



**HAL**  
open science

## Total Intravenous Anesthesia (TIVA) in pediatric cardiac anesthesia

Grace Lai Sze Wong

► **To cite this version:**

Grace Lai Sze Wong. Total Intravenous Anesthesia (TIVA) in pediatric cardiac anesthesia. *Pediatric Anesthesia*, 2011, 15 (s1 CV), pp.560. 10.1111/j.1460-9592.2011.03565.x . hal-00623320

**HAL Id: hal-00623320**

**<https://hal.science/hal-00623320v1>**

Submitted on 14 Sep 2011

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Pediatric Anesthesia

## Total Intravenous Anesthesia (TIVA) in pediatric cardiac anesthesia

Journal:	<i>Pediatric Anesthesia</i>
Manuscript ID:	PAN-2010-0418.R2
Wiley - Manuscript type:	Review (commissioned)
Date Submitted by the Author:	21-Jan-2011
Complete List of Authors:	Wong, Grace; Royal Hospital of Sick Children, Glasgow, Department of Anaesthesia; Queen Mary Hospital, Department of Anaesthesiology
Key Words:	TIVA, Pediatric, propofol, cardiac surgery

SCHOLARONE™  
Manuscripts

view

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

*Title Page*

*Total Intravenous Anesthesia (TIVA) in pediatric cardiac anesthesia*

Grace L S Wong, MB BS, FANZCA, FHKCA, FHKAM(Anaes) \*, Neil S Morton,  
MB ChB, MD, FRCA, FRCPCH, FFFPMRCA#

\*Senior Clinical Fellow in Pediatric Anesthesia and #Consultant & Reader in  
Pediatric Anesthesia & Pain management, Department of Anesthesia, Royal Hospital  
for Sick Children, Yorkhill, Glasgow, UK

Correspondence author\*: Grace L S Wong

Correspondence email: [gracewong531@hotmail.com](mailto:gracewong531@hotmail.com)

Correspondence postal address: Flat F, 9/FI, Block 6, Beacon Heights, 6 Lung Ping  
Road, Kowloon Tong, Hong Kong

'The enclosed manuscript has been read and approved by all authors, it is not under active  
consideration for publication elsewhere, has not been accepted for publication, nor has it been  
published in full or in part (except in abstract form).'

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

### *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

1  
2  
3  
4 Total intravenous anesthesia (TIVA) (1, 2) is useful for certain pediatric cardiac procedures  
5 and has become more feasible with improved infusion pump design, more appropriate  
6 pediatric software and more clinical experience. There is a better understanding of the  
7 pharmacodynamics and pharmacokinetics of intravenous anesthetic agents in children  
8 undergoing cardiopulmonary bypass and potential beneficial effects of these agents.  
9  
10  
11  
12  
13  
14  
15  
16

### 17 *Pharmacodynamic effects of anesthetic agents during cardiac surgery*

18  
19 Cardiopulmonary bypass (CPB) may be associated with multi-organ damage, resulting in  
20 both immediate and long term effects (3, 4). This damage may be related in part to inadequate  
21 regional tissue oxygen delivery, and also to the “stress response” during and after CPB(3).  
22  
23 Reduction in the stress response to cardiac surgery in neonates and children is associated with  
24 improved postoperative outcome (3, 5-9). Damage caused by inadequate oxygen delivery and  
25 tissue hypoxia may be reduced by metabolic depression using both hypothermia and  
26 anesthetic agents. These effects may be additive; for example, cerebral metabolic depression,  
27 in addition to that caused by hypothermia, may be produced with thiopentone or propofol or  
28 isoflurane titrated to EEG suppression during CPB (3, 10). With thiopentone, this may result  
29 in reduced cerebral damage(3, 11). **However, in order to achieve EEG suppression, a large  
30 dose of thiopentone is usually required, which can produce hemodynamic instability,  
31 prolonged anesthetic effects, delayed tracheal extubation and increased sedation during the  
32 first few postoperative days(11).**  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49

### 50 *Cardiovascular effects of ketamine, propofol and opioids*

#### 51 Ketamine

52  
53 Ketamine is frequently chosen for anesthetic induction in patients with cyanotic conditions, as  
54 it increases systemic vascular resistance and cardiac output but without worsening right to left  
55 shunting(12). A recent prospective, randomized study by Tugrul et al. (13) demonstrated that  
56 ketamine anesthesia provided more stable precardiopulmonary bypass conditions than  
57  
58  
59  
60

1  
2  
3 isoflurane anesthesia. Arterial oxygen tension, oxygen saturation and mean arterial pressure  
4  
5 were better maintained poststernotomy in those patients receiving ketamine(13). Ketamine  
6  
7 does not significantly increase the pulmonary vascular resistance in children with pulmonary  
8  
9 hypertension(14) .

