.92	3.36	34.7	2	3		1	0.93	40	79	1848	3.4	35	2	4
7		1.5	1.3	45	73	1569.89	3.72	34.1	2	6		1.5	1.3	41	71	1486.9	3.8	35	2	4
8		1.5	1.3	40	70	1521.73	3.68	34.3	2	4		1.5	1.3	43	70	1466	3.8	35	2	4
9		2	1.5	50	72	1586.78	3.63	34.2	2	4		2	1.8	48	72	1719	3.6	35	2	4
10		1	1	40	67	1928.06	2.78	34.8	2	5		1	1.1	40	78	1835.3	3.4	35	2	6
11		1	1.1	40	69	1586.21	3.48	34.1	2	3		1.5	1.3	41	70	1568.6	3.6	35	2	5
12		1	1	41	72	1500	3.84	33.3	2	4		1.5	1.2	47	74	1436.9	4.1	34	2	6
13		1.5	1.1	44	75	1421.8	4.22	33.1	1.9	5		2	1.8	50	78	1475.2	4.2	34	2	5
14		1	1	40	74	1409.52	4.2	34	2	3		1.5	1.2	43	77	1466.7	4.2	35	2	4
15		1	1.1	40	72	1465.65	3.93	33.6	2	6		1.5	1.2	42	72	1559.5	4	34	2	3
16		1	1.2	41	72	2071.94	2.78	34	2	5		1.5	1.2	43	74	1741.2	3.4	35	2	6
17		1	1.1	41	70	1225.38	4.57	33.9	2	6		1.5	1.2	49	74	1292.6	4.6	34	2	3
18		1	1	42	70	1707.32	3.28	33.5	2	3		1	1.2	43	69	1508.2	3.7	35	2	6
19		1	1	42	69	1283.72	4.3	33.6	2	4		1.5	1.2	44	69	1240.4	4.5	35	2	5
20		2	1.6	50	78	1809.91	3.3	33	1.5	4		2	1.8	50	78	1824.6	3.4	35	2	3
21		1.5	1.3	49	72	1536	3.75	34.7	1.5	5		1.5	1.4	42	72	1507.9	3.8	35	1.5	7
22		1	0.93	41	80	2206.89	2.9	33.3	2	4		1.5	1.1	41	78	2094	3	34	2	4
23		1	0.94	41	70	1314.55	4.26	32.7	2	5		1	0.94	41	70	1314.6	4.3	34	2	5
24		1	0.77	40	75	1408.45	4.26	33	2	6		1.5	1.1	45	76	1277.3	4.8	35	2	4
25		2	1.8	51	78	1529.41	4.08	33.1	2	3		2	1.8	51	78	1482.9	4.1	34	2	6
26		1	1.1	40	76	1458.03	4.17	33.1	2	3		1.5	1.2	48	78	1489.3	4.2	34	2	3
27		1	0.99	42	78	1642.11	3.8	33.9	2	4		1	1	40	78	1642.1	3.8	34	2	8
28		1	1	43	80	2133.33	3	33	2	5		1.5	1.2	46	79	1770.3	3.6	35	2	5
29		1	1.1	42	73	1327.27	4.4	33.5	2	5		1.5	1.2	45	76	1375.6	4.4	34	2	6
30		1	1	40	67	1928.06	2.78	34.8	2	5		1	1.1	42	78	1835.3	3.4	35	2	6
31		1.5	1.6	52	70	1842.11	3.04	34.2	1.5	4		1.5	1.8	41	76	2000	3	34	2	8
32		2	1.6	52	78	1809.91	3.3	33	1.5	4		2	1.8	49	78	1824.6	3.4	35	2	3
33		1	1	40	80	2133.33	3	33	2	5		1.5	1.2	42	79	1770.3	3.6	35	2	5
34		1	1.1	40	72	1465.65	3.93	33.6	2	6		1.5	1.2	40	72	1458.2	4	34	2	3
35		2	1.5	45	72	1586.78	3.63	34.2	2	4		2	1.8	52	72	1586.8	3.6	35	2	4
36		2	2	52	78	1548.39	4.03	34.2	2	7		2	2.1	48	77	1524.8	4	35	2	6
37		1.5	1.3	50	73	1569.89	3.72	34.1	2	6		1.5	1.3	41	71	1486.9	3.8	35	2	4
38		1	1.1	40	71	1632.18	3.48	34.1	2	3		1.5	1.3	48	70	1568.6	3.6	35	2	5
39		1	1	40	74	1409.52	4.2	34	2	3		1.5	1.2	43	77	1466.7	4.2	35	2	4
40		1.5	1.3	50	70	1733.75	3.23	33.8	2	7		1.5	1.3	49	77	1907.1	3.2	34	2	5
