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High dose propofol enhances red cell antioxidant capacity during CPB in humans

Purpose: To compare low *vs* high dose propofol and isoflurane on red cell RBC antioxidant capacity in patients during aortocoronary bypass surgery (ACBP).

Methods: Twenty-one patients, for ACBP, were anesthetized with sufentanil 0.5-10 $\mu g \cdot kg^{-1}$ and isoflurane 0-2%; ISO = control; n=7), or sufentanil 0.3 $\mu g \cdot kg^{-1}$, propofol 1-2.5 $mg \cdot kg^{-1}$ bolus then 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ before, and 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during CPB (LO; n=7), or sufentanil 0.3 $\mu g \cdot kg^{-1}$, propofol 2-2.5 $mg \cdot kg^{-1}$ bolus then 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (HI; n=7). Venous blood was drawn pre- and post-induction, after 30 min CPB, 5, 10, and 30 min of reperfusion, and 120 min post-CPB to measure red cell antioxidant capacity (malondialdehyde (MDA) production in response to oxidative challenge with t-butyl hydrogen peroxide) and plasma propofol concentration. Pre- induction blood samples were analyzed for antioxidant effects of nitrates on red cells. The tBHP concentration response curves for RBC MDA in ISO, LO and HI were determined.

Results: Preoperative nitrate therapy did not effect RBC MDA production. Perioperative RBC MDA production was similar in ISO and LO groups. Sustained intraoperative decrease in RBC MDA was seen with propofol 8.0 ± 2.4 - 11.8 ± 4.5 $\mu g.ml^{-1}$ in HI ($P < 0.05$- 0.0001). MDA production *vs* log plasma propofol concentration was linear in HI dose.

Conclusions: During CPB, RBC antioxidant capacity is enhanced and maintained with HI dose propofol. Propofol, at this dose, may prove useful in protecting against cardiopulmonary ischemia-reperfusion injury associated with ACBP.

Objectif : Comparer une faible dose (LO) *vs* une forte dose (HI) de propofol et d'isoflurane sur la capacité antioxydante des globules rouges (GR) lors d'un pontage aortocoronarien (PAC).

Méthode : Lors d'un PAC, 21 patients ont reçu une anesthésie avec du sufentanil 0,5-10 $\mu g \cdot kg^{-1}$ et de l'isoflurane 0-2 %; (ISO = témoin, n = 7) ou du sufentanil 0,3 $\mu g \cdot kg^{-1}$, un bolus de propofol 1-2,5 $mg \cdot kg^{-1}$suivi d'une perfusion de 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ avant le PAC et de 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ pendant le PAC (LO, n = 7), ou du sufentanil 0,3 $\mu g \cdot kg^{-1}$, un bolus de propofol 2-2,5 $mg \cdot kg^{-1}$ et une perfusion de 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (HI, n = 7). Le sang veineux a été prélevé avant et après l'induction, 30 min après le PAC, à 5, 10 et 30 min pendant la reperfusion et 120 min après la CEC afin de mesurer la capacité antioxydante des GR (production de dialdéhyde malonique DAM en réponse à la provocation oxydante avec du peroxyde d'hydrogène t-butyl PHtB) et la concentration plasmatique de propofol. Les échantillons de sang prélevés avant l'induction ont été analysés pour vérifier les effets antioxydants des nitrates sur les GR. Les courbes illustrant la réaction des GR au DAM chez les patients des groupes ISO, LO et HI ont été déterminées.

Résultats : La thérapie préopératoire aux nitrates n'a pas changé la capacité antioxydante des GR, donc la production de DAM a été semblable dans les groupes ISO et LO. Une baisse peropératoire de production de DAM a toutefois été observée avec 8,0 ± 2,4 - 11,8 ± 4.5 $\mu g.ml^{-1}$ de propofol dans le groupe HI ($P < 0,05$ - 0,0001). La production de DAM *vs* le logarithme de la concentration plasmatique de propofol était linéaire dans le groupe HI.

Conclusion : Pendant la CEC, la capacité antioxydante des GR a été améliorée et maintenue par une forte dose de propofol. Administré selon cette dose, le propofol peut se révéler utile pour protéger des lésions cardio-pulmonaires liées à l'ischémie de reperfusion associée au PAC.

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Presented at the 20th Annual Meeting of the Society of Cardiovascular Anesthesiologists, April 25-29, 1998, Seattle, WA, USA.