### 12 Propofol

14 Propofol, has a short half-life and context-sensitive half time and when given by infusion with  
15  
16 opioids, propofol can significantly attenuate the adverse hemodynamic and metabolic effects  
17  
18 of bypass and surgery while producing rapid smooth recovery and transition to postoperative  
19  
20 care(1). Propofol reduces whole body oxygen uptake during hypothermic CPB (28°C ) in  
21  
22 adults (3, 15), reduces cerebral perfusion pressure, oxidative stress, cerebral blood flow,  
23  
24 velocity and microembolic delivery. Propofol has also been shown to suppress seizures(3, 16,  
25  
26 17) and may act as an oxygen free radical scavenger (3, 18). Propofol during CPB caused  
27  
28 significant increases in mixed venous oxygen saturation, significant reductions in systemic  
29  
30 oxygen uptake, reduction in glucose and cortisol concentrations with no difference in lactate  
31  
32 concentrations, mean arterial pressure during CPB and inotrope requirement after CPB, or in  
33  
34 recovery times (3). Catecholamine and cortisol are released during stress that produces  
35  
36 alterations in microvascular permeability and multi-organ damage(3, 19, 20). These hormonal  
37  
38 changes also result in hyperglycemia, which is known to worsen neurological outcome after  
39  
40 cerebral ischemia (3). During rewarming and normothermia, propofol can prevent  
41  
42 hyperglycemia, attenuate the stress response and produce rapid recovery(3). Propofol can be  
43  
44 used in patients with or at risk of long QT syndrome without increasing the risk of torsades  
45  
46 de pointes (TdP)(21).

51 Propofol produces arterial and venous dilation, both in systemic and pulmonary circulation.  
52  
53 These effects will be more prominent with the concomitant use of other vasodilators like  
54  
55 alpha blockers, phosphodiesterase(PDE) III inhibitors, and angiotensin converting enzymes  
56  
57 (ACE) inhibitors. These circulatory effects can be modulated by optimizing the patient's  
58  
59  
60

1  
2  
3 intravascular volume, by surgical stimulation, propofol dose increments and the rate of dose  
4  
5 changes.

### 6 7 Opioids

8  
9 Opioids do not cause myocardial depression and protect the heart by a preconditioning-like  
10 mechanism and therefore concurrent administration of opioids with either propofol or volatile  
11 agents produces an additive effect (22).  
12  
13  
14  
15  
16  
17

### 18 *Preconditioning*

19  
20 Previous exposure of the brain and myocardium to minor insults, chemicals, or  
21 pharmacological agents can “precondition” or increase the tolerance of neural and cardiac  
22 cells to lethal ischemic injury. Preconditioning with either volatile or intravenous agents may  
23 be advantageous. Some volatile agents, most notably isoflurane, when given before an  
24 ischemic insult have been found to induce ischemic tolerance in the brain and spinal cord (23-  
25 26), and to prevent ischemia-reperfusion(I/R) myocardial injury (27). There are several  
26 proposed mechanisms for protection (e.g. attenuating calcium overload, anti-inflammatory  
27 and antioxidant effects, pre- and post-conditioning-like protection) (22). Anesthetic  
28 preconditioning with volatile anesthetics improves recovery of contractile function and  
29 reduced calcium overload after ischemia/reperfusion(28). Clarke et al (29) showed recently  
30 that a critical factor mediating reperfusion injury of the heart is the mitochondrial  
31 permeability transition pore (MPTP). The opening of the MPTP causes mitochondrial  
32 swelling with release of proapoptotic proteins and uncoupling of mitochondrial oxidative  
33 phosphorylation. The resulting ATP deprivation causes disruption of ionic homeostasis and  
34 contractile function and ultimately sarcolemma rupture and necrosis. Inhibition of MPTP  
35 opening during reperfusion protects hearts from reperfusion injury.  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54

55 Propofol has been shown to protect the heart against cardiac insults in a variety of  
56 experimental models (30-32). These effects are attributed to its ability to act as a free radical  
57 scavenger (33), enhancing tissue antioxidant capacity(34), and through inhibition of plasma  
58 membrane calcium channels (35, 36). Its antioxidant properties are responsible for its  
59  
60

1  
2  
3 inhibitory action of **MPTP** opening in the Langendorff perfused rat heart (30), and its  
4  
5 antiapoptotic properties (36). The clinical benefits of propofol's antioxidant capacity during  
6  
7 cardiopulmonary bypass are more evident when using a high maintenance dose (plasma levels  
8  
9 of approximate 4.2ng/ml) by Xia et al (37). Propofol protects the myocardium against  
10  
11 ischemia-reperfusion injury, due to its antioxidant effect and inhibition of the MPTP.  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For Peer Review



### *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

1  
2  
3 may remain unchanged. A prolonged elimination half-life has been demonstrated in one  
4 study, but the redistribution half-life was short, concentration decreased rapidly after stopping  
5 the drug and patients made a rapid recovery. In general, the free active concentrations of these  
6 drugs remain unchanged but their action may be prolonged (38, 41, 42).  
7  
8