41		1	1.1	40	69	1586.21	3.48	34.1	2	3		1.5	1.3	50	70	1568.6	3.6	35	2	5
42		1	1.2	41	72	2071.94	2.78	34	2	5		1.5	1.2	43	74	1741.2	3.4	35	2	6
43		1	1.1	42	70	1609.2	3.48	35.1	2	6		1.5	1.3	42	70	1564.2	3.6	35	2	4
44		1	0.92	40	79	1880.95	3.36	34.7	2	3		1	0.93	40	79	1848	3.4	35	2	4
45		1	1	46	71	1551.91	3.66	34.6	2	4		1	1	40	74	1613.1	3.7	35	2	5
46		1.50	1.30	44.00	78.00	1255.53	4.97	34.50	2.00	9.00		1.50	1.30	50.00	80.00	1223.7	5.2	35	2.00	5.00
47		1	1.2	40	68	1536.72	3.54	34	2	4		1	1.2	52	73	1595.8	3.8	36	2.00	6.00
48		1	1.00	40.00	73	1753.75	3.33	34.1	2	5		1	1.10	40.00	76	1793.5	3.4	35	2	6
49		1	1.00	40.00	74	1730.99	3.42	34.2	2	5		1	1	40	77	1780.4	3.5	35	2	6
50		1	1	41.00	72.00	1536	3.75	34.8	2	6		1	1.1	40.00	71.00	1498.7	3.8	35	2	7

Patient		34	Dial	Exp sevo	BIS	MAP	SVR	CPB	TEMP	FGF	Rewarm		35	Dial	Exp sevo	BIS	MAP	SVR	CPB	TEMP	FGF	Rewarm
1			1	1.3	42	70	1733.75	3.23	35.4	2	5			1.5	1.4	52	68	1684.21	3.23	35.1	2	7
2			1.5	1.4	51	78	1873.87	3.33	34.4	2	8			1.5	1.4	50	69	1657.66	3.33	35	2	9
3			1	1.3	44	70	1501.34	3.73	34.8	2	7			1	1.3	40	71	1531.00	3.71	35.4	2	9
4			2	2.1	55	77	1528.54	4.03	35.3	2	7			2	2.1	55	74	1468.98	4.03	35.3	2	7
5			2	1.5	50	67	1558.14	3.44	35.7	2	5			2	1.5	50	70	1462.14	3.83	35.7	2	9
6			1	0.98	40	76	1772.59	3.43	35.7	2	4			1	1	41	76	1772.59	3.43	35.5	2	4
7			1.5	1.4	48	81	1678.76	3.86	35.5	2	7			1.5	1.4	56	88	1809.77	3.89	35.5	2	7
8			1.5	1.4	51	70	1465.97	3.82	35.3	2	5			1.5	1.4	51	70	1465.97	3.82	35.3	2	5
9			2	1.8	52	72	1586.78	3.63	35.1	2	4			2	1.8	57	72	1586.78	3.63	35.2	2	4
10			1	1.1	42	69	1614.04	3.42	35	2	5			1	1.1	42	69	1609.33	3.43	35.1	2	6
11			1.5	1.36	50	70	1517.62	3.69	35.3	2	5			1.5	1.4	45	71	1535.14	3.7	35.6	2	6
12			1.5	1.3	42	74	1436.89	4.12	34.9	2	4			1.5	1.4	57	76	1479.32	4.11	35.1	2	4
13			2	1.8	50	76	1437.35	4.23	35	2	6			2	2	55	83	1533.49	4.33	35.1	2	4
14			1.5	1.3	43	78	1451.1628	4.3	35.1	2	5			1.5	1.4	45	78	1451.16	4.3	35.2	2	4
15			1.5	1.3	42	75	1507.5377	3.98	35.2	2	7			1.5	1.3	54	75	1507.54	3.98	35.2	2	7
16			1.5	1.3	44	74	1730.9942	3.42	35	2	5			1.5	1.4	55	76	1772.59	3.43	35.1	2	6
17			1.5	1.3	42	72	1257.6419	4.58	35.3	2	5			1.5	1.5	50	75	1273.89	4.71	35.2	2	7
18			1	1.2	42	70	1513.5135	3.7	35.6	2	6			1	1.2	42	70	1513.51	3.7	35.6	2	6
19			1.5	1.3	46	70	1258.427	4.45	34.9	2	4			1.5	1.3	50	70	1258.43	4.45	35.5	2	4
20			2	1.8	51	78	1824.5614	3.42	35.1	2	3			2	2	48	80	1871.35	3.42	35.5	2	3
