Similar long-term cardiovascular effects of propofol or isoflurane anesthesia during ischemia/reperfusion in dogs

[Effets cardiovasculaires prolongés similaires de l'anesthésie au propofol ou à l'isoflurane pendant l'ischémie/reperfusion chez les chiens]

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Purpose: To compare the long-term functional and metabolic effects of propofol or isoflurane general anesthesia in a canine model of ischemia/reperfusion.

Methods: Using magnetic resonance (MR) techniques, we monitored both regional metabolism (^{31}P MR spectroscopy) and systolic function of the heart (^1H MR imaging) throughout a two-hour occlusion of the left anterior descending coronary artery and ten days of reperfusion. Twenty-two beagles were randomized into isoflurane and propofol general anesthesia groups ($n = 10$, $n = 12$ respectively). Contrast-enhanced MR imaging was used to measure infarct size (% of left ventricle that was necrotic) and coronary blood flow was determined using radioactively labelled microspheres.

Results: Cardiac metabolism, as monitored by intracellular pH and high-energy phosphate ratios, was not significantly different between the two groups throughout the protocol. Relative to propofol, isoflurane reduced the depression of left ventricular ejection fraction (EF) during the ischemic period [isoflurane $68.5\% \pm 4.2\%$, propofol $58.3\% \pm 2.0\%$ of baseline (B); $P = 0.04$], propofol increased the recovery of EF at day three (isoflurane $63.9\% \pm 4.3\%$, propofol $74.0\% \pm 2.5\%$ of B; $P = 0.05$). By day ten, EF in both groups was similar. Infarct sizes were also similar at day ten (isoflurane $15.7\% \pm 3.0\%$, propofol $13.2\% \pm 2.2\%$). Normalizing these by the region at risk (volume of tissue with low blood flow during the occlusion) to assess infarct ratios was also not significant (isoflurane $0.58\% \pm 0.08\%$, propofol $0.54\% \pm 0.07\%$).

Conclusions: There were no significant differences between the two anesthetic groups at day ten, suggesting that any apparent dissimilarities in early cardiovascular effects were short-term only. These results indicate that isoflurane and propofol produce equivalent long-term cardiovascular effects following ischemia/reperfusion.

Objectif: Comparer les effets fonctionnels et métaboliques prolongés de l'anesthésie générale avec du propofol ou de l'isoflurane chez un modèle canin d'ischémie/reperfusion.

Méthode : Nous avons mesuré, grâce aux techniques d'imagerie par résonance magnétique (IRM), le métabolisme régional (spectroscopie IRM ^{31}P) et la fonction systolique cardiaque (IRM ^1H) tout au long d'une occlusion de deux heures de l'artère descendante antérieure et pendant dix jours de reperfusion. Vingt-deux beagles ont été répartis au hasard en deux groupes d'anesthésie générale : isoflurane et propofol ($n = 10$, $n = 12$ respectivement). L'IRM avec injection d'un agent de contraste a permis de mesurer la taille de l'infarctus (% du ventricule gauche nécrotique) et des microsphères radioactives ont servi à déterminer le débit coronarien.

Résultats : Les paramètres du métabolisme cardiaque, enregistrés par les ratios de pH et de phosphate de grande énergie intracellulaires, n'ont pas été significativement différents entre les groupes pendant toute la durée du protocole. Comparé au propofol, l'isoflurane a réduit la dépression de la fraction d'éjection (FE) du ventricule gauche pendant l'ischémie [isoflurane : $68,5\% \pm 4,2\%$, propofol : $58,3\% \pm 2,0\%$ des données de base (B) ; $P = 0,04$], le propofol a accéléré la récupération de la FE au jour trois (isoflurane : $63,9\% \pm 4,3\%$, propofol : $74,0\% \pm 2,5\%$ de B ; $P = 0,05$). Au dixième jour, la FE était similaire dans les deux groupes, de même la taille de l'infarctus (isoflurane : $15,7\% \pm 3,0\%$, propofol : $13,2\% \pm 2,2\%$). La normalisation de ces données, selon la région à risque (volume de tissu soumis à un faible débit sanguin pendant l'occlusion), réalisée pour évaluer les ratios d'infarctus n'a pas été significative non plus (isoflurane : $0,58\% \pm 0,08\%$, propofol : $0,54\% \pm 0,07\%$).

