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Title Page

Total Intravenous Anesthesia (TIVA) in pediatric cardiac anesthesia

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Summary

Although inhalational anesthesia with moderate to high-dose opioid analgesia has been the mainstay of pediatric cardiac anesthesia, the **availability** of new **short-acting** drugs, **new** concepts in pharmacokinetic modelling and computer technology, **and advances in surgery and perfusion** have made total intravenous anesthesia (TIVA) an attractive option. In this article, we review some of the TIVA techniques used in pediatric cardiac anesthesia.

Keywords: total intravenous anesthesia (TIVA), pediatrics, cardiac surgery, Propofol

Total intravenous anesthesia (TIVA) (1, 2) is useful for certain pediatric cardiac procedures and has become more feasible with improved infusion pump design, more appropriate pediatric software and more clinical experience. There is a better understanding of the pharmacodynamics and pharmacokinetics of intravenous anesthetic agents in children undergoing cardiopulmonary bypass and potential beneficial effects of these agents.

Pharmacodynamic effects of anesthetic agents during cardiac surgery

Cardiopulmonary bypass (CPB) may be associated with multi-organ damage, resulting in both immediate and long term effects (3, 4). This damage may be related in part to inadequate regional tissue oxygen delivery, and also to the “stress response” during and after CPB(3). Reduction in the stress response to cardiac surgery in neonates and children is associated with improved postoperative outcome (3, 5-9). Damage caused by inadequate oxygen delivery and tissue hypoxia may be reduced by metabolic depression using both hypothermia and anesthetic agents. These effects may be additive; for example, cerebral metabolic depression, in addition to that caused by hypothermia, may be produced with thiopentone or propofol or isoflurane titrated to EEG suppression during CPB (3, 10). With thiopentone, this may result in reduced cerebral damage(3, 11). However, in order to achieve EEG suppression, a large dose of thiopentone is usually required, which can produce hemodynamic instability, prolonged anesthetic effects, delayed tracheal extubation and increased sedation during the first few postoperative days(11).

Cardiovascular effects of ketamine, propofol and opioids

Ketamine

Ketamine is frequently chosen for anesthetic induction in patients with cyanotic conditions, as it increases systemic vascular resistance and cardiac output but without worsening right to left shunting(12). A recent prospective, randomized study by Tugrul et al. (13) demonstrated that ketamine anesthesia provided more stable precardiopulmonary bypass conditions than

isoflurane anesthesia. Arterial oxygen tension, oxygen saturation and mean arterial pressure were better maintained poststernotomy in those patients receiving ketamine(13). Ketamine does not significantly increase the pulmonary vascular resistance in children with pulmonary hypertension(14) .

Propofol

Propofol, has a short half-life and context-sensitive half time and when given by infusion with opioids, propofol can significantly attenuate the adverse hemodynamic and metabolic effects of bypass and surgery while producing rapid smooth recovery and transition to postoperative care(1). Propofol reduces whole body oxygen uptake during hypothermic CPB (28°C) in adults (3, 15), reduces cerebral perfusion pressure, oxidative stress, cerebral blood flow, velocity and microembolic delivery. Propofol has also been shown to suppress seizures(3, 16, 17) and may act as an oxygen free radical scavenger (3, 18). Propofol during CPB caused significant increases in mixed venous oxygen saturation, significant reductions in systemic oxygen uptake, reduction in glucose and cortisol concentrations with no difference in lactate concentrations, mean arterial pressure during CPB and inotrope requirement after CPB, or in recovery times (3). Catecholamine and cortisol are released during stress that produces alterations in microvascular permeability and multi-organ damage(3, 19, 20). These hormonal changes also result in hyperglycemia, which is known to worsen neurological outcome after cerebral ischemia (3). During rewarming and normothermia, propofol can prevent hyperglycemia, attenuate the stress response and produce rapid recovery(3). Propofol can be used in patients with or at risk of long QT syndrome without increasing the risk of torsades de pointes (TdP)(21).

