Laboratory Report

Propofol, but not thiopentone or etomidate, enhances isoflurane-induced coronary vasodilatation in dogs

Paul S. Pagel MD PhD,*§¶
Douglas A. Hettrick PhD,*§
Judy R. Kersten MD,*§
Dermot Lowe MB FFARCSI,*§
David C. Warltier MD PhD*†‡§¶

Purpose: To test the hypothesis that thiopentone, propofol, and etomidate alter the coronary vascular effects of abruptly administered isoflurane.

Methods: Dogs (n = 6) received inspired isoflurane 5% in the presence of thiopentone (20 $mg \cdot kg^{-1}$ induction dose and 20 $mg \cdot kg^{-1} \cdot hr^{-1}$ infusion), propofol (5 $mg \cdot kg^{-1}$ induction dose and 40 $mg \cdot kg^{-1} \cdot hr^{-1}$ infusion), etomidate (2 $mg \cdot kg^{-1}$ induction dose and 5 $mg \cdot kg^{-1} \cdot hr^{-1}$ infusion), or isoflurane (1.0 MAC) anaesthesia in a random fashion. Haemodynamics were assessed in the conscious state, during baseline anaesthesia, and at 30 sec intervals for five minutes after beginning isoflurane 5%.

Results: Rapidly administered isoflurane caused greater ($P < 0.05$) reductions in coronary vascular resistance in thiopentone- or propofol- than in isoflurane-anaesthetized dogs. Isoflurane produced greater ($P < 0.05$) increases in the ratio of coronary blood flow velocity to pressure-work index (an index of myocardial oxygen consumption; +109 ± 19 % during isoflurane alone *vs* +182 ± 27 % change from baseline during propofol and isoflurane) consistent with relatively greater direct coronary vasodilatation during baseline propofol than during baseline isoflurane anaesthesia. Isoflurane caused larger increases in coronary blood flow velocity in dogs anaesthetized with etomidate concomitant with higher coronary perfusion pressure and pressure-work index than in those anaesthetized with isoflurane alone.

Conclusions: The results suggest that thiopentone, propofol, and etomidate each uniquely modify the coronary vascular responses to abrupt administration of high inspired concentrations of isoflurane in chronically instrumented dogs.

Objectif : Vérifier l'hypothèse qui veut que le thiopental, le propofol et l'étomidate modifient les effets vasculaires coronariens de l'administration rapide d'isoflurane.

Méthode : Des chiens (n = 6) ont reçu une anesthésie par inhalation d'isoflurane 5 % combiné au thiopental (20 $mg \cdot kg^{-1}$ comme dose d'induction et 20 $mg \cdot kg^{-1} \cdot hr^{-1}$ pour la perfusion), au propofol (5 $mg \cdot kg^{-1}$ à l'induction et 40 $mg \cdot kg^{-1} \cdot hr^{-1}$ à la perfusion), à l'étomidate (2 $mg \cdot kg^{-1}$ à l'induction et 5 $mg \cdot kg^{-1} \cdot hr^{-1}$ à la perfusion), ou à l'isoflurane (1,0 CAM) de façon aléatoire. Les paramètres hémodynamiques ont été évalués chez l'animal éveillé, pendant l'anesthésie de base et à intervalles de 30 s pendant cinq minutes après le début de l'isoflurane 5 %.

Résultats : L'administration rapide d'isoflurane a causé des réductions plus importantes ($P < 0,05$) de résistance vasculaire coronarienne chez les chiens qui ont reçu du thiopental, ou du propofol, que chez ceux qui ont reçu une anesthésie avec l'isoflurane. L'isoflurane a produit un accroissement plus grand ($P < 0,05$) du rapport entre la vitesse du flux sanguin coronarien et l'index travail-pression (un index de la consommation d'oxygène par le myocarde; +109 ± 19 % pendant l'anesthésie avec l'isoflurane seul *vs* +182 ± 27 % de changement par rapport à l'anesthésie de base avec l'emploi de propofol et d'isoflurane) concordant avec une vasodilatation coronarienne directe relativement plus grande pendant l'anesthésie de base au propofol que pendant l'anesthésie de base à l'isoflurane. L'isoflurane a provoqué des hausses plus marquées de la vitesse du flux sanguin coronarien chez les chiens anesthésiés avec l'étomidate, hausses qui étaient concomitantes à des pressions de perfusion coronarienne et à un index plus élevés que chez ceux qui ont reçu de l'isoflurane seulement.