Conclusion : Au dixième jour, l'absence de différence significative entre les deux anesthésiques laisse croire que toute dissimilarité apparente des effets cardiovasculaires précoces n'a été que de courte

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Funded by a grant from the Heart and Stroke Foundation of Ontario.

Accepted for publication April 11, 2002.

Revision accepted August 14, 2002.

durée. Ces résultats indiquent que l'isoflurane et le propofol produisent des effets cardiovasculaires prolongés équivalents à la suite d'une ischémie/reperfusion.

ISOFLURANE, a commonly used inhalational anesthetic, has been shown to provide myocardial protection during ischemia/reperfusion.^{1–10} Others, however, have found isoflurane to confer no cardioprotection.^{11,12} Propofol, an alternative to isoflurane, is a widely used anesthetic that has also been inconsistently reported to offer protective effects against reperfusion injury.^{13–19}

The primary mechanism of the cardioprotection associated with isoflurane is thought to be through the activation of adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channels.^{2,6,7} This, along with other potential mechanisms, has been studied in a variety of ischemia/reperfusion models; with evidence for the following clinically important endpoints: reduction in infarct volume;^{1–3,7–10} improved functional recovery;^{4,5} and preservation of ATP.^{4,6} The purported mechanisms of cardioprotection by propofol include oxygen free radical scavenging,^{15,16} reductions in Ca^{2+} overloading,¹⁵ and increases in coronary flow.¹⁵ Enhanced functional recovery,^{13,15–17} as well as reductions in myocardial necrosis,¹⁵ and retention of ATP¹⁶ have all been reported with propofol.

We have previously reported the protective benefits of propranolol, nitroglycerin, and superoxide dismutase on limiting infarct size with our laboratory's canine two-hour occlusion/ten-day reperfusion model.^{20,21} The current study was undertaken to directly compare the cardiovascular effects of two commonly used general anesthetics: propofol and isoflurane. Rather than create a true control group, the two anesthetics were directly compared against one another, as there is no acceptable anesthetic that has not been shown to have some effects on the cardiovascular system.

We used both ³¹P (Phosphorus (³¹P) MR spectroscopy (MRS) and ¹H MR Imaging (MRI) to determine if any differences exist in the cardiovascular effects of propofol and isoflurane, as general anesthetics, during and following ischemia/reperfusion. ³¹P spectroscopy monitored changes in regional myocardial metabolism by assessing the high-energy phosphate ratios as well as intracellular pH, and ¹H MRI determined the functional effects on systolic left ventricular performance and myocardial salvage (infarct extent) following ten days of reperfusion.

Methods

Animals used in this study were handled in accordance with the guidelines of the Animal Care Committee at the University of Western Ontario, London, Canada.

Surgery

Twenty-two female beagles ranging in weight from 9 to 15 kg were used for this study. The dogs were randomly separated into a control group (isoflurane anesthesia $n = 10$) and a treatment group (propofol anesthesia only, $n = 12$). General anesthesia was induced intravenously with 4 mg·kg⁻¹ propofol [Abbott Laboratories, Saint-Laurent, QC, Canada; 2,6-diisopropylphenol in a lipid emulsion (10 mg·mL⁻¹, 1% w/v)] in both groups. Anesthesia was maintained in the isoflurane group with 1.5–2.5% isoflurane (Abbott Laboratories, Montreal, QC, Canada) whereas in the propofol group anesthesia was maintained with a constant infusion of propofol at a rate of 0.6–1.0 mg·kg⁻¹·min⁻¹.²² The dogs were intubated with an endotracheal tube and ventilated using an A.D.S. 1000 (Engler Engineering Corp., Hialeah, FL, USA) pressure limited respirator, using oxygen-enriched room air to maintain arterial pH (~7.40), pO_2 (> 100 mmHg), and pCO_2 (< 40 mmHg). A pulse oximeter (Nonin, Plymouth, MN, USA) was used for constant monitoring of heart rate and pO_2 . A capnograph (Datex: Capnomac Ultima, Helsinki, Finland) monitored pCO_2 , pO_2 , and isoflurane levels at all times.