Propofol produces arterial and venous dilation, both in systemic and pulmonary circulation. These effects will be more prominent with the concomitant use of other vasodilators like alpha blockers, phosphodiesterase(PDE) III inhibitors, and angiotensin converting enzymes (ACE) inhibitors. These circulatory effects can be modulated by optimizing the patient's

intravascular volume, by surgical stimulation, propofol dose increments and the rate of dose changes.

Opioids

Opioids do not cause myocardial depression and protect the heart by a preconditioning-like mechanism and therefore concurrent administration of opioids with either propofol or volatile agents produces an additive effect (22).

Preconditioning

Previous exposure of the brain and myocardium to minor insults, chemicals, or pharmacological agents can “precondition” or increase the tolerance of neural and cardiac cells to lethal ischemic injury. Preconditioning with either volatile or intravenous agents may be advantageous. Some volatile agents, most notably isoflurane, when given before an ischemic insult have been found to induce ischemic tolerance in the brain and spinal cord (23-26), and to prevent ischemia-reperfusion(I/R) myocardial injury (27). There are several proposed mechanisms for protection (e.g. attenuating calcium overload, anti-inflammatory and antioxidant effects, pre- and post-conditioning-like protection) (22). Anesthetic preconditioning with volatile anesthetics improves recovery of contractile function and reduced calcium overload after ischemia/reperfusion(28). Clarke et al (29) showed recently that a critical factor mediating reperfusion injury of the heart is the mitochondrial permeability transition pore (MPTP). The opening of the MPTP causes mitochondrial swelling with release of proapoptotic proteins and uncoupling of mitochondrial oxidative phosphorylation. The resulting ATP deprivation causes disruption of ionic homeostasis and contractile function and ultimately sarcolemma rupture and necrosis. Inhibition of MPTP opening during reperfusion protects hearts from reperfusion injury.

Propofol has been shown to protect the heart against cardiac insults in a variety of experimental models (30-32). These effects are attributed to its ability to act as a free radical scavenger (33), enhancing tissue antioxidant capacity(34), and through inhibition of plasma membrane calcium channels (35, 36). Its antioxidant properties are responsible for its

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3 inhibitory action of **MPTP** opening in the Langendorff perfused rat heart (30), and its
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5 antiapoptotic properties (36). The clinical benefits of propofol's antioxidant capacity during
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7 cardiopulmonary bypass are more evident when using a high maintenance dose (plasma levels
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9 of approximate 4.2ng/ml) by Xia et al (37). Propofol protects the myocardium against
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11 ischemia-reperfusion injury, due to its antioxidant effect and inhibition of the MPTP.
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Cardiopulmonary bypass and pharmacokinetics of anesthetic agents

During CPB, a variety of factors act to alter drug disposition, metabolism and elimination to a clinically significant extent. At the onset of CPB the bypass circuit priming fluid is mixed with the patient's blood. The volume of the prime and reservoir varies with age from around 350ml in the neonate to 1500ml in the adult. This prime may be crystalloid or crystalloid mixed with albumin or blood. This mixture between patient's blood and bypass circuit priming fluid will lead to a reduction in the patient's packed red cell volume (PCV) to approximately 25%, plasma volume will be increased by 40-50%. All these changes may alter drug protein binding and distribution (38). This results in reduction in total drug concentration, although not always free drug. The potential changes in acid-base balance during CPB will result in changes in ionized and unionized drug concentrations which affects protein binding. The ratio of the CPB circuit volume to the patients' blood volume is greater for smaller patients than adults; consequently, this hemodilution effect and its effects on protein binding, volume of distribution, and drug clearance may be more pronounced in children as opposed to adults (39).

The mean arterial pressure is determined by the pump speed and the systemic vascular resistance which can be altered by the use of vasodilators and vasoconstrictors. Regional blood flow distribution, and thus the drug distribution and metabolism can be varied. Hypothermia reduces hepatic and renal enzyme function, which affects drug metabolism. Many drugs bind to components of the CPB circuit (e.g. fentanyl) (39, 40). There are important developmental influences on body composition (lipid, body water), body proportions, blood brain barrier maturation, regional blood flow distribution, hepatic and renal functions which must be considered.