Conclusion : Les résultats suggèrent que, selon ses caractéristiques propres, chacun des anesthésiques, thiopental, propofol et étomidate, modifient les réactions vasculaires coronariennes à l'administration rapide de grandes concentrations d'isoflurane inhalées par des chiens en monitorage prolongé.

From the Departments of Anesthesiology,* Pharmacology and Toxicology,† Medicine (Division of Cardiovascular Diseases),‡ the Medical College of Wisconsin,§ the Clement J. Zablocki Veterans Affairs Medical Center,¶ Milwaukee, Wisconsin, and the Department of Biomedical Engineering, Marquette University, Milwaukee, Wisconsin.

Address correspondence to: Paul S. Pagel MD PhD, Medical College of Wisconsin, MEB - Room 462C, 8701 Watertown Plank Road, Milwaukee, Wisconsin 53226. Phone: 414-456-5735; Fax: 414-456-6507; Email: abarnes@mcw.edu

This work was supported by a grant from the Foundation for Anesthesia Education and Research (JRK), US PHS grants HL54820 (DCW) and HL03690 (JRK), and Anesthesiology Research Training Grant GM08377 (DCW).

Accepted for publication May 27, 1998.

ABRUPT administration of isoflurane has been shown to cause marked coronary vasodilatation in blood-perfused hearts *in situ*, in contrast to the modest increases in coronary blood flow observed when the concentration of isoflurane was gradually increased.[1] These findings indicated that the rate of administration of isoflurane profoundly affects the coronary vasodilating actions of this volatile anaesthetic. The effects of intravenous anaesthetics on the coronary vascular responses to abrupt increases in isoflurane concentration have not been examined. High concentrations of thiopentone, propofol, and etomidate have been shown to produce modest vasodilatation in coronary artery rings[2,3] and in isolated[4,5] and intact hearts.[6,7] However, the direct coronary vasodilatation produced by these drugs may be overcome by decreases in coronary blood flow caused by metabolic and pressure autoregulation.[8] In fact, decreases in coronary blood flow concomitant with reductions in myocardial oxygen consumption have been observed in dogs[9] and patients with[10,11] and without[12] coronary artery disease anaesthetized with intravenous anaesthetics. We tested the hypothesis that thiopentone, propofol, and etomidate modify the coronary vascular effects of abrupt administration of isoflurane in chronically instrumented dogs. This model was employed to facilitate direct comparison between experimental groups and to avoid the confounding influences of baseline anaesthetics and acute surgical instrumentation.

Materials and methods

All experimental procedures and protocols used in this investigation were reviewed and approved by the Animal Care and Use Committee of the Medical College of Wisconsin. All procedures conformed to the *Guiding Principles in the Care and Use of Animals* of the American Physiological Society and were performed in accordance with the *Guide for the Care and Use of Laboratory Animals*, [DHEW(DHHS) publication (NIH) no. 85-23, revised 1996].