Subsequently, a left thoracotomy was performed between the fourth and fifth intercostal space, the pericardium was incised, and the heart was exposed. The left anterior descending coronary artery (LAD) was dissected free just distal to the first major diagonal branch. A ligature was positioned around the isolated region of the LAD, and the ligature ends were then threaded through a chest tube, acting as a snare. The left atrial appendage was cannulated for microsphere injections. A femoral artery was catheterized to allow an arterial blood reference sample to be taken for microsphere blood flow measurements. A cephalic vein was also catheterized for administration of drugs and/or fluids. Body temperature, during anesthesia, was maintained between 36.0°C and 38.0°C using hot water bottles placed around the animal's torso.

Experimental protocol

All 22 dogs underwent a two-hour occlusion (after an average of 4.75 hr of anesthetic) followed by ten days of reperfusion. The anesthetic protocol used on the day of surgery for each dog was exactly the same during all subsequent experiments. The protocol incorporated approximately 12 hr of anesthesia on the day of

surgery, 3.5 hr on day three, and 4.75 hr on day ten. Images were obtained with a 55-cm bore Siemens Vision 1.5T MR scanner (Siemens, Erlangen, Germany). Cine MR images and ^{31}P chemical shift imaging (CSI) spectra were acquired on the day of surgery (before, during, and immediately following the release of the occlusion), as well as three days and ten days postoperation. Radioactively labelled microspheres were injected at baseline (B), occlusion, reperfusion, and day ten to assess regional myocardial blood flow. On day ten the dogs were sacrificed and the hearts excised for imaging and dissection.

MR set-up and protocol

A) ^{31}P SPECTROSCOPY

Two-dimensional ^{31}P CSI was performed seven times throughout the ten-day protocol with a Siemens ^1H - ^{31}P radiofrequency surface coil, as previously described.^{20,21,23} The data were acquired from a 30-mm thick slice, positioned in the transverse plane, and centered just proximal to the most apical region of the heart. Multivoxel ^{31}P 2D-CSI [TR 500 msec, α 90°, field of view (FOV) 320 mm, Bandwidth $\pm$ 2 kHz, acquisition time 34 min] were obtained from this transverse slice once at B, twice during the occlusion period (O1 and O2), twice immediately upon reperfusion (R1 and R2) and once at each follow-up (D3 and D10 respectively).

Using Siemens' software the raw data were filtered and zero filled (2,048 points) during the initial localized reconstruction. These spectra were then fitted using FITMAN, a software package designed in our laboratory, which incorporates prior knowledge of the spectrum as determined from the literature and our previous results.^{20,21,23,24} Each slice consisted of 2 x 2 cm² voxels through the 3-cm thick transverse slab, in a 16 x 16 grid that could be positioned retrospectively. This ensured that the volumes of interest (VOI) contained predominantly or exclusively, infarcted tissue, as opposed to non-infarcted tissue.

Using the chemical shift between the phosphocreatine (PCr) and the inorganic phosphate (Pi) peaks, the myocardial pH was determined for each VOI.^{20,21,23} A spectral template was used to fit the blood peaks, allowing for the discrimination of the myocardial Pi peaks. If more than one Pi peak was fit within a spectrum then the peak corresponding to the most acidic environment was chosen as the intracellular pH for that VOI. However, only Pi peak areas corresponding to at least 10% of the PCr area were included.

B) CINE MRI

Interleaved with the CSI acquisitions were cine

images, acquired with the dogs positioned prone and the heart centred in a rigid Siemens ^1H radiofrequency transmit/receive coil, also previously described.²⁵⁻²⁷ An electrocardiogram-gated segmented cine FLASH sequence with echo sharing (TR/TE 60/4.8 msec, α 20°, thickness 6 mm) was used to obtain five to six short axis slices through the heart. Depending on the heart rate, eight to ten cardiac phases were acquired with a rectangular FOV.

End diastole (ED) and end systole (ES) images were identified for each slice through the heart using the Siemens cardiac analysis software ARGUS (Siemens Canada, Mississauga, ON, Canada). Endocardial contours were drawn for each slice providing absolute measurement of ED and ES blood volumes (EDV and ESV respectively). The global left ventricular ejection fraction (EF) was then determined for the entire heart.