Propofol

Conflicting results have been obtained for propofol. The total concentration of propofol may decrease on commencing CPB with increase in the free fraction, or the total concentration

may remain unchanged. A prolonged elimination half-life has been demonstrated in one study, but the redistribution half-life was short, concentration decreased rapidly after stopping the drug and patients made a rapid recovery. In general, the free active concentrations of these drugs remain unchanged but their action may be prolonged (38, 41, 42).

In a prospective trial of the accuracy of a pediatric target-controlled infusion of propofol which employed the Paedfusor pharmacokinetic dataset (43), children did not show a significant change in pharmacodynamic effect (level of consciousness), because, even in small children, the volume of bypass circuit and reservoir is small in comparison with the volume of the central and other compartments. For example, in a child weighing 10kg, the volume of prime would be 270ml, whereas the volumes of the theoretical central, second and third compartments would be 4600, 1340 and 8200ml respectively (43). Developments are underway to allow effect-site targeting in children(2).

Opioids

All opioids show a decrease in total drug concentration on commencing CPB. The degree of this decrease is greater with fentanyl where a significant proportion of the drug adheres to the surface of the CPB circuit (38). The decrease is least with opioids that have a high volume of distribution when the addition of the prime volume is less important and in those that can equilibrate rapidly to minimize the dilution effect (38). For alfentanil, fentanyl and sufentanil (i.e. drugs that undergo hepatic biotransformation and elimination), CPB is associated with marked changes in pharmacokinetic properties. After CPB, the elimination half-life of fentanyl is prolonged, plasma clearance is decreased, and volume of distribution is increased (39, 40). Alfentanil, CPB appears to prolong the elimination half-life and increase the volume of distribution, whereas clearance is unchanged (39, 44). Free alfentanil concentrations remain relatively stable throughout CPB and pharmacologically active concentration remains unchanged (38). Remifentanyl kinetics appears to be minimally affected by CPB with no change in the volume of distribution at steady state, the volume of the central compartment, or the elimination half-life (39). Target effect site concentration of

remifentanyl commonly used in TIVA vary. A target of 2-3mcg/L is adequate for laryngoscopy, 6-8mcg/L for laparotomy, and 10-12mcg/L for ablating the stress response associated with cardiac surgery (45).

Context sensitive half time (CSHT) is defined as the time taken for blood plasma concentration of a drug to decline by 50% after an infusion designed to maintain a state has stopped. CSHT is important when TIVA is used. Fentanyl has a short CSHT when given by infusion for a short time, but, this dramatically increases as the duration of the infusion increases. Alfentanil's CSHT becomes constant after 90minutes infusion. (Figure 1). Remifentanyl in contrast is context-insensitive with offset time independent of the duration of infusion because of its unique elimination by esterase cleavage.

Use of target-controlled infusion (TCI) of propofol in children

TIVA in children has been reviewed in detail recently(2). TIVA can be delivered either by using a manual infusion scheme or by using a **target-controlled infusion (TCI)**. TCI uses a real-time pharmacokinetic (PK) model to calculate the bolus dose and infusion rates, to achieve a user-defined target blood or effect site concentration. This is achieved by an infusion pump controlled by a microprocessor, which incorporates PK models with age-appropriate parameters. Comparative studies between TCI and manual infusion have shown better hemodynamic stability, lower induction dose and faster recovery with TCI (46-49).