9  
10 In a prospective trial of the accuracy of a pediatric target-controlled infusion of propofol  
11 which employed the Paedfusor pharmacokinetic dataset (43), children did not show a  
12 significant change in pharmacodynamic effect (level of consciousness), because, even in  
13 small children, the volume of bypass circuit and reservoir is small in comparison with the  
14 volume of the central and other compartments. For example, in a child weighing 10kg, the  
15 volume of prime would be 270ml, whereas the volumes of the theoretical central, second and  
16 third compartments would be 4600, 1340 and 8200ml respectively (43). Developments are  
17 underway to allow effect-site targeting in children(2).  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30

### 31 *Opioids*

32  
33 All opioids show a decrease in total drug concentration on commencing CPB. The degree of  
34 this decrease is greater with fentanyl where a significant proportion of the drug adheres to the  
35 surface of the CPB circuit (38). The decrease is least with opioids that have a high volume of  
36 distribution when the addition of the prime volume is less important and in those that can  
37 equilibrate rapidly to minimize the dilution effect (38). For alfentanil, fentanyl and  
38 sulfentanil (i.e. drugs that undergo hepatic biotransformation and elimination), CPB is  
39 associated with marked changes in pharmacokinetic properties. After CPB, the elimination  
40 half-life of fentanyl is prolonged, plasma clearance is decreased, and volume of distribution is  
41 increased (39, 40). Alfentanil, CPB appears to prolong the elimination half-life and increase  
42 the volume of distribution, whereas clearance is unchanged (39, 44). Free alfentanil  
43 concentrations remain relatively stable throughout CPB and pharmacologically active  
44 concentration remains unchanged (38). Remifentanyl kinetics appears to be minimally  
45 affected by CPB with no change in the volume of distribution at steady state, the volume of  
46 the central compartment, or the elimination half-life (39). Target effect site concentration of  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 remifentanil commonly used in TIVA vary. A target of 2-3mcg/L is adequate for  
4 laryngoscopy, 6-8mcg/L for laparotomy, and 10-12mcg/L for ablating the stress response  
5 associated with cardiac surgery (45).  
6  
7

8  
9  
10 Context sensitive half time (CSHT) is defined as the time taken for blood plasma  
11 concentration of a drug to decline by 50% after an infusion designed to maintain a state has  
12 stopped. CSHT is important when TIVA is used. Fentanyl has a short CSHT when given by  
13 infusion for a short time, but, this dramatically increases as the duration of the infusion  
14 increases. Alfentanil's CSHT becomes constant after 90minutes infusion. (Figure 1).  
15  
16  
17  
18  
19  
20  
21 Remifentanil in contrast is context-inssensitive with offset time independent of the duration of  
22 infusion because of its unique elimination by esterase cleavage.  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

### *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

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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.

1  
2  
3  
4 *Clinical example of TIVA for pediatric cardiac anesthesia in the Royal Hospital for Sick*  
5  
6 *Children, Glasgow*  
7

8  
9 After preoperative assessment and patient preparation, we insert an intravenous cannula after  
10 EMLA cream application. *Alternatively, we can perform inhalational induction with*  
11 *sevoflurane prior to iv catheter insertion.* In order to reduce injection pain of 2% propofol, we  
12 preinject lignocaine 0.2mg/kg and alfentanil 10-20microgram/kg, *wait for around one minute*  
13 *and then start a blood- targeted infusion of 2% propofol using an Alaris PK pump*  
14 *programmed with the Paedfusor dataset. An initial set blood target concentration of*  
15 *2micrograms/ml delivers a loading bolus dose of approximately 1mg/kg. We assess the*  
16 *patient's response, titrate up the target concentration by increments of 1micrograms/ml to*  
17 *achieve the desired induction conditions. Pancuronium is used for muscle relaxation as it*  
18 *counteracts any tendency of the induction agents to reduce heart rate. We taper our TCI target*  
19 *during vascular access.*  
20  
21

22 Alfentanil *will be titrated manually* prior to sternotomy to a total of 50micrograms/kg, then  
23 maintained with an infusion *of 1-5micrograms/kg/min, alfentanil is maintained* during surgery  
24 *and bypass* with additional increments of 10 micrograms/kg prior to surgical stimulation,  
25 sternotomy, chest closure, drain insertion etc. *The propofol target is maintained* around  
26 3micrograms/ml during bypass. Since propofol is a vasodilator, *systemic vascular resistance*  
27 *is reduced and caution must be exercised during concomitant use of other vasodilators such as*  
28 *milrinone. Morphine and midazolam are typically given* 30-60 minutes prior to discharge to  
29 the pediatric intensive care unit to assist transitioning to ongoing sedation and analgesia.  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