Accepted for publication March 28, 1999

CARDIOPULMONARY dysfunction remains the major cause of perioperative morbidity and mortality after cardiac surgery. The origins of this problem are multifactorial and include ischemia-reperfusion injury (IRI).[1-7]

Interest has focused on the potential of anesthetics to protect the heart and lung against IRI, due to their ability to modify oxidant mediated cell injury.[8,9] Recently, the intravenous anesthetic, 2,6-diisopropylphenol, propofol, has been shown to have antioxidant properties.[10,11] Experimental evidence suggests propofol may protect the myocardium and lung against peroxide and peroxynitrite.[12,13] However, a recent study did not provide clinical evidence of protection with propofol anesthesia used for cardiac procedures.[14] The dose of propofol administered (50 to 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was limited by the concern that propofol may produce hypotension secondary to cardiac depression and vasodilatation. This dose may not be sufficient to achieve a protective concentration of the drug. Examination of propofol's antioxidant properties at concentrations known to convey protection against cardiopulmonary injury and the effects of this mechanism of action on clinical recovery following cardiac surgery have not been performed.

Our previous work has shown that propofol can acutely change the antioxidant capacity of red cells and that red cell antioxidant capacity may be a useful measure for optimizing the effects of antioxidant agents in experimental and clinical settings.[15] The purpose of the present study was to determine the antioxidant properties of propofol (50,100 and 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$) compared with those of isoflurane in patients undergoing aortocoronary bypass (ACBP) surgery, a setting where IRI is a risk. The effects of extracorporeal circulation on red cell antioxidant capacity are not known. The accompanying hemodilution may effect the concentration and, therefore, the level of protection offered by a given propofol dose. We hypothesize that propofol will enhance the antioxidant status of patients undergoing ACBP and that this will be reflected in the red cell susceptibility to oxidative challenge. Our question is "Under what conditions can an optimal antioxidant endpoint be achieved with propofol during cardiac surgery?" These findings should provide information that might prove useful in efforts to modify or protect against cardiopulmonary IRI.

Methods

This study was approved by the University of British Columbia Ethics Committee on Human Research and all patients gave written informed consent before participation in this trial.

Experimental design

Twenty one patients aged 35 yr and older, presenting for scheduled ACBP surgery during January to October 1997 were selected at random on Tuesdays and Thursdays and enrolled in a phase II open label study. Patients were assigned to provide seven evaluable subjects in three anesthetic groups studied in the following order: isoflurane, low propofol, then high propofol. Previous *in vitro* testing of the soya-bean oil-glycerol-lecithin drug carrier vehicle indicated no effect on malondialdehyde (MDA) formation[15] and, therefore, no Intralipid placebo was incorporated into this study design. Only patients who were hemodynamically stable with no history of evolving myocardial infarction or previous ACBP surgery were included. Patients received no aspirin or steroid therapy within seven days of surgery. No patient was taking vitamin C or E preoperatively. Five anesthesiologists and four surgeons participated in this preliminary trial. The investigators responsible for red cell (RBC) MDA analysis (DVG, MEG) were blinded to anesthetic technique.

Power analysis

We used the results of our previous swine model study to calculate the appropriate number of patients to be enrolled in each group.[15] With = 0.05 and of 0.9, and expecting a 25% inhibition of MDA production based on anticipated plasma propofol concentrations, we determined a sample size of seven patients per group for pharmacological/biological analysis and reporting.

Anesthetic technique and perioperative management

Patients received their cardiac medications, 0.04 $mg \cdot kg^{-1}$ lorazepam, 10 mg metoclopramide, and 150 mg ranitidine *po* 90 min preoperatively. Prior to induction of anesthesia, a large bore *iv* cannula and a 20 G intra-arterial cannula were inserted under local anesthesia.

Seven patients (ISO group) were anesthetized with 0.5 - 10 $\mu g \cdot kg^{-1}$ sufentanil and isoflurane, 0 - 2% end tidal, in air/oxygen (FiO_2 < 0.5), or 1- 2.5 $mg \cdot kg^{-1}$ propofol bolus followed by 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ before cardiopulmonary bypass (CPB), 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during and following CPB (low dose propofol; LO group), or 2-2.5 $mg \cdot kg^{-1}$ propofol bolus followed by 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ before and during CPB (high dose propofol; HI group). Patients receiving propofol were given 0.3 $\mu g \cdot kg^{-1}$ sufentanil at induction and 0.25-1 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ *prn* to maintain blood pressure and heart rate within ± 20% of ward control values. Pancuronium bromide, 0.8 - 1.0 $mg \cdot kg^{-1}$, was used to produce muscle relaxation. A pulmonary artery catheter was utilized in all patients. After heparinization (300 $U \cdot kg^{-1}$) and aortic and venous cannulation, CPB was initiated