Pediatric pharmacokinetic models

There are several **PK** models for pediatric TCI devices, among them, with Paedfusor and Kataria **datasets** the most often used (50). TCI with propofol is limited to the age group of 3 years or more for most models (51). Recently, the Paedfusor has been modified to allow use **down** to age one year and **a** lower weight limit **of** 5 kg. The Paedfusor is a prototype **TCI** system developed from a model concept developed by Schuttler whereby the clearance is adjusted for age. **In children less than age 12 years, clearance increases as age decreases (2).** In the Paedfusor, the central compartment volume and clearance have a nonlinear correlation with weight, and the size of the central compartment is quite larger compared to the Marsh pediatric (52) and Schuttler models. Thus the user enters weight and age and the pump automatically enters the correct microconstants into the three compartment PK algorithm. The accuracy of the Paedfusor system has been prospectively evaluated in 29 children aged from 1-15 scheduled for cardiac procedures (43, 46, 51) , general anesthesia was provided using **propofol** administered by the Paedfusor system. Accuracy of the system was evaluated by obtaining up to 9 arterial samples for measurement of propofol concentration both during anesthesia and in the recovery period. The predictive indices of median performance error and

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median absolute performance error of the Paedfusor system were found to be much better than those found with the adult “Diprifusor” system.

For Peer Review

Potential problems with propofol

Propofol infusion syndrome is a metabolic disease usually associated with high dose (53-56) or long duration (55, 57, 58) of propofol and low carbohydrate intake. With the impairment of mitochondrial fatty acid oxidation, ATP production will be reduced and thus build up of long chain acyl-carnitine intermediates. Propofol infusion syndrome can manifest as unexplained severe metabolic, usually lactic acidosis, rhabdomyolysis, cardiac failure, renal failure and usually of high mortality. In contrast to adults, higher target plasma and effect site concentration is needed for children to induce anesthesia and takes longer to reach the peak effect (2, 59) and slower recovery from propofol infusion (2). This creates potential problems such as lipid overload and propofol infusion syndrome, especially after a long cardiac surgery. A healthy child requires 2-3g/kg/day of lipid per day, equivalent to 4mg/kg/hour of 1% propofol in 10% soya oil. Lipid overload can be overcome by using 2% propofol solution, or by reducing soya oil to 5% from 10%, or by using propofol sparing measures such as premedication, regional blockade and/or concurrent use of systemic opioids, using target-controlled infusion, monitoring depth of anesthesia and tapering the infusion towards end of case if possible could allow more rapid recovery and may reduce such complications in children (2).

Propofol induces a drop in systemic vascular resistance, which may worsen the hemodynamics in patients with aortic stenosis, tetralogy of fallot, hypertrophic obstructive cardiomyopathy, balanced circulation or right-to-left shunt.

Also, there are considerable gaps in PK models for some drugs for ill children and for young children, infants, and neonates, so caution is needed when applying such programs to these populations. Future models will incorporate more sophisticated pharmacokinetic-pharmacodynamic algorithms. Hence, when using the TCI technique at present, the anesthesiologist must still use knowledge and experience to titrate the intravenous agents to effect to avoid awareness, pain and adverse effects (2).

Future of TIVA/TCI

The wide variability of PK parameters in the pediatric population compared to adults (46, 60) suggests that the ability of a mathematical model to predict propofol cerebral effect is limited. This variability may be attenuated by using an open-loop TCI with clinical feedback input from EEG analysis, may play this role. Despite the lack of pediatric algorithm in the BIS monitor, several studies have demonstrated a very good correlation between BIS values and measured or estimated propofol concentrations in children (59, 61, 62). Jeleazcov also reported that BIS can be used to monitor anesthetic effect produced by propofol in children above 1 year (63).

Currently, closed-loop TCI devices remain the purview of research laboratories and have not reached the open market for use in humans. One major advance reported recently was the application of mass spectroscopy to measure propofol concentrations in the exhaled breath of adult and pediatric patients (64). There is a very good correlation between the exhaled and blood concentrations of propofol.

The importance of inter-individual variability that characterizes the children population may be investigated using covariates as weight, age, height to describe metabolic processes during physiological development in pediatric PK-PD modelling (46).

Possible new formulations of propofol include emulsions that contain medium rather than long chain triglycerides (to possibly avoid propofol infusion syndrome), formulations with greater concentrations of propofol (2%) and water solution emulsions (micro-emulsions and phosphorylated propofol pro-drugs) (65).