C) CONTRAST-ENHANCED MRI

Prior to sacrifice, the dogs received a bolus (0.2 mmol·kg⁻¹) followed by a one-hour constant infusion (0.004 mmol·kg⁻¹·min⁻¹) of Gd-DTPA (gadolinium diethylene triamine pentaacetic acid, Magnevist™; Berlex Canada, Lachine, QC, Canada). The animal was sacrificed with an *iv* bolus of 10 mL KCl (149 mg·mL⁻¹, Abbott Laboratories, Montreal, QC, Canada) and the heart was excised and then imaged using a T₁-weighted 3D FLASH sequence (TR/TE 22/10 msec, FOV 80–120 mm, thickness 1 mm). Previous works in our laboratory and others have validated this technique of contrast-enhanced MRI against triphenyltetrazolium chloride histochemical staining to delineate myocardial necrosis.^{20,21,25,26,28}

AnalyzeAVW (Biomedical Imaging Resources, Mayo Foundation, Rochester, MN, USA) was used to volume render the Gd-DTPA enhanced 3D *ex vivo* images. The left ventricle (LV) volume was determined, as was the volume of enhanced tissue, which indicates myocardial necrosis. Therefore, all regions of hyper-enhancement were defined as infarcted tissue. These volumes were summed, as well as the entire LV volume, providing a percentage of infarcted LV or infarct size.

Blood flow measurements

Radioactively labelled microspheres (15 μm diameter, 100 μCi , Dupont Canada, Markham, ON, Canada) were injected as a bolus into the left atrial appendage cannula one minute into a five-minute blood withdrawal (2 mL·min⁻¹) from the femoral artery. Four sets of microspheres were used (isotopes ^{85}Sr , ^{46}Sc , ^{95}Nb , and ^{141}Ce) throughout the protocol. The first

TABLE I Intracellular pH (mean $\pm$ SEM) throughout the ten-day protocol

	<i>B</i>	<i>O1</i>	<i>O2</i>	<i>R1</i>	<i>R2</i>	<i>D3</i>	<i>D10</i>
Isoflurane (<i>n</i> = 10)	7.14 (0.04)	6.62 (0.09)*	6.44 (0.09)	6.59 (0.11)	6.78 (0.14)	6.90 (0.10)	7.06 (0.08)
Propofol (<i>n</i> = 11)	7.11 (0.03)	6.51 (0.11)*	6.25 (0.07)*	6.60 (0.13)*	6.83 (0.13)	6.81 (0.10)	7.04 (0.07)*

B = baseline; O1 and O2 = first and second consecutive measurements during occlusion; R1 and R2 = first and second consecutive measurements during immediate reperfusion; D3 and D10 = follow-ups on day three and day ten respectively. **P* < 0.05, relative to the previous time-point, within group only.

TABLE II Functional data (mean $\pm$ SEM) throughout the ten-day protocol

	<i>B</i>	<i>O</i>	<i>R</i>	<i>D3</i>	<i>D10</i>
Isoflurane (<i>n</i> = 10)					
EDV (mL)	19.9 (1.8)	21.2 (2.2)	22.5 (2.2)	21.7 (1.8)	20.6 (1.5)
SV (mL)	13.2 (0.8)	9.9 (0.9)*	9.5 (0.8)	9.2 (0.5)	11.7 (0.6)*
Heart rate (beats·min ⁻¹)	86 (2)	98 (5)*	97 (4)	111 (6)*	99 (3)†
Propofol (<i>n</i> = 11)					
EDV (mL)	18.8 (1.0)	23.0 (1.1)*	20.3 (1.4)	20.2 (1.4)	20.2 (1.1)
SV (mL)	13.5 (0.7)	9.6 (0.6)*	9.1 (0.6)	10.6 (0.7)	12.5 (0.5)*
Heart rate (beats·min ⁻¹)	83 (4)	99 (6)*	100 (6)	96 (6)	87 (4)†

EDV = end diastolic volume; SV = stroke volume; B = baseline; O = occlusion; R = reperfusion; D3 and D10 = follow-ups on day three and day ten respectively. **P* < 0.05, relative to the previous time-point, within group only; †*P* < 0.05 between groups significant difference at time-point.