Experimental model

The surgical implantation of instruments has been previously described in detail.[13] Briefly, in the presence of general anaesthesia [inspired isoflurane 1.5 to 2.0% in oxygen, 2.5 to 5 $\mu g \cdot kg^{-1}$ fentanyl, and 0.1 $mg \cdot kg^{-1}$ vecuronium] and using aseptic techniques, a left thoracotomy was performed in conditioned mongrel dogs for placement of instruments for measurement of aortic and left atrial pressures (heparin-filled catheters), aortic blood flow (Doppler flow transducer), left anterior descending coronary artery (LAD) blood flow velocity (ultrasonic flow transducer), subendocardial segment length (ultrasonic crystals), left ventricular (LV) pressure (high fidelity, miniature micromanometer), and the maximum rate of increase of LV pressure ($+dP/dt_{max}$). All instrumentation was firmly secured, tunnelled between the scapulae, and exteriorized *via* several small incisions. The pericardium was left widely open, the chest wall closed in layers, and the pneumothorax evacuated by a chest tube. All dogs received 5 $\mu g \cdot kg^{-1}$ fentanyl, *im*, prn for analgesia as needed after surgery. Dogs were allowed to recover a minimum of seven days prior to experimentation. All dogs were treated with antibiotics [40 $mg \cdot kg^{-1}$cephalothin and 4.5 $mg \cdot kg^{-1}$gentamicin, *im*] and trained to stand quietly in a sling during haemodynamic monitoring. Segment length and coronary blood flow velocity signals were monitored by ultrasonic amplifiers. End-systolic (ESL) and end-diastolic segment length (EDL) were measured 30 msec before LV diastolic negative dP/dt and prior to the onset of LV isovolumic contraction, respectively. The segment lengths were normalized using the method of Theroux *et al.*[14] Percent segment shortening (%SS) was determined using the equation: $\%SS = (EDL\text{-}ESL) \cdot 100 \cdot EDL^{-1}$. Relative diastolic and mean coronary vascular resistances were calculated as the quotients of diastolic and mean arterial pressure to diastolic and mean coronary blood flow velocity, respectively. Coronary perfusion pressure was calculated as the difference between diastolic arterial pressure and LV end-diastolic pressure. An estimate of myocardial oxygen consumption, the pressure work index (PWI), was determined using a previously validated formula.[15] Haemodynamic data were continuously recorded on a polygraph and simultaneously digitized and recorded on a computer.

Experimental protocol

Each dog [n = 6; weight = 25.7 ± 0.7 kg [mean ± SEM]] fasted overnight prior to experimentation. Fluid deficits were replaced with 500 ml saline 0.9%, and intravenous saline infusion was continued at 3 $ml \cdot kg^{-1} \cdot hr^{-1}$ for the duration of each experiment. After instruments were calibrated, baseline systemic and coronary haemodynamics were recorded in the conscious state. Dogs were assigned to receive isoflurane alone or thiopentone, propofol, or etomidate before and during abrupt administration of isoflurane in a random manner on different days. In the first group of experiments, isoflurane was used as the baseline anaesthetic. After inhalational induction and tracheal intubation, anaesthesia was maintained during positive pressure ventilation at 1.0 MAC (end-tidal concentration) isoflurane in an air-oxygen 25% mixture, and haemodynamics were recorded after 30 min anaesthetic equilibration. The canine MAC value for isoflu-

rane used in the present investigation was 1.28%.[16] Acid-base status (pH = 7.35 to 7.42) and arterial blood gas tensions (PO_2 = 80 to 110 and PCO_2 = 30 to 35 mmHg) were maintained at levels obtained in the conscious state by adjustment of air and oxygen concentrations and respiratory rate throughout the experiment. End-tidal concentrations of isoflurane were measured at the tip of the endotracheal tube using an infrared gas analyser that was calibrated with known standards before and during experimentation. After 30 min equilibration at 1.0 MAC isoflurane, the inspired concentration of isoflurane was then acutely increased to 5% inspired, and haemodynamics and end-tidal anaesthetic concentrations were recorded at 30 sec intervals for five minutes.