using crystalloid/mannitol (50 g) prime and a membrane oxygenator at a non-pulsatile flow rate of 2 -2.8 $L \cdot m^{-2} \cdot min^{-1}$, maintaining mean arterial pressure at 55 to 70 mmHg. During bypass, the lungs were not ventilated and the endotracheal tube was open to the air, so that the lungs were flaccid and partially collapsed. The surgical technique consisted of sequential myocardial revascularization by vein and internal mammary artery grafts. Intermittent, potassium enriched, warm blood cardioplegia (4:1 blood : crystalloid ratio; 1st dose 100 meq KCl per litre crystalloid (High K^+), then 20 $meq \cdot L^{-1}$ (Low K^+) thereafter) was delivered via an aortic root cannula, every 20 min, during continuous cross- clamping of the aorta under conditions of mild hypothermia (32 - 34C) for CPB. Separation from CPB and postoperative hemodynamic stability (CI > 2.2 $L \cdot min^{-1} \cdot m^{-2}$) was achieved with dopamine, dobutamine or epinephrine at the discretion of the attending anesthesiologist.

In all patients, the lungs were artificially ventilated in the post-operative period. Weaning of artificial ventilation and extubation was done according to the standard regimen used in our Cardiac Surgery Intensive Care Unit. Postoperative sedation included morphine with 0.5 - 2.0 mg midazolam *iv*, *prn* in ISO group; 25 - 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ propofol for the other two groups. Pain was treated with 1 - 2 mg morphine *iv*, *prn*.

Blood sample collection

Venous blood was drawn for determination of red cell antioxidant capacity pre- and post- induction, after 30 min of CPB, 5, 10 and 30 min of reperfusion (ie. following release of aortic crossclamp), and 120 min post CPB. Blood for determination of plasma propofol concentration was sampled at 30 min post - induction, after 30 min of CPB, following 30 min of reperfusion and 120 min post - CPB.

Biochemical/pharmacologic blood analysis

Red cell antioxidant capacity was determined by malondialdehyde (MDA) formation in response to *in vitro* oxidative challenge with t-butyl hydrogen peroxide (1.5 mM) as previously reported.[15] The TBA assay is based on the reactivity of colourless malondialdehyde (MDA) with thiobarbituric acid (TBA) to produce a red adduct, which is measured by spectrophotometry. Briefly, following blood sampling, erythrocytes were separated by centrifugation at 3,000 rpm for five minutes at 4°C to remove plasma and white cells. The red cells were washed twice with isotonic saline containing 2.0 mM sodium azide. Aliquots of 1 ml of a 10% suspension of erythrocytes in saline-azide were pre-incubated for five minutes at 37°C.

Peroxidative challenge was induced by the addition of an equal volume (1ml) of saline-azide solution containing t-butlhydroperoxide (1.5 mM tBHP). After 30 min incubation at 37°C the reaction was terminated by the addition of 1 ml trichloroacetic acid solution 28% in 0.025 M NaOH. Colour development was achieved by boiling for 15 min, and the extent of MDA formation, an indirect measure of lipid peroxidation, was estimated from the absorbances at 532 nm. Final values for red cell MDA were determined using the method of Gilbert *et al.* by correcting for errors caused by interfering compounds: delta = (abs@532-blank@532) - 20% (abs@435- blank@435) MDA ($nmol \cdot g^{-1}$ RBC) = (delta-0.0053)/1.931 *50/RBC weight in gram.[16]

Standard concentration response curves to tBHP were determined on pre induction blood samples from each group to ensure comparability.

The red cell antioxidant capacity of pre induction blood samples was compared in patients who were treated or not treated with preoperative nitrate therapy to evaluate their potential confounding antioxidant effects.

Plasma propofol concentrations were determined by high performance liquid chromatography (HPLC) with fluorescence detection according to the methods of Plummer.

Data analysis included two way ANOVA and student's t test, with Bonferroni's correction for multiple comparisons where needed. Values are presented as mean ± SD with $P < 0.05$ and $P < 0.0125$ respectively, considered statistically significant.

Results

Patient profile

The patient characteristics, preoperative hemodynamic data, duration of cardiopulmonary bypass and aortic cross-clamping, and preoperative pharmacological profiles for the ISO, LO, and HI groups are presented in Table I. The patients were demographically similar.