TABLE III Viability data for both groups

	<i>Region at risk (% LV)</i>		<i>Infarct size (% LV)</i>		<i>Infarct ratio</i>	
	<i>Mean $\pm$ SEM</i>	<i>95% CI</i>	<i>Mean $\pm$ SEM</i>	<i>95% CI</i>	<i>Mean $\pm$ SEM</i>	<i>95% CI</i>
Isoflurane (<i>n</i> = 9)	29.0 $\pm$ 2.9	22.3–35.8	15.7 $\pm$ 3.0	8.6–22.7	0.58 $\pm$ 0.08	0.39–0.76
Propofol (<i>n</i> = 12)	26.2 $\pm$ 3.1	19.4–33.0	13.2 $\pm$ 2.2	8.2–18.1	0.54 $\pm$ 0.07	0.38–0.69

LV = left ventricle; 95% CI = 95% confidence intervals.

three sets were injected prior to, during, and immediately after the release of the occlusion, and the last set was injected ten days postocclusion, just before sacrifice. Blood flow determination (F, expressed in mL·min⁻¹·g⁻¹) has been previously described in detail.^{20,21,23,26,27}

Infarct ratio

To minimize the biological variability between animals we normalized the infarct size based on the region at risk (RAR). The RAR was defined as the volume of tissue with myocardial blood flows less than 0.3 mL·min⁻¹·g⁻¹ during occlusion, as determined by the microsphere data.

Statistics

All data that were measured repeatedly over the course of the ten-day protocol were analyzed with a two-way

repeated measures ANOVA with a repeated factor of time and a non-repeated factor of group. One-way single factor ANOVAs were used to determine significance at specific time-points, as well as for infarct size, region at risk, and damage ratio group means. Data are presented as mean $\pm$ SEM as well as 95% confidence intervals when specified for all 22 beagles, unless noted. Differences in *n*-values reflect technical difficulties experienced throughout the protocol. The program SPSS 10.0 (SPSS Inc., Chicago, IL, USA) was employed for all statistical tests.

Results

There were no differences between groups (*n* = 10 isoflurane, *n* = 12 propofol) in pO₂, pCO₂, or temperature throughout the experimental protocol. Heart rates in the isoflurane group were significantly higher at day 10, *P* = 0.04 (Table II).

MR results

A) ^{31}P SPECTROSCOPY

Myocardial pH was determined at each of the seven time-points for both groups ($n = 10$ isoflurane, $n = 11$ propofol). There were no significant differences in myocardial intracellular pH at any time-point between the two groups. Both groups had a significant ($P < 0.005$) drop in pH immediately upon occlusion compared to the B values (Table I). Metabolite ratios determined from the fitted PCr and (α -ATP) peak amplitude areas were not significantly different between groups. All dogs did however, experience a reduction in their PCr/ α -ATP during the occlusion, followed by a PCr overshoot upon reperfusion.

B) CINE MRI

EDV was compared between the two groups at each of the five time-points. There were no significant differences between anesthetic groups, indicating equal volume loading of all dogs throughout the protocol (Table II). B EF measurements were $70.3\% \pm 4.2\%$ and $71.6\% \pm 1.4\%$ for the isoflurane ($n = 10$) and propofol ($n = 11$) groups respectively (NS). Normalizing all other time-points by these B values resulted in significant differences in EF during the occlusion, where propofol treated animals had slightly lower values; at day three the pattern was reversed and the propofol group had slightly higher values (Figure). By day ten there were no longer any significant differences between the two groups, although these values were lower than the B values.

C) CONTRAST-ENHANCED MRI

The mean infarct sizes between the two groups were not significantly different [$(P = 0.50)$, Table III].

Blood flow measurements

The blood flow data were separated into four distinct regions of flow: low, intermediate, normal, and high (< 0.3 , $0.3\text{--}0.8$, $0.8\text{--}1.8$, $> 1.8 \text{ mL}\cdot\text{min}^{-1}\cdot\text{g}^{-1}$ respectively). The isoflurane group had a mean RAR of $29.0\% \pm 2.9\%$ and the propofol group's RAR was $26.2\% \pm 3.1\%$ (NS), indicating the consistency of our model (Table III).

Infarct ratio

The infarct ratios for both groups were not significantly different (Table III).