In a second group of experiments, anaesthesia was induced with 20 mg·kg^{-1} thiopentone *iv* and maintained with a thiopentone infusion at 20 mg·kg^{-1}·hr^{-1}. After tracheal intubation, the lungs of each dog were mechanically ventilated with an air-oxygen mixture as described above. Haemodynamics were recorded after 30 min equilibration with the thiopentone infusion. Isoflurane (5% inspired) was then administered while the thiopentone infusion was continued and systemic and coronary haemodynamics were recorded at 30 sec intervals for five minutes. In two final groups of experiments conducted on different days, dogs received propofol (5 mg·kg^{-1} induction dose and 40 mg·kg^{-1}·hr^{-1} infusion) or etomidate (2 mg·kg^{-1} induction dose and 5 mg·kg^{-1}·hr^{-1} infusion) as the baseline intravenous anaesthetic before and during acute administration of isoflurane 5% inspired, and haemodynamics were recorded as described previously. At the completion of each experiment, all anaesthetics were discontinued and emergence was allowed to occur. Dogs recovered for at least 24 hr before subsequent experimentation. Thus, a total of 24 experiments in four separate groups (isoflurane, thiopentone, propofol, or etomidate as baseline anaesthetics before and during acute administration of isoflurane 5% inspired) were performed using the same six chronically instrumented dogs.

Statistical analysis

Statistical analysis of the data within and between groups in the conscious state and during anaesthetic interventions was performed by analysis of variance (ANOVA) with repeated measures, followed by Student's t test with Duncan's adjustment for multiplicity.[17] Changes were considered to be statistically significant when the P was < 0.05. All data are expressed as mean ± SEM.

Results

Isoflurane (1.0 MAC) caused increases in heart rate and decreases in mean arterial and LV systolic pressures, $+dP/dt_{max}$, %SS, cardiac output, and stroke volume ($P < 0.05$) (Table I). Data are presented at 60 sec intervals

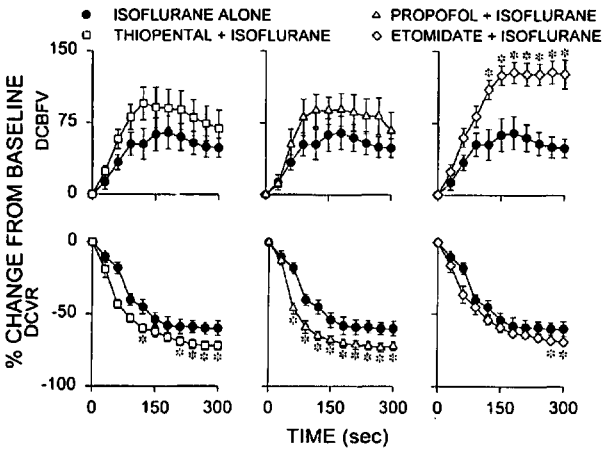

FIGURE 1 Time-course of alterations in diastolic coronary blood flow velocity (DCBFV; top panels) and diastolic coronary vascular resistance (DCVR; bottom panels) represented as the percent (%) change from the baseline anaesthetic before and during the abrupt administration of 5% inspired isoflurane in dogs anaesthetized with 1.0 MAC isoflurane alone (solid circles in all panels), thiopentone (open squares; left panels), propofol (open triangles; middle panels), or etomidate (open diamonds; right panels). *Significantly ($P < 0.05$) different from 1.0 MAC isoflurane alone.

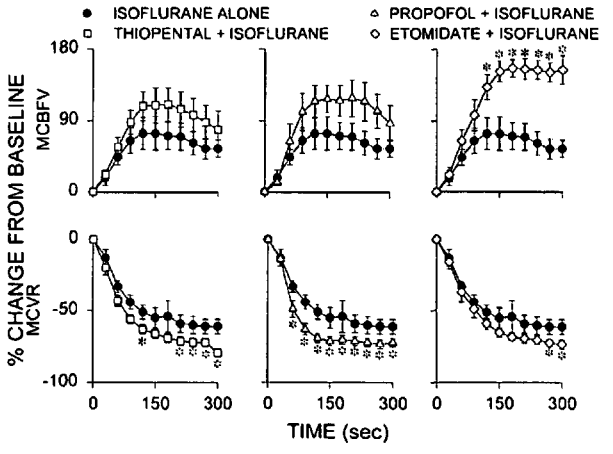

FIGURE 2 Time-course of alterations in mean coronary blood flow velocity (MCBFV; top panels) and mean coronary vascular resistance (MCVR; bottom panels) represented as the percent (%) change from the baseline anaesthetic before and during the abrupt administration of 5% inspired isoflurane in dogs anaesthetized with 1.0 MAC isoflurane alone (solid circles in all panels), thiopentone (open squares; left panels), propofol (open triangles; middle panels), or etomidate (open diamonds; right panels). *Significantly ($P < 0.05$) different from 1.0 MAC isoflurane alone.