Refinement of fast-tracking cardiac anesthesia techniques may be useful in the future. Experience with TIVA techniques in cardiac anesthesia is increasing. The next step is in making TCI equipment and pediatric software more widely available.

Clinical example of TIVA for pediatric cardiac anesthesia in the Royal Hospital for Sick Children, Glasgow

After preoperative assessment and patient preparation, we insert an intravenous cannula after EMLA cream application. Alternatively, we can perform inhalational induction with sevoflurane prior to iv catheter insertion. In order to reduce injection pain of 2% propofol, we preinject lignocaine 0.2mg/kg and alfentanil 10-20microgram/kg, wait for around one minute and then start a blood- targeted infusion of 2% propofol using an Alaris PK pump programmed with the Paedfusor dataset. An initial set blood target concentration of 2micrograms/ml delivers a loading bolus dose of approximately 1mg/kg. We assess the patient's response, titrate up the target concentration by increments of 1micrograms/ml to achieve the desired induction conditions. Pancuronium is used for muscle relaxation as it counteracts any tendency of the induction agents to reduce heart rate. We taper our TCI target during vascular access.

Alfentanil will be titrated manually prior to sternotomy to a total of 50micrograms/kg, then maintained with an infusion of 1-5micrograms/kg/min, alfentanil is maintained during surgery and bypass with additional increments of 10 micrograms/kg prior to surgical stimulation, sternotomy, chest closure, drain insertion etc. The propofol target is maintained around 3micrograms/ml during bypass. Since propofol is a vasodilator, systemic vascular resistance is reduced and caution must be exercised during concomitant use of other vasodilators such as milrinone. Morphine and midazolam are typically given 30-60 minutes prior to discharge to the pediatric intensive care unit to assist transitioning to ongoing sedation and analgesia.

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Cover letter

Black ink: Reviewer’s comment and blue ink are my response (blue ink in manuscript are new changes)

P.3 sequence of paragraph of opioids, propofol and ketamine has been rearranged. With Ketamine first, then propofol and finally opioids

P.3 Subheading of Ketamine, propofol and opioids created

P.5 Subheading of Preconditioning added

P.7 Reviewer: deleted “The volume of the prime and reservoir varies with age from around 350ml in the neonate to 1500ml in the adults.

Sentence deleted

P.7 Reviewer: ***Volatile anesthetic agents paragraph to be deleted***

The effect of CPB on MAC remains uncertain; electroencephalogram changes have been demonstrated in humans during CPB at relatively low isoflurane concentrations and it has been suggested that there may be enhanced sensitivity to isoflurane, possibly because of increased distribution to the brain (38, 41). Hemodilution with a crystalloid prime which decreased PCV from 40% to 20% would result in a 30% decrease in blood-gas solubility (42). Hypothermia causes 4-5% increase in blood solubility per °C. The predicted net change in solubility of isoflurane with crystalloid prime to hematocrit 20% and hypothermia from 37 to 28°C is +2%(38, 42). Volatile agent started during hypothermic CPB takes longer to equilibrate and agents already in use need to re-equilibrate, potentially changing the depth of anesthesia, until equilibration is complete. As these agents are metabolized to a small degree and washout is fast, the duration of action is not prolonged after CPB (38).

Paragraph deleted

P.14 Line 17 Review: delete “ will be”

“will be” deleted and changed to “is”

P.14 Line 18 Reviewer: delete “we expect a low” and changed to “systemic vascular resistance is reduced”

“we expect a low” deleted, changed to “Systemic vascular resistance is reduced”

P.14 Line 18 Reviewer: delete “so have to beware ” and changed into “caution must be exercised during”

Done

P.14 Line 18 Reviewer: add “other”

Done

P.14 Line18: Reviewer: delete “ including ACE inhibitors”

Done

P.14 Line 19 Reviewer: delete “Dopamine and noradrenaline may be needed to avoid exacerbating right to left shunt with low systemic vascular resistance and if low diastolic pressure may be hazardous for the lesion.”