## References

- 1 Anderson BJ, Hodkinson B. Are there still limitations for the use of target-controlled infusion in children? *Current Opinion in Anaesthesiology* 2010; **23**: 356-362.
- 2 Mani V, Morton NS. Overview of total intravenous anesthesia in children. *Pediatric anesthesia* 2010; **20**: 211-222.
- 3 Laycock GJA, Mitchell IM, Paton RD, *et al.* EEG burst suppression with propofol during cardiopulmonary bypass in children: A study of the haemodynamic, metabolic and endocrine effects. *British Journal of Anaesthesia* 1992; **69**: 356-362.
- 4 Tinker JH. Cardiopulmonary bypass: Current concepts and controversies. In: Goview AV, ed. *Central nervous system complications after cardiopulmonary bypass*. Philadelphia: W.B. Saunders, 1989:41-68.
- 5 Anand KJS, Sippell WG, Aynsley-Green A. Randomised trial of fentanyl anesthesia in preterm babies undergoing surgery: Effects on the stress response. *Lancet* 1987; **1**: 243-247.
- 6 Anand KJS, Sippell WG, Schofield NM, *et al.* Does halothane anesthesia decrease the metabolic and endocrine stress responses of newborn infants undergoing operation? *British Medical Journal* 1988; **296**: 668-672.
- 7 Anand KJ, Hansen DD, PR H. Hormonal-metabolic stress responses in neonates undergoing cardiac surgery. *Anesthesiology* 1990; **73**: 661-670.
- 8 Anand KJ, A A-G. Measuring the severity of surgical stress in newborn infants. *Journal of pediatric surgery* 1988; **23**: 297-305.
- 9 Anand KJ, PR H. Halothane-morphine compared with high-dose sulfentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery. *New England Journal of Medicine* 1992; **326**: 1-9.
- 10 Woodcock TE, Murkin JM, Farrar JK, *et al.* Pharmacological EEG suppression during cardiopulmonary bypass: cerebral hemodynamic and metabolic effects of thiopental or isoflurane during hypothermia and normothermia. *Anesthesiology* 1987; **67**: 218-224.
- 11 Nussmeier NA, Arlund C, Alston RP. EEG suppression induced by propofol during hypothermic cardiopulmonary bypass. *Journal of cardiothoracic anesthesia* 1990; **4**: 106.
- 12 Miller R. Anaesthesia. In: Greeley W, Kern F, eds. *Anesthesia for pediatric cardiac surgery*, 4th edn. New York: Churchill Livingstone, 1994:1811-1850.
- 13 Tugrul M, Camci E, Pembeci K. Ketamine infusion versus isoflurane for the maintenance of anesthesia in the prebypass period in children with tetralogy of Fallot. *Journal of cardiothoracic Vascular Anesthesia* 2000; **14**: 557-561.
- 14 Glyn D. Williams, Bridget M. Philip, Larry F. Chu, *et al.* Ketamine does not increase the pulmonary vascular resistance in children with pulmonary hypertension. *Anaesthesia and analgesia* 2007; **105**: 1578-1584.
- 15 Laycock GJA, Alston RP. Propofol during hypothermic cardiopulmonary bypass: Effects on hemodynamics and metabolism. *Journal of cardiothoracic anesthesia* 1990; **4**: 105.
- 16 Lawson S, Gent JP, Goodchild CS. Anticonvulsant properties of propofol and thiopentone: Comparison using tow tests in laboratory mice. *British Journal of Anaesthesia* 1990; **64**: 59-63.
- 17 Mackenzie S, Kapadia F, Grant IS. Propofol infusion for control of status epilepticus. *Anesthesia* 1990; **45**: 1043-1045.