Discussion

There are many studies assessing the effects of isoflurane and propofol in the setting of ischemia/reperfusion, yet most do not directly compare these two

FIGURE Ejection fraction (EF; mean $\pm$ SEM) normalized by the baseline (B) for both groups at each time-point (O = occlusion; R = reperfusion; D3 = day three follow-up; D10 = day ten follow-up). Significance * was determined for $P < 0.05$ between groups, as determined by single factor ANOVA.

anesthetics, but instead compare each with a variety of anesthetics. Often in acute studies, laboratories use chloralose as their general anesthesia control group.^{6,11} It is purported to have no hemodynamic effects, however, it is also not recommended for long-term survival surgeries.²⁹ Other alternatives include barbiturates, which have been shown to affect cardiac function;³⁰ opioids, such as fentanyl, are associated with improved post-ischemic function³¹ as well as reductions in infarct size.³² The inhalational anesthetic xenon has also been shown to reduce infarct size in rabbits.³³ Due to the varying effects of different anesthetics on the cardiovascular system, we opted to compare isoflurane and propofol general anesthesia during an acute myocardial infarction directly, rather than creating a true control group. In doing so we found only short-term cardiovascular differences between the two groups. There were relative differences in left ventricular systolic function during the occlusion, as well as immediately upon early reperfusion. As stated, these were short-term effects; by day ten there were no relative functional or metabolic differences between anesthetic groups.

Propofol has been reported to produce both metabolic and functional effects in the setting of ischemia/reperfusion. Kokita *et al.* reported that propofol preserved the high-energy phosphates ATP and PCr in their Langendorff rat heart model of hydrogen peroxide-induced myocardial damage.¹⁶ Although some have shown propofol to improve contractility following reperfusion,^{13–17} others have shown no effects.^{18,19} Reduction of myocardial necrosis by propo-

fol has been reported in a small number of laboratories, mostly using a perfused heart model.^{15,18} Also, these propofol studies involved induction and/or general anesthesia with different anesthetics, followed by a bolus or infusion of propofol at some specific limited time-point.^{13,15-19} This leads to further confounding variables within the studies as the two different anesthetics are now integrated, making it extremely difficult to interpret the effects of propofol alone.

Yet another complication of propofol studies is that animals require significantly increased doses of propofol as compared to humans. The recommended dose for maintaining general anesthesia in humans is 0.1–0.2 mg·kg⁻¹·min⁻¹, whereas in dogs it is 0.4–0.5 mg·kg⁻¹·min⁻¹.³⁴ Despite this, complete elimination of propofol following a constant infusion is similar in humans and dogs (four to six hours *vs* five hours, respectively).³⁴ Bryson *et al.* have reported that the volume of distribution of propofol at steady-state (V_d^{ss}) in humans during a 0.15 mg·kg⁻¹·min⁻¹ infusion is 5.3 L·kg⁻¹, while Nolan and Reid reported a V_d^{ss} of 6.51 L·kg⁻¹ in dogs during a 0.4 mg·kg⁻¹·min⁻¹ infusion.^{22,35} Considering that the canine infusion rate has increased by 167%, it is surprising that the V_d^{ss} has only increased by 23%. Therefore, although the infusion rates of propofol are distinctively higher in dogs, it appears that the increase in concentration of the propofol is not linearly related. However, these discrepancies in dose and affect must be taken into consideration.

Isoflurane has been reported to produce beneficial cardioprotective effects in a variety of ischemia/reperfusion settings as compared to many different anesthetic agents. It has been reported to preserve ATP^{4,6} as well as to improve myocardial contractility following a reperfused ischemic insult through a variety of mechanisms.^{1,2,5} As was the case with propofol, most laboratories have not maintained anesthesia with isoflurane, but have briefly exposed their animals to isoflurane at some point during the protocol. Using this technique, exposure to isoflurane has reduced infarct size relative to the following anesthetized control groups: ketamine and xylazine,³ sodium pentobarbital,^{1,2} and propofol.^{7,9,10}