Red Cell MDA and propofol concentration

The t-BHPconcentration response curves were similar for each group (Figure 1). The ED_{50} and ED_{95} for HI *vs* LO were 1.51 *vs* 1.375 and 2.25 *vs* 2.0 mM t-BHP, respectively (*P*:NS).

Pre-induction MDA levels were not different in patients who received or did not receive preoperative nitrate therapy (128 ± 32 *vs* 115 ± 15 $nM \cdot g^{-1}$ RBC; $P = 0.43$).

The peroxide induced formation of RBC MDA for each group is presented in Table II. The plasma concentrations of propofol in the intervals under investigation are included for comparison. Levels of RBC MDA were similar in the ISO and LO groups, except for 30

TABLE I Patient Profile, by Group
CPB, cardiopulmonary bypass; preCPB, prior to CPB; hematocrit-CPB, hematocrit during CPB; EF, ejection fraction; ACC, aortic cross-clamp; NYHA, New York Heart Association; MI, myocardial infarction; ACE, angiotension converting enzyme. There are no differences among groups. Mean ± SD.

	Isoflurane	*Propofol-Low*	*Propofol-High*
n	7	7	7
Sex (M/F)	6/1	6/1	7/0
Age (yr)	70 ± 2	65 ± 5	65 ± 5
Body surface area (m^2)	1.92 ± 0.1	1.94 ± 0.1	1.90 ± 0.06
Body weight (kg)	78 ± 8	79 ± 7	77 ± 4
Hematocrit - PreCPB	0.40 ± 0.02	0.41 ± 0.01	0.42 ± 0.01
Hematocrit - CPB	0.23 ± 0.01	0.24 ± 0.02	0.025 ± 0.01
Left Ventricular EF (%)	53 ± 6.3	52 ± 5.1	50 ± 4.4
Duration of CPB (min)	147 ± 12	185 ± 15	148 ± 17
Duration of ACC (min)	98 ± 8	137 ± 14	107 ± 12
NYHA Class 3 or 4	6	6	4
MI within 3 mo	2	1	2
Nitrates	6	3	6
ß-Blocker	4	5	3
ACE Inhibitor	2	1	1
Calcium Channel Blocker	5	4	5
Diuretic	1	2	0

TABLE II Red Cell MDA Production and Plasma Concentration of Propofol, by time intervals
Red cell MDA production is based on *in vitro* oxidative challenge with tBHP (1.5 mM).
There are no differences between low dose propofol and isoflurane over time, and among the three groups at the pre-induction interval. The plasma propofol concentration is higher at 30 min of CPB, 30 min post-ACC, and 120 min post-CPB in the high dose propofol group. Data are expressed as mean ± SD. *$P < 0.05$, significantly different from propofol -LO, †$P < 0.005$, significantly different from preinduction and ISO, ‡$P < 0.0001$, significantly different from ISO and propofol-LO.

	Preinduction	30' Induction	30' CPB	5' Post ACC	10' Post ACC	30' Post ACC	120' Post ACC
MDA ($nmol \cdot g^{-1}$ rbc)							
Isoflurane	122 ± 14	122 ± 13	139 ± 19	132 ± 19	131 ± 15	126 ± 16	127 ± 16
Propofol-LO	124 ± 31	92 ± 27†	124 ± 33	122 ± 38	123 ± 30	123 ± 36	124 ± 33
Propofol-HI	108 ± 5	51 ± 17†‡	43 ± 5‡	41 ± 12‡	46 ± 13‡	49 ± 13‡	81 ± 21*
Propofol ($\mu g \cdot ml^{-1}$ plasma)							
Propofol -LO		5.1 ± 2.1	4.0 ± 0.4			1.8 ± 0.4	2.2 ± 0.7
Propofol-HI		10.9 ± 4.3	11.8 ± 4.5*			8.0 ± 2.4†	3.4 ± 1.3*

min postinduction. A sustained, intra - operative decrease in MDA production was seen only in the HI group ($P < 0.05$ - 0.0001). This effect persisted at 120 min post CPB. Except at 30 min postinduction, plasma levels of propofol were higher in the HI group than in the LO group ($P < 0.05$ - 0.005). Propofol concentrations from induction to 30 min reperfusion were 5.1 ± 2.1 to 1.8 ± 0.4 $\mu g \cdot ml^{-1}$ in LO; 11.8 ± 4.5 to 8.0 ± 2.4 $\mu g \cdot ml^{-1}$ in HI. Post CPB propofol concentrations were similar in LO and HI groups (2.2 ± 0.7 $\mu g \cdot ml^{-1}$; 3.4 ± 1.3 $\mu g \cdot ml^{-1}$, respectively). A linear relationship between MDA production and log plasma propofol concentration was found only in the HI group (y = 105.7 - 58.422x ; r = 0.824) (Figure 2).