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
- 18 Murphy PG, Myers D, Webster NR, *et al.* The antioxidant potential of propofol. *British Journal of Anaesthesia* 1991; **67**: 209P.
- 19 Tinker JH. Cardiopulmonary bypass: Current concepts and controversies. In: Kirklin JK, ed. *The Postperfusion syndrome: INflammation and the damaging effects of cardiopulmonary bypass*. Philadelphia: W.B. Saunders, 1989:131-146.
- 20 Tinker JH. Cardiopulmonary bypass: Current Concepts and Controversies. In: Reves JG, Croughwell N, Jacobs JR, *et al.*, eds. *Anesthesia during cardiopulmonary bypass: does it matter?* Philadelphia: W. B. Saunders, 1989:69-97.
- 21 Whyte SD, Booker PD, Buckley DG. The effects of propofol and sevoflurane on the OT interval and transmural dispersion of repolarization in children. *Anesthesia and Analgesia* 2005; **100**: 71-77.
- 22 Suleiman M-S, Zacharowski K, Angelini GD. Inflammatory response and cardioprotection during open-heart surgery: the importance of anaesthetics. *British Journal of Pharmacology* 2008; **153**: 21-33.
- 23 Sang H, Cao L, Qiu P, *et al.* Isoflurane produces delayed preconditioning against spinal cord ischemic injury via release of free radicals in rabbits. *Anaesthesiology* 2006; **105**: 953-960.
- 24 Wang L, Traystman RJ, Murphy SJ. Inhalational anesthetics as preconditioning agents in ischemic brain. *Current opinion in Pharmacology* 2008; **8**: 104-110.
- 25 Xiong L, Zheng Y, Wu M, *et al.* Preconditioning with isoflurane produces dose-dependent neuroprotection via activation of adenosine triphosphate-regulated potassium channels after focal cerebral ischemia in rats. *Anesthesia and Analgesia* 2003; **96**: 233-237.
- 26 Zhang HP, Yuan LB, Zhao RN, *et al.* Isoflurane preconditioning induces neuroprotection by attenuating Ubiquitin-conjugated protein aggregation in a mouse model of transient global cerebral ischemia. *Anesthesia and Analgesia* 2010; **111**: 506-514.
- 27 Julier K, da Silva R, Garcia C, *et al.* Preconditioning by sevoflurane decreases biochemical markers for myocardial and renal dysfunction in coronary artery bypass graft surgery: A double-blinded, placebo-controlled, multicenter study. *Anaesthesiology* 2003; **98**: 1315-1327.
- 28 An J, Bosnjak ZJ, Jiang MT. Myocardial protection by isoflurane preconditioning preserves Ca<sup>2+</sup> cycling proteins independent of sarcolemmal and mitochondrial K<sub>ATP</sub> channels. *Anesthesia and Analgesia* 2007; **105**: 1207-1213.
- 29 Clarke SJ, Khaliulin I, Das M, *et al.* Inhibition of mitochondrial permeability transition pore opening by ischemic preconditioning is probably mediated by reduction of oxidative stress rather than mitochondrial protein phosphorylation. *Circulation research* 2008; **102**: 1082-1090.
- 30 Javadov SA, Lim KHH, Kerr PM, *et al.* Protection of hearts from reperfusion injury by propofol is associated with inhibition of the mitochondrial permeability transition. *Cardiovascular Research* 2000; **45**: 360-369.
- 31 Kokita N, Hara A. Propofol attenuates hydrogen peroxide-induced mechanical and metabolic derangements in the isolated rat heart. *Anaesthesiology* 1996; **84**: 117-127.
- 32 Kokita N, Hara A, Abiko Y, *et al.* Propofol improves functional and metabolic recovery in ischemic reperfused isolated rat hearts. *Anesthesia and Analgesia* 1998; **86**: 252-258.
- 33 Stratford N, Murphy P. Antioxidant activity of propofol in blood from anaesthetized patients. *European Journal of Anaesthesiology* 1998; **15**: 158-160.