21			2	1.7	50	76	1571.0594	3.87	35.5	1.5	6			2	1.8	45	74	1529.72	3.87	35.5	1.5	7
22			1.5	1.1	49	78	1931.8885	3.23	35.6	2	4			1.5	1.4	46	78	1902.44	3.28	35.5	2	4
23			1	1	41	70	1314.554	4.26	35.2	2	7			2	1.56	51	72	1309.09	4.4	35.6	2	5
24			2	1.6	45	75	1260.5042	4.76	35.1	2	5			2.5	1.9	58	75	1260.50	4.76	35.6	2	5
25			2	1.9	45	78	1514.5631	4.12	35	2	7			2	2.1	45	74	1436.89	4.12	35.5	2	8
26			1.5	1.3	45	78	1441.1085	4.33	35.1	2	6			1.5	1.4	51	78	1441.11	4.33	35.6	2	7
27			1.5	1.2	42	78	1552.2388	4.02	35.6	2	4			1.5	1.4	49	70	1393.03	4.02	35.4	2	7
28			1.5	1.2	43	76	1612.7321	3.77	35	2	5			1.5	1.4	56	76	1612.73	3.77	35.1	2	5
29			1.5	1.3	45	70	1194.0299	4.69	35.1	2	4			1.5	1.5	49	70	1194.03	4.69	35.2	2	7
30			1	1.1	41	69	1614.0351	3.42	35	2	5			1	1.1	42	69	1609.33	3.43	35.1	2	6
31			1	1.3	42	70	1733.7461	3.23	35.4	2	5			1.5	1.4	48	68	1684.21	3.23	35.1	2	7
32			2	1.8	52	78	1824.5614	3.42	35.1	2	3			2	2	52	80	1871.35	3.42	35.5	2	3
33			1.5	1.2	43	76	1612.7321	3.77	35	2	5			1.5	1.4	53	76	1612.73	3.77	35.1	2	5
34			1.5	1.3	49	75	1507.5377	3.98	35.2	2	7			1.5	1.3	40	75	1507.54	3.98	35.2	2	7
35			2	1.8	50	72	1586.7769	3.63	35.1	2	4			2	1.8	55	72	1586.78	3.63	35.2	2	4
36			2	2.1	55	77	1528.536	4.03	35.3	2	7			2	2.1	56	74	1468.98	4.03	35.3	2	7
37			1.5	1.4	47	81	1678.7565	3.86	35.5	2	7			1.5	1.4	45	88	1809.77	3.89	35.5	2	7
38			1.5	1.36	46	70	1517.6152	3.69	35.3	2	5			1.5	1.4	57	71	1535.14	3.7	35.6	2	6
39			1.5	1.3	40	78	1451.1628	4.3	35.1	2	5			1.5	1.4	55	74	1376.74	4.3	35.2	2	4
40			1.5	1.4	40	78	1873.8739	3.33	34.4	2	8			1.5	1.4	58	69	1657.66	3.33	35	2	9
41			1.5	1.36	50	70	1517.6152	3.69	35.3	2	5			1.5	1.4	51	71	1535.14	3.7	35.6	2	6
42			1.5	1.3	40	74	1730.9942	3.42	35	2	5			1.5	1.4	55	76	1772.59	3.43	35.1	2	6
43			2	1.5	50	67	1558.1395	3.44	35.7	2	5			2	1.5	54	70	1462.14	3.83	35.7	2	9
44			1	0.98	40	76	1772.5948	3.43	35.7	2	4			1	1	40	76	1772.59	3.43	35.5	2	4
45			1	1	40	74	1613.079	3.67	35.2	2	5			1.5	1.3	43	70	1497.33	3.74	35.4	2	6
46			1.50	1.50	48.00	79.00	1149.0909	5.50	35.40	2.00	8.00			1.50	1.50	50	80	1163.64	5.50	35.40	2	7
47			1.00	1.20	40.00	73.00	1532.8084	3.81	35.5	2	5			1	1.2	41	77	1612.57	3.82	35.8	2	3
48			1.5	1.20	41.00	75	1754.386	3.42	35	2	5			1.5	1.30	56	70	1632.65	3.43	35.2	2	7
49			1.5	1.20	50.00	73	1678.1609	3.48	35.5	2	6			1.5	1.20	58	71	1627.51	3.49	35.3	2	6
50			1	0.78	41.00	71.00	1498.68	3.79	35.6	2	5			1.5	1.5	51	71	1539.30	3.69	35.6	2	6