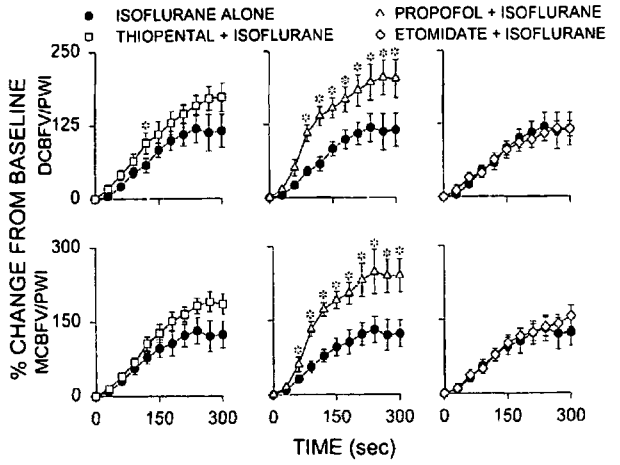

FIGURE 3 Time-course of alterations in the ratio of diastolic and mean coronary blood flow velocity (DCBFV and MCBFV, respectively) to pressure-work index (PWI) represented as the percent (%) change from the baseline anaesthetic before and during the abrupt administration of 5% inspired isoflurane in dogs anaesthetized with 1.0 MAC isoflurane alone (solid circles in all panels), thiopentone (open squares; left panels), propofol (open triangles; middle panels), or etomidate (open diamonds; right panels). *Significantly ($P < 0.05$) different from 1.0 MAC isoflurane alone.

for brevity in Tables I to IV. No changes in LV end-diastolic pressure, coronary perfusion pressure, diastolic and mean coronary blood flow velocity (63 ± 8 and 39 ± 5 during control to 55 ± 7 and 35 ± 4 $Hz \cdot 10^2$ during 1.0 MAC, respectively), diastolic and mean coronary vascular resistance (1.51 ± 0.22 and 2.84 ± 0.39 during control to 1.52 ± 0.19 and 2.57 ± 0.24 $mmHg \cdot Hz^{-1} \cdot 10^{-2}$ during 1.0 MAC, respectively), systemic vascular resistance, and pressure-work index occurred. Acute administration of isoflurane 5% inspired to dogs anaesthetized with 1.0 MAC isoflurane produced time-dependent decreases in mean arterial, LV systolic, and coronary perfusion pressures, $+dP/dt_{max}$ and %SS. Increases in heart rate and decreases in cardiac output, systemic vascular resistance, stroke volume, and pressure-work index were also observed. LV end-diastolic pressure was unchanged. Abrupt increases in isoflurane concentration produced increases in diastolic coronary blood flow velocity (e.g., 55 ± 7 during 1.0 MAC to 89 ± 14 $Hz \cdot 10^2$ 210 sec after beginning 5%) and decreases in diastolic coronary vascular resistance (e.g., 1.52 ± 0.19 during 1.0 MAC to 0.64 ± 0.12 $mmHg \cdot Hz^{-1} \cdot 10^{-2}$ 210 sec after beginning 5%; Figure 1). Corresponding time-dependent alterations in mean coronary blood flow velocity and vascular resistance were also observed (Figure 2). Acute administration of isoflurane 5% caused time-dependent increases in the ratio of diastolic coronary blood flow velocity to pressure work index (e.g., +109 ± 19 % change from 1.0 MAC alone 210 sec after beginning isoflurane 5%; Figure 3). Similar increases in the ratio of mean coronary blood flow velocity to pressure-work index were also observed.