Deleted

P.14 Line 20 Reviewer: delete “will be” and change to “are typically”

Done

Cover Letter

Total Intravenous Anesthesia (TIVA) in pediatric cardiac anesthesia

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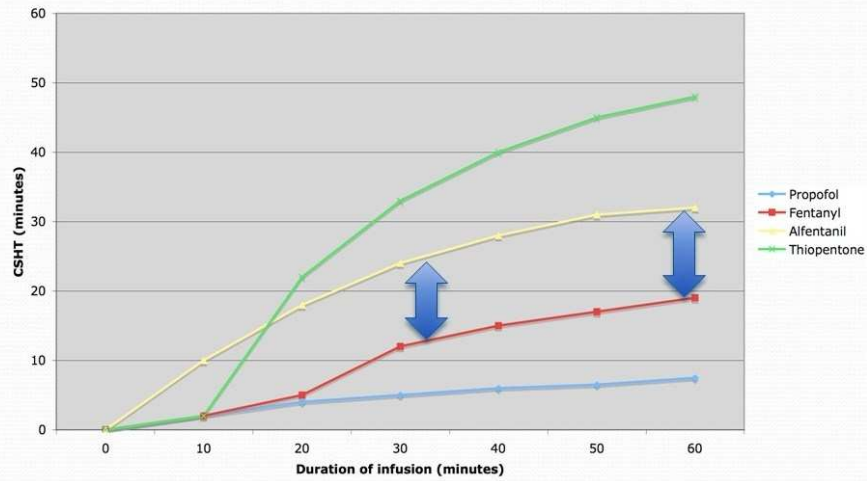


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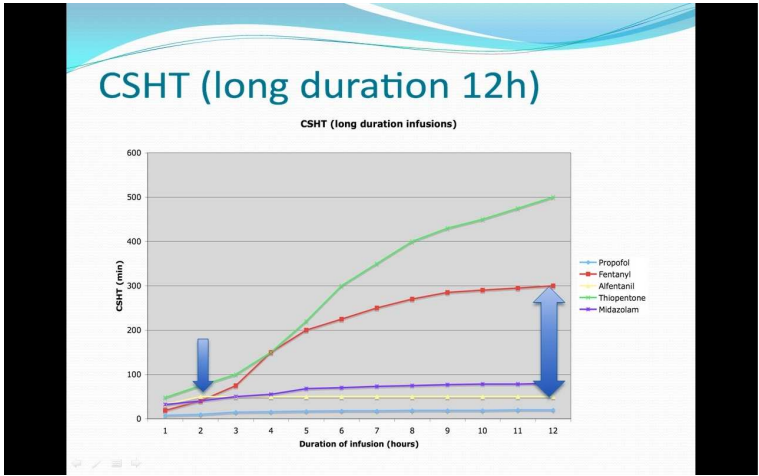
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CSHT (short duration 60 min)

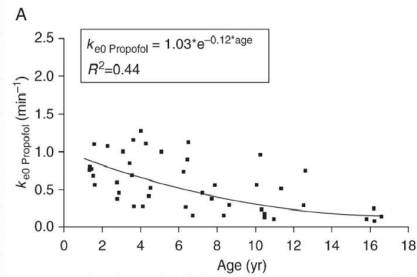
CSHT (short duration infusions)



274x175mm (96 x 96 DPI)



449x211mm (96 x 96 DPI)

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449x169mm (96 x 96 DPI)

Table 1

Context sensitive half times (CSHT) of opioids in children [adopted from V. Mani, N Morton Overview of total intravenous anesthesia in children. Pediatric Anesthesia 2010; 20:211-222]

Infusion duration (minutes)	10	100	200	300	600
Remifentanil	3-6	3-6	3-6	3-6	3-6
Alfentanyl	10	45	55	58	60
Fentanyl	12	30	100	200	
Sulfentanil		20	25	35	60

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