Hemodynamic effects of low and high dose propofol

Propofol use was not associated with postinduction hypotension (decrease in mean arterial pressure > 20% of control) in this series. The number of patients requiring neosynephrine to maintain mean arterial pressure between 55 and 70 mm Hg during CPB was similar in all groups (ISO = 7/7; LO = 7/7; HI = 6/7). Hemodynamic support for separation from bypass and ICU maintenance required two or more inotropes in 4/7patients in ISO, 3/7 patients in LO, and 4/7 patients in HI (P = 0.18). Epinephrine (≥0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was required in 7/14 patients receiving propofol, compared with 5/7 of patients receiving isoflurane anesthesia (P = 0.21). Cardiac index ranged

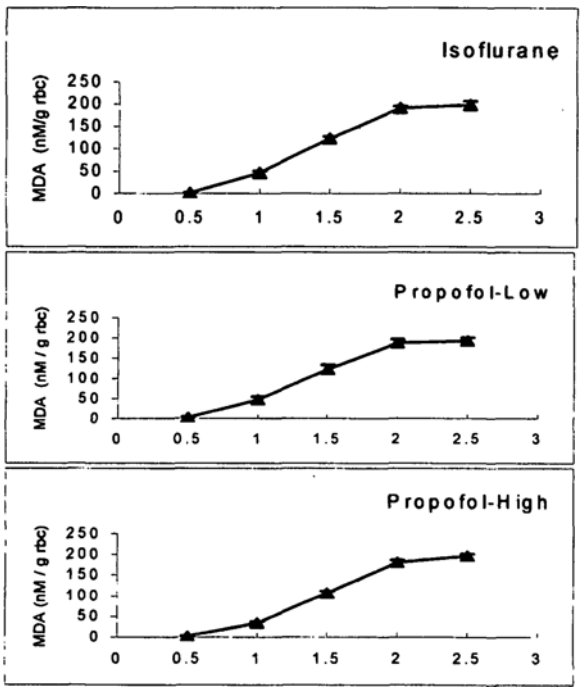

FIGURE 1 tBHP concentration response curves for each group. No differences in the characteristic response of pre-induction red cell samples to peroxidation challenge was observed between groups. Data is expressed as mean ± SD.

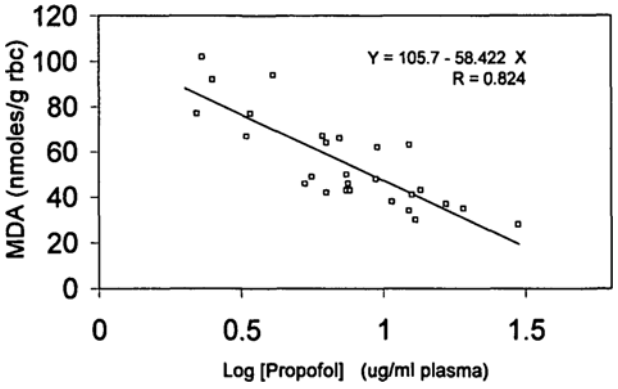

FIGURE 2 The relationship of red cell MDA production to plasma propofol concentration in patients receiving high dose propofol

from 2.4 ± 0.1 - 3.1 ± 0.2 $L \cdot min^{-1}$ m^{-2} for 24 hr postoperatively in the isoflurane group. The use of low dose propofol was associated with higher cardiac index in the first 3 to 12 hr postoperatively (3.3 ± 0.6 - 3.6 ± 0.7 $L \cdot min^{-1} \cdot m^{-2}$) compared with ISO and HI groups ($P = 0.06$). The use of high dose propofol was associated with higher cardiac index at 12 to 24 hr postoperatively (3.1 ± 0.2 - 3.8 ± 0.8 $L \cdot min^{-1} \cdot m^{-2}$) compared with ISO and LO groups ($P = 0.08$). No patients required hemodynamic support beyond 20 hr in ISO, 16 hr in LO, and 13 hr in HI ($P = 0.17$).