- 1  
2  
3  
4 34 Xia Z, Godin DV, Ansley DM. Propofol enhances ischemic tolerance of  
5 middle-aged rat hearts: effects on 15-F<sub>2t</sub>-isoprostane formation and tissue antioxidant  
6 capacity. *Cardiovascular Research* 2003; **59**: 113-121.
- 7 35 Buljubasic N, Marijic J, Berczi V, *et al.* Differential effects of etomidate,  
8 propofol, and midazolam on calcium and potassium channel currents in canine  
9 myocardial cells. *Anaesthesiology* 1996; **85**: 1092-1099.
- 10 36 Roy N, Friehs I, Cowan DB, *et al.* Dopamine induces postischemic  
11 cardiomyocyte apoptosis in vivo: An effect ameliorated by propofol. *Annals of*  
12 *Thoracic surgery* 2006; **82**: 2192-2199.
- 13 37 Xia Z, Huang Z, Ansley DM. Large-dose propofol during cardiopulmonary  
14 bypass decreases biochemical markers of myocardial injury in coronary surgery  
15 patients: A Comparison with isoflurane. *Anesthesia and Analgesia* 2006; **103**: 527-  
16 532.
- 17 38 Gedney JA, Ghosh S. Pharmacokinetics of analgesics, sedatives and  
18 anaesthetic agents during cardiopulmonary bypass. *British Journal of Anaesthesia*  
19 1995; **75**: 344-351.
- 20 39 Davis PJ, Wilson AS, Siewers RD, *et al.* The effects of cardiopulmonary  
21 bypass on remifentanyl kinetics in children undergoing atrial septal defect repair.  
22 *Anesthesia and Analgesia* 1999; **89**: 904-908.
- 23 40 Bovill JG, Sebel PS. Pharmacokinetics of high-dose fentanyl: A study in  
24 patients undergoing cardiac surgery. *British Journal of Anaesthesia* 1980; **52**: 795-  
25 801.
- 26 41 Massey NJA, Sherry KM, Oldroyd S, *et al.* Pharmacokinetics of an infusion of  
27 propofol during cardiac surgery. *British Journal of Anaesthesia* 1990; **65**: 475-479.
- 28 42 Russell GN, Wright EL, Fox MA, *et al.* Propofol-fentanyl anaesthesia for  
29 coronary artery surgery and cardiopulmonary bypass. *Anaesthesia* 1988; **44**: 205-208.
- 30 43 Absalom A, Amutike D, Lai A, *et al.* Accuracy of the "Paedfusor" in children  
31 undergoing cardiac surgery or catheterization. *British Journal of Anaesthesia* 2003;  
32 **91**: 507-513.
- 33 44 Hug CC, Burm AGL, de Lange S. Alfentanil pharmacokinetics in cardiac  
34 surgical patients. *Anesthesia and Analgesia* 1994; **78**: 231-239.
- 35 45 Sammartino M, Garra R, Sbaraglia F, *et al.* Remifentanyl in children. *Pediatric*  
36 *anesthesia* 2010; **20**: 246-255.
- 37 46 Constant I, Rigouzzo A. Which model for propofol TCI in children. *Pediatric*  
38 *anesthesia* 2010; **20**: 233-239.
- 39 47 Hentgen E, Houfani M, Billard V, *et al.* Propofol-Sufentanil anesthesia for  
40 thyroid surgery: Optimal concentrations for hemodynamic and electroencephalogram  
41 stability, and recovery. *Anesthesia and Analgesia* 2002; **95**: 597-605.
- 42 48 Passot S, Servin F, Allary R, *et al.* Target-controlled versus manually-  
43 controlled infusion of propofol for direct laryngoscopy and bronchoscopy. *Anesthesia*  
44 *and Analgesia* 2002; **94**: 1212-1216.
- 45 49 Servin FS. TCI compared with manually controlled infusion of propofol: a  
46 multicentre study. *Anesthesia* 1998; **53**: 82-86.
- 47 50 Varveris DA, Morton NS. Target controlled infusion of propofol for induction  
48 and maintenance of anaesthesia using the paedfusor: an open pilot study. *Pediatric*  
49 *anesthesia* 2002; **12**: 589-593.
- 50 51 Absalom A, Kenny G. "Paedfusor" pharmacokinetic data set. *British Journal*  
51 *of Anaesthesia* 2005; **95**: 110-113.
- 52 52 Marsh B, White M, Morton NS, *et al.* Pharmacokinetic model driven infusion  
53 of propofol in children. *British Journal of Anaesthesia* 1991; **67**: 41-48.
- 54  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4 53 Burow BK, Johnson ME, Packer DL. Metabolic acidosis associated with  
5 propofol in the absence of other causative factors. *Anaesthesiology* 2004; **101**: 239-  
6 241.
- 7 54 Liolios A, Guerit J-M, Scholtes J-L, *et al.* Propofol infusion syndrome  
8 associated with short term large dose infusion during surgical anesthesia in an adult.  
9 *Anesthesia and Analgesia* 2005; **100**: 1804-1806.
- 10 55 Rozet I, Lam AM. Propofol infusion syndrome or probably overinterpretation  
11 syndrome? *Anaesthesiology* 2008; **108**: 330.
- 12 56 Salengros J-C, Velghe-Lenelle CE, Bollens R, *et al.* lactic acidosis during  
13 propofol-remifentanil anesthesia in an adult. *Anaesthesiology* 2004; **101**: 241-243.
- 14 57 Cremer OL, Moons KGM, Bouman EAC, *et al.* Long term propofol infusion  
15 and cardiac failure in adult head-injured patients. *Lancet* 2001; **357**: 117-118.
- 16 58 Merz TM, Regli B, Rothen HU. Propofol infusion syndrome-A fatal case at a  
17 low infusion dose. *Anesthesia and Analgesia* 2006; **103**: 1050.
- 18 59 Jeleazcov C, Ihmsen H, Schmidt J, *et al.* Pharmacodynamic modelling of the  
19 bispectral index response to propofol-based anaesthesia during general surgery in  
20 children. *British Journal of Anaesthesia* 2008; **100**: 509-516.
- 21 60 Hu C, Horstman DJ, Shafer SL. Variability of target-controlled infusion is less  
22 than the variability afterbolus injection. *Anaesthesiology* 2005; **102**: 639-645.
- 23 61 Powers KS, Nazarian EB, Tapyrik SA, *et al.* Bispectral index as a guide for  
24 titration of propofol during procedural sedation among children. *Pediatrics* 2005; **115**:  
25 1666-1674.
- 26 62 Rigouzzo A, Girault L, Louvet N, *et al.* The relationship between bispectral  
27 index and propofol during target-controlled infusion anesthesia: A comparative study  
28 between children and young adults. *Anesthesia and Analgesia* 2008; **106**: 1109-1116.
- 29 63 Munoz HR, Cortinez LI, Ibacache ME, *et al.* Effect site concentrations of  
30 propofol producing hypnosis in children and adults: comparison using the bispectral  
31 index. *Acta Anaesthesiology Scandinavia* 2006; **50**: 882-887.
- 32 64 Hornuss C, Praun S, Villinger J, *et al.* Real-time monitoring of propofol in  
33 expired air in humans undergoing total intravenous anesthesia. *Anaesthesiology* 2007;  
34 **106**: 665-674.
- 35 65 Lerman J. TIVA, TCI, and pediatrics: where are we and where are we going?  
36 *Pediatric anesthesia* 2010; **20**: 273-278.  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 **Cover letter**  
4