There are only a few studies directly comparing general anesthesia with isoflurane and propofol during a period of ischemia/reperfusion.^{8,36} One such study assessed the red blood cell (RBC) antioxidant capacity of isoflurane and clinical low- and high-dose propofol. They found high-dose propofol (200 µg·kg⁻¹·min⁻¹) resulted in enhanced RBC antioxidant capacity, suggesting that high-dose propofol anesthesia could increase the threshold for oxidative injury during ischemia/reperfusion.³⁶ Cope *et al.* have

directly compared infarct size in animals where general anesthesia was maintained with either propofol or isoflurane in a model of ischemia/reperfusion. They determined that isoflurane protected the reperfused ischemic rabbit heart from infarction to a greater extent than propofol.⁸ They used an *in vivo* rabbit model, with a 30-min occlusion followed by three hours of reperfusion. Normalized myocardial necrosis was significantly lower in the isoflurane group. This would be in agreement with the results from the Cason laboratory where they have used propofol as their general anesthesia in control rabbits. The treatment groups were exposed to 15 min of isoflurane prior to a 30-min occlusion, during which time the propofol infusion was briefly interrupted to ensure a nearly constant level of anesthesia. All of the isoflurane groups resulted in reduced infarcts and infarct ratios as compared to the propofol controls.^{7,9,10} They have suggested a variety of mechanisms to be involved in these effects that are seen only with isoflurane. By adding colchicine, a drug that depolymerizes microtubules, they blocked the reductions in necrosis found with the isoflurane pre-treatment group, but not the propofol control group.¹⁰ Another study by this group found that by adding glyburide, a K_{ATP} channel blocker, or 8-(p-sulphophenyl)-theophylline, a non-specific adenosine receptor antagonist, the benefits of isoflurane on infarct size were eliminated.⁹ Again though, treatment of the propofol controls with either of these blockers did not affect the final volumes of necrotic tissue in these groups.

In our study of a two-hour occlusion followed by ten days of reperfusion, we found that the high-energy phosphate levels provided cellular metabolic information, but the normalized PCr/ α -ATP ratios were not significantly different between groups at any time point during the protocol; neither was the intracellular pH. Our functional data indicated that isoflurane reduced the relative negative inotropic effects that occurred during ischemia as compared to propofol anesthesia. However, during the early stages of reperfusion there was a significantly faster recovery of cardiac function in the propofol group as compared to isoflurane. Our final time-point, ten days postocclusion, showed no differences between the two groups suggesting that there are no long-term functional differences between these two anesthetics.

The absolute infarct sizes, and normalized infarct ratios of the two anesthetic groups, as determined at day ten, were not different; contrary to the reports suggesting isoflurane's relative protective effects *vs* other anesthetic agents for reducing myocardial necrosis.^{1-3,7-10} Unfortunately, there have been no

previously reported long-term studies on the potential cardiovascular effects of anesthetics when these agents are administered during an acute reperfused ischemic insult. It is documented that reperfusion injury may not become manifest until 72 hr following normalization of blood flow³⁷ and yet all of the infarct size data reported were those obtained within the first four hours of reperfusion.^{1-3,7-10,18} This significant difference in the model, to a longer period of observation, may contribute to the differences between these results and other studies.

In summary, we have shown the following: 1) propofol, relative to isoflurane, hastens the recovery of global left ventricular function following a reperfused ischemic insult; 2) isoflurane, relative to propofol, better preserved EF during a two-hour period of ischemia; and 3) neither anesthetic is significantly better at limiting the degree of myocardial necrosis. These data suggest that there are no differences in long-term effects of either anesthetic following a period of ischemia and reperfusion. Considering these canine results, one can postulate that either propofol or isoflurane general anesthesia would be appropriate for maintaining a similar cardiovascular outcome following cardiac and major non-cardiac surgery, in patients with significant underlying coronary artery disease. However, further clinical studies would need to address any potential differences associated with these anesthetics in humans as opposed to dogs.

Acknowledgements

This work was funded by a grant to G.W. and R.T.T. from the Heart and Stroke Foundation of Ontario, as well as the Ontario Research and Development Challenge Fund, and the Imaging Networks of Ontario Cardiac Consortium. Financial support for K.T. was provided by a Natural Sciences and Engineering Research Council of Canada scholarship. We would like to thank both Dr. Rob Bartha and Siemens Canada for technical support, as well as Berlex Canada for the donation of Magnevist™. Drs. Carolyn Kerr and Adrian Gelb are acknowledged for their anesthesia insight.

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