Discussion

This study was designed to explore the clinical utility of red cell antioxidant capacity as a tool to assess the antioxidant potential of propofol during ACBP surgery. Patients undergoing ACBP surgery are at risk for ischemia-reperfusion injury (IRI) of the heart and lung. Our interest was to determine the amount of antioxidant protection at different concentrations of propofol to be used in an expanded clinical trial. Since the effect of dose under conditions of CPB on RBC MDA are unknown, we conducted this phase of experimentation.

The principal findings of this study include the following: 1) red cell antioxidant capacity can be enhanced with propofol; 2) a sustained decrease in RBC MDA production during CPB is achieved only with high dose propofol; 3) the antioxidant effect of propofol continued when the drug was administered as postoperative sedation; 4) preoperative nitrates did not modify red cell antioxidant capacity.

Exposure to volatile anesthetics may increase the susceptibility of cells to oxidant damage.[17] The exact mechanism remains to be elucidated. These anesthetics serve as substrates for the production of their own free radicals.[18] They may act as a source of $Cl^{\cdot}$ moieties involved in electron transfers responsible for the alternate generation of oxygen derived free radicals or production of the potent oxidant, hypochlorous acid.[19]

Intravenous anesthetics may have a different effect on the pathogenesis of IRI. It has been reported recently that the use of intravenous anesthesia (fentanyl and droperidol) is associated with lower indices of lung injury than volatile anesthesia (desflurane) following experimental aortic occlusion/reperfusion.[20] Opioids, such as morphine, may have complex central and peripheral immunomodulatory effects, but the effects of synthetic opioids are not known.[21] The interaction of volatile anesthesia, but not intravenous anesthesia, with the xanthine oxidase system, as a potential source of oxidant mediated damage, has been implicated.

Recent experimental evidence utilizing an isolated heart model has demonstrated that propofol can increase the antioxidant capacity of the myocardium and scavenge peroxynitrite, a potent mediator of lung

injury.[12,13] The plasma concentrations of propofol achieved by our regimen were similar to those known to protect against *in vitro* oxidative damage of the heart and lung (25 and 50 μM (ie. 4.45 and 8.9 $\mu g \cdot ml^{-1}$ respectively)).[12,13] A concentration effect relationship for the antioxidant effects of propofol on red cells was achieved under conditions of cardiopulmonary bypass only with the use of high dose propofol. The dose used in a previous clinical study (50 to 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was not sufficient to sustain this degree of antioxidant potential and could explain why differences in clinical outcome could not be seen when compared with a volatile technique.[14] The magnitude of the antioxidant protection we achieved with high dose propofol was similar to that seen with allopurinol pretreatment in experimental heart - lung transplantation (>50% decrease in MDA in response to oxidative challenge).[22] This degree of protection was associated with improved postoperative recovery of cardiopulmonary function.

Malondialdehyde is not the only oxidation byproduct, but it is a simple and sensitive assay of lipid peroxidation for application to laboratory and clinical studies. There are two assays available for the measurement of MDA in plasma, cells and tissues: the TBA assay utilized in this study, and high performance liquid chromatography (HPLC). For the purposes of this study, HPLC technology for MDA analysis was not available. The specificity of the TBA assay has been criticized for the quantitative analysis of lipid peroxidation. Besides MDA, the generation of non lipid related, MDA like TBA-reactive substances may occur, resulting in overestimation of MDA production. This may be a more important issue when analyzing tissue rather than red cells. Gilbert *et al.* recommended a method to correct these errors.[16] The improved accuracy utilizing this correction factor has been corroborated with the HPLC method. This method formed the basis of our assay. Our previous study demonstrated assay variability of less than 5-10% using this method.[15]

It is important to distinguish the interpretive differences between use of the MDA assay and HPLC. The MDA assay used in our studies serves as a functional measure of protection against a predetermined level of oxidant mediated damage. The HPLC technique has been used to determine changes in the serum and tissue level of MDA, indicating the presence of oxidant mediated injury, in response to conditions of ischemia-reperfusion,. An increase in MDA is seen in the myocardium following ischemia-reperfusion.[23] Indirect measurement of MDA formation has demonstrated peaks of plasma MDA following release of aortic crossclamp in cardiac surgery. The effect of achieving an optimal antioxidant endpoint, on tissue and plasma MDA levels following ischemia-reperfusion, has not yet been performed.