5 Black ink: Reviewer's comment and blue ink are my response (blue ink in manuscript are new changes)  
6

7  
8 P.3 sequence of paragraph of opioids, propofol and ketamine has been rearranged. With Ketamine first,  
9 then propofol and finally opioids  
10

11 P.3 Subheading of Ketamine, propofol and opioids created  
12

13 P.5 Subheading of Preconditioning added  
14

15  
16 P.7 Reviewer: deleted "The volume of the prime and reservoir varies with age from around 350ml in the  
17 neonate to 1500ml in the adults.  
18

19 Sentence deleted  
20

21 P.7 Reviewer: ***Volatile anesthetic agents paragraph to be deleted***  
22  
23

24 The effect of CPB on MAC remains uncertain; electroencephalogram changes have been demonstrated  
25  
26 in humans during CPB at relatively low isoflurane concentrations and it has been suggested that there  
27  
28 may be enhanced sensitivity to isoflurane, possibly because of increased distribution to the brain (38,  
29  
30 41). Hemodilution with a crystalloid prime which decreased PCV from 40% to 20% would result in a 30%  
31  
32 decrease in blood-gas solubility (42). Hypothermia causes 4-5% increase in blood solubility per °C. The  
33  
34 predicted net change in solubility of isoflurane with crystalloid prime to hematocrit 20% and  
35  
36 hypothermia from 37 to 28°C is +2%(38, 42). Volatile agent started during hypothermic CPB takes  
37  
38 longer to equilibrate and agents already in use need to re-equilibrate, potentially changing the depth of  
39  
40 anesthesia, until equilibration is complete. As these agents are metabolized to a small degree and  
41  
42 washout is fast, the duration of action is not prolonged after CPB (38).  
43  
44  
45  
46  
47

48 Paragraph deleted  
49

50  
51 P.14 Line 17 Review: delete " will be"  
52

53  
54  
55 "will be" deleted and changed to "is"  
56  
57  
58  
59  
60

1  
2  
3 P.14 Line 18 Reviewer: delete “we expect a low” and changed to “systemic vascular resistance is  
4 reduced”  
5  
6

7  
8  
9 “we expect a low” deleted, changed to “Systemic vascular resistance is reduced”  
10

11  
12 P.14 Line 18 Reviewer: delete “so have to beware “ and changed into “caution must be exercised  
13 during”  
14  
15

16  
17 Done  
18

19  
20 P.14 Line 18 Reviewer: add”other”  
21  
22

23  
24 Done  
25

26  
27 P.14 Line18: Reviewer: delete “ including ACE inhibitors”  
28  
29

30  
31 Done  
32

33 P.14 Line 19 Reviewer: delete “Dopamine and noradrenaline may be needed to avoid exacerbating right  
34 to left shunt with low systemic vascular resistance and if low diastolic pressure may be hazardous for the  
35 lesion.”  
36  
37

38 Deleted  
39  
40

41  
42 P.14 Line 20 Reviewer: delete “will be” and change to “are typically”  
43  
44

45  
46 Done  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27

Cover Letter

28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

*Total Intravenous Anesthesia (TIVA) in pediatric cardiac anesthesia*

Grace L S Wong, MB BS, FANZCA, FHKCA, FHKAM(Anaes) \*, Neil S Morton, MB ChB,  
MD, FRCA, FRCPCH, FFFPMRCA#

\*Senior Clinical Fellow in Pediatric Anesthesia and #Consultant & Reader in Pediatric  
Anesthesia & Pain management, Department of Anesthesia, Royal Hospital for Sick Children,  
Yorkhill, Glasgow, UK

Correspondence author\*: Grace L S Wong

Correspondence email: [gracewong531@hotmail.com](mailto:gracewong531@hotmail.com)

Correspondence postal address: Flat F, 9/F1, Block 6, Beacon Heights, 6 Lung Ping Road,  
Kowloon Tong, Hong Kong

'The enclosed manuscript has been read and approved by all authors, it is not under active consideration  
for publication elsewhere, has not been accepted for publication, nor has it been published in full or in  
part (except in abstract form).'



---

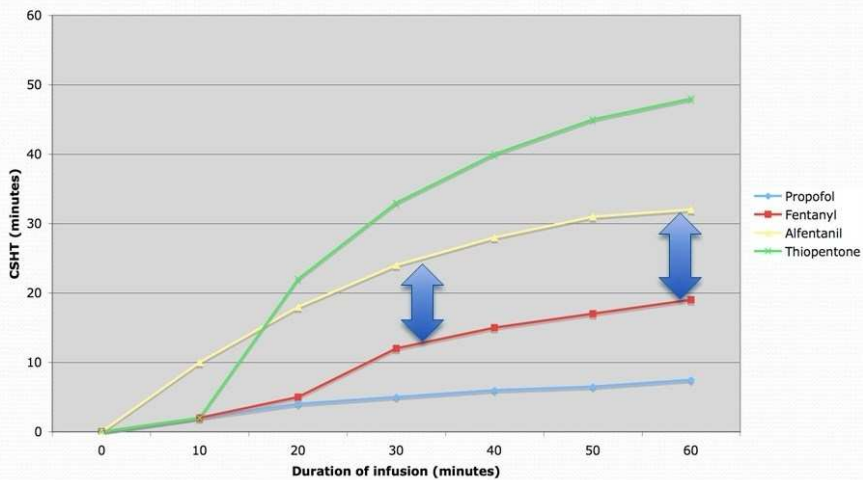
Dr Grace Lai Sze Wong

*For the Cardiovascular Themed Issue*

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

# CSHT (short duration 60 min)

CSHT (short duration infusions)

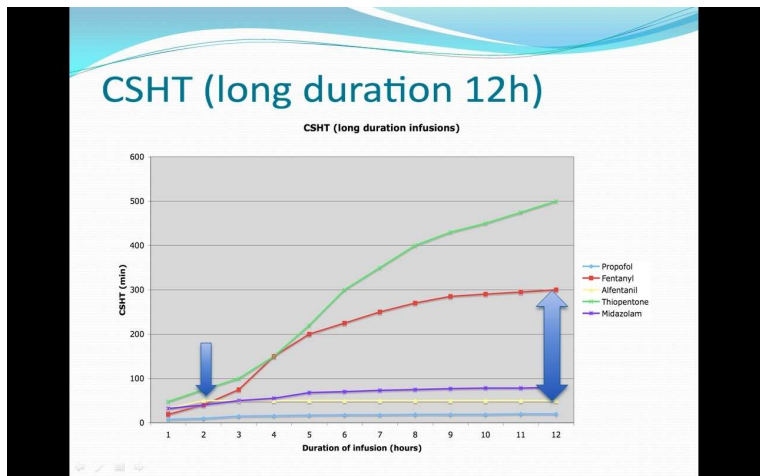


274x175mm (96 x 96 DPI)

Review



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

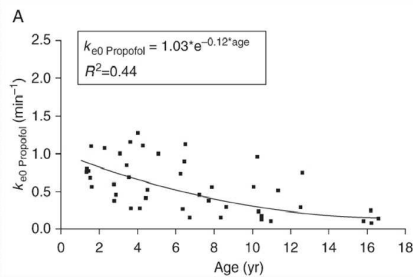


449x211mm (96 x 96 DPI)

Peer Review

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

### Age-specific $k_{e0}$



449x169mm (96 x 96 DPI)

Peer Review

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

For Peer Review

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## OXFORD UNIVERSITY PRESS LICENSE TERMS AND CONDITIONS

Aug 29, 2010

---



---

This is a License Agreement between Grace Lai Sze Wong ("You") and Oxford University Press ("Oxford University Press") provided by Copyright Clearance Center ("CCC"). The license consists of your order details, the terms and conditions provided by Oxford University Press, and the payment terms and conditions.

**All payments must be made in full to CCC. For payment instructions, please see information listed at the bottom of this form.**

License Number	2498371416913
License date	Aug 29, 2010
Licensed content publisher	Oxford University Press
Licensed content publication	British Journal of Anaesthesia
Licensed content title	Pharmacodynamic modelling of the bispectral index response to propofol-based anaesthesia during general surgery in children
Licensed content author	C. Jeleazcov, et. al.
Licensed content date	April 2008
Type of Use	Thesis/Dissertation
Institution name	
Title of your work	Total intravenous anesthesia (TIVA) in pediatric cardiac anesthesia
Publisher of your work	n/a
Expected publication date	Oct 2010
Permissions cost	0.00 GBP
Value added tax	0.00 GBP
Total	0.00 GBP
Total	0.00 GBP

1  
2  
3  
4  
5  
6  
7  
8  
9  
10

## JOHN WILEY AND SONS LICENSE TERMS AND CONDITIONS

Aug 29, 2010

---



---

11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

This is a License Agreement between Grace Lai Sze Wong ("You") and John Wiley and Sons ("John Wiley and Sons") provided by Copyright Clearance Center ("CCC"). The license consists of your order details, the terms and conditions provided by John Wiley and Sons, and the payment terms and conditions.

**All payments must be made in full to CCC. For payment instructions, please see information listed at the bottom of this form.**

License Number	2498370892882
License date	Aug 29, 2010
Licensed content publisher	John Wiley and Sons
Licensed content publication	Paediatric Anesthesia
Licensed content title	Overview of total intravenous anesthesia in children
Licensed content author	VAITHIANADAN MANI, NEIL S. MORTON
Licensed content date	Mar 1, 2010
Start page	211
End page	222
Type of use	Dissertation/Thesis
Requestor type	University/Academic
Format	Print and electronic
Portion	Figure/table
Number of figures/tables	2
Original Wiley figure/table number(s)	Figure 5 and table 3
Will you be translating?	No
Order reference number	
Total	0.00 USD