Nonenzymatic antioxidants (eg., vitamin E) are depleted during ischemia.[24] If oxidants are involved in cardiopulmonary IRI during ACBP surgery, the antioxidant potential of propofol would serve as a useful adjunct. We have previously demonstrated that propofol's antioxidant effect likely occurs at the level of the cell membrane.[15] Propofol has no effect on antioxidant enzymes. We theorize that red cells may serve as a buffer against oxidative injury. Enhancement of red cell antioxidant capacity with propofol would serve to increase the threshold at which injury would occur, independent of any direct protection at the tissue level. This is important because the myocardium is vulnerable to oxidative injury due to low levels of antioxidant enzymes found in these tissues.[25,26]

Our intention is to substantiate this finding with expanded study of propofol's antioxidant potential during ACBP. This study was designed to find the appropriate dose of propofol to enhance red cell antioxidant status, not to find the appropriate dose for optimal hemodynamic stability. The effects of propofol dose become an important consideration, since the potential of myocardial depression related to the use of the drug must be balanced against what may be an antioxidant treatment endpoint. Our clinical observations included no increased risk of postinduction hypotension with the careful administration of high dose propofol and a reduced dose of narcotic. Neosynephrine was required during the continuous administration of propofol to maintain a minimum mean arterial pressure of 55 mmHg during CPB. The increased need for neosynephrine with the use of propofol in cardiac surgery has been previously reported.[27]

Although the sample size of this study makes any clinical observation anecdotal, our data suggest a difference in the pattern of clinical recovery in patients who receive high dose propofol. Of interest, the use of low dose and high dose propofol was associated with a different pattern of recovery of myocardial function than after isoflurane. Postoperative inotropic requirements and duration of inotropic use was increased in the isoflurane group. These differences occurred even though the ischemic interval was 10 to 40 min longer in patients receiving propofol than in those receiving isoflurane. However, the data from this sample size is insufficient to demonstrate a statistically significant difference between groups.

These data point to the need to study further this drug's effects in an expanded clinical trial. An experi-

mental study correlating red cell antioxidant capacity to tissue antioxidant capacity during propofol anesthesia is currently underway and will complement these studies. A recent experimental study by Yoo and colleagues supports the potential for antioxidant protection of the myocardium with propofol following ischemia-reperfusion.[28]

In summary, this investigation has shown that propofol has an antioxidant effect, when red cell antioxidant capacity is utilized as a functional measure of antioxidant alterations *in vivo*, during cardiac surgery. This effect is most pronounced with the use of high dose propofol. The plasma concentration of propofol achieved at this dose, 8-12 $\mu g \cdot ml^{-1}$, is within the range associated with experimental cardiopulmonary protection against oxidant mediators. This must be substantiated because of the concern for potential intra-operative hemodynamic instability and post-operative cardiac depression that may be associated with the use of high doses of the drug. The determination of a dose thought to be "protective" with minimal side effects should form the basis for a large randomized clinical trial comparing propofol to isoflurane based anesthesia for ACBP. This would increase our understanding of the effects of volatile or intravenous anesthetics on IRI during cardiac surgery, under conditions of extracorporeal circulation.

Acknowledgment

The authors wish to acknowledge the contributions of the members of the Divisions of Cardiac Anesthesia and Surgery, and Mr. Azim Jamani whose assistance was invaluable in the completion of this study.

References

1 *Mangano DT.* Biventricular function after myocardial revascularization in humans: deterioration and recovery patterns during the first 24 hours. Anesthesiology 1985; 62: 571–7.

2 *Breisblatt WM, Stein KL, Wolfe CJ, et al.* Acute myocardial dysfunction and recovery: a common occurrence after coronary bypass surgery. J Am Coll Cardiol 1990; 15: 1261–9.

3 *Leung JM, O'Kelly BF, Mangano DT.* Relationship of regional wall motion abnormalities to hemodynamic indices of myocardial oxygen supply and demand in patients undergoing CABG surgery. Anesthesiology 1990; 73: 802–14.

4 *Weintraub WS, Jones EL, Craver J, Guyton R, Cohen C.* Determinants of prolonged length of hospital stay after coronary bypass surgery. Circulation 1989; 80: 276–84.

5 *Turnbull KW, Miyagashima RT, Gerein AN.* Pulmonary complications and cardiopulmonary bypass: a clinical study in adults. Can Anaesth Soc J 1974; 21: 181–94.

6 *Forman MB, Virmani R, Puett DW.* Mechanisms and therapy of myocardial reperfusion injury. Circulation 1990; 81: IV69–78.

7 *McCord JM.* Oxygen-derived radicals: a link between reperfusion injury and inflammation. FASAB J 1987; 46: 2402–6.

8 *Marijic J, Stowe DF, Turner LA, Kampine JP, Bosnjak ZJ.* Differential protective effects of halothane and isoflurane against hypoxic and reoxygenation injury in the isolated guinea pig heart. Anesthesiology 1990; 73: 976–83.

9 *Shayevitz JR, Johnson KJ, Knight PR.* Halothane-oxidant interactions in the *ex vivo* perfused rabbit lung. Fluid conductance and eicosanoid production. Anesthesiology 1993; 79: 129–38.

10 *Murphy PG, Myers DS, Davies MJ, Webster NR, Jones JG.* The antioxidant potential of propofol (2,6-diisopropylphenol). Br J Anaesth 1992; 68: 613–8.

11 *Green TR, Bennet SR, Nelson VM.* Specificity and properties of propofol as an antioxidant free radical scavenger. Toxicol Appl Pharmacol 1994; 129: 163–9.

12 *Kokita N, Hara A.* Propofol attenuates hydrogen peroxide-induced mechanical and metabolic derangements in the isolated rat heart. Anesthesiology 1996; 84: 117–27.

13 *Kahraman S, Demiryürek AT.* Propofol as a peroxynitrite scavenger. Anesth Analg 1997; 84: 1127–30.

14 *Myles PS, Buckland MR, Weeks AM, et al.* Hemodynamic effects, myocardial ischemia, and timing of tracheal extubation with propofol-based anesthesia for cardiac surgery. Anesth Analg 1997; 84: 12–9.

15 *Ansley DM, Lee J-U, Godin DV, Garnett ME, Qayumi AK.* Propofol enhances red cell antioxidant capacity in swine and humans. Can J Anaesth 1998; 45: 233–9.

16 *Gilbert HS, Stump DD, Roth EF Jr.* A method to correct for errors caused by generation of interfering compounds during erythrocyte lipid peroxidation. Ann Biochem 1984; 137: 282–6.

17 *Shayevitz JR, Varani J, Ward PA, Knight PR.* Halothane and isoflurane increase pulmonary artery endothelial cell sensitivity to oxidant-mediated injury. Anesthesiology 1991; 74: 1067–77.

18 *Lal M, Schöneich C, Mnig J, Asmus K-D.* Rate constants for the reactions of halogenated organic radicals. Int J Radiat Biol 1988; 54: 773–85.

19 *Ansley DM.* Ischaemia-reperfusion: time to increase our awareness during anaesthesia (Editorial). Can J Anaesth 1998; 45: 195–8.

20 *Nielsen VG, Baird MS, McAdams ML, Freeman BA.* Desflurane increases pulmonary alveolar-capillary membrane permeability after aortic occlusion-reperfusion in

rabbits. Evidence of oxidant-mediated lung injury. Anesthesiology 1998; 88: 1524–34.

21 *Webster NR.* Opioids and the immune system (Editorial). Br J Anaesth 1998; 81: 835–6.

22 *Qayumi AK, Godin DV, Jamieson WRE, Ko KM, Poostizadeh A.* Correlation of red cell antioxidant status and heart-lung function in swine pretreated with allopurinol (a model of heart-lung transplantation). Transplantation 1993; 56: 37–43.

23 *Coghlin JG, Flitter WD, Clutton SM, et al.* Lipid peroxidation and changes in vitamin E levels during coronary artery bypass grafting. J Thorac Cardiovasc Surg 1993; 106: 268–74.

24 *Kim K-B, Chung HH, Kim MS, Rho JR.* Changes in the antioxidative defensive system during open heart operations in humans. Ann Thorac Surg 1994; 58: 170–5.

25 *Wohaieb SA, Godin DV.* Starvation-related alterations in free radical tissue defence mechanisms in rats. Diabetes 1987; 36: 169–73.

26 *Godin DV, Wohaieb SA, Garnett ME, Goumeniouk AD.* Antioxidant enzyme alterations in experimental and clinical diabetes. Mol Cell Biochem 1988; 84: 223–31.

27 *Mora CT, Dudek C, Torjman MC, White PF.* The effects of anesthetic technique on the hemodynamic response and recovery profile in coronary revascularization patients. Anesth Analg 1995; 81: 900–10.

28 *Yoo KY, Yang SY, Lee J, et al.* Intracoronary propofol attenuates myocardial but not coronary endothelial dysfunction after brief ischaemia and reperfusion in dogs. Br J Anaesth 1999; 82: 90–6.