Thiopentone increased heart rate and systemic vascular resistance and decreased $+dP/dt_{max}$, cardiac output, and stroke volume (Table II). No changes in mean arterial, LV systolic, LV end-diastolic, and coronary perfusion pressures or pressure-work index occurred. Diastolic and mean coronary blood flow velocity (73 ± 12 and 45 ± 7 during control to 72 ± 9 and 48 ± 6 $Hz \cdot 10^2$ during thiopentone alone, respectively) and the corresponding coronary vascular resistances (1.41 ± 0.20 and 2.62 ± 0.38 during control to 1.52 ± 0.20 and 2.48 ± 0.33 $mmHg \cdot Hz^{-1} \cdot 10^{-2}$ during thiopentone alone, respectively), were unchanged. Abrupt administration of isoflurane produced haemodynamic effects in thiopentone-anaesthetized dogs that were similar to those observed in dogs anaesthetized with 1.0 MAC isoflurane. Time-dependent increases in heart rate and decreases in mean arterial and LV systolic pressures, coronary perfusion pressure, $+dP/dt_{max}$, %SS, cardiac output, stroke volume, and pressure-work index were observed. Isoflurane increased diastolic and mean coronary blood flow velocity in thiopentone-anaesthetized dogs. Isoflurane-induced reductions in diastolic and mean coronary vascular resistance were more pronounced in dogs receiving thiopentone than those observed in dogs anaesthetized with isoflurane alone (Figures 1,2). Increases in the ratios of diastolic and mean coronary blood flow velocity to pressure-work index produced by isoflurane in dogs anaesthetized with thiopentone were similar to those observed with isoflurane alone (Figure 3).

Propofol increased heart rate and decreased mean arterial, LV systolic pressure, and coronary perfusion pressures, $+dP/dt_{max}$, and cardiac output (Table III). No changes in systemic vascular resistance, stroke volume, and %SS occurred. Diastolic and mean coronary blood flow velocity were unchanged (68 ± 12 and 43 ± 8 during control to 70 ± 13 and 45 ± 8 $Hz \cdot 10^2$ during propofol alone, respectively) but mean coronary vascular resistance decreased (2.91 ± 0.48 during control to 2.30 ± 0.42 $mmHg \cdot Hz^{-1} \cdot 10^{-2}$ during propofol alone). Isoflurane caused haemodynamic effects in dogs anaesthetized with propofol that were somewhat different from those observed when isoflurane or thiopentone was used as the baseline anaesthetic. Isoflurane increased heart rate, produced negative inotropic effects (e.g., reductions in $+dP/dt_{max}$, %SS, and cardiac output), and decreased pressure-work

TABLE I Haemodynamic effects of isoflurane

		Isoflurane	*Time after beginning isoflurane 5% (sec)*				
	Conscious	*(1.0 MAC)*	*60*	*120*	*180*	*240*	*300*
HR (bpm)	78 ± 3*	117 ± 11	138 ± 8*	141 ± 8*	135 ± 8*	131 ± 7	136 ± 5*
MBP (mmHg)	101 ± 4*	85 ± 3	81 ± 6	68 ± 5*	58 ± 5*	52 ± 5*	50 ± 6*
LVSP (mmHg)	122 ± 5*	97 ± 5	95 ± 7	81 ± 4*	72 ± 4*	64 ± 6*	61 ± 6*
LVEDP (mmHg)	7 ± 1	6 ± 1	7 ± 1	7 ± 1	7 ± 2	7 ± 2	7 ± 2
CPP (mmHg)	80 ± 4	72 ± 4	68 ± 7*	56 ± 5*	45 ± 5*	40 ± 5*	39 ± 5*
$+dP/dt_{max}$ ($mmHg \cdot sec^{-1}$)	2398 ± 175*	1685 ± 224	1644 ± 141	1326 ± 109*	1110 ± 93*	972 ± 81*	985 ± 89*
SS (%)	23.7 ± 1.9*	16.3 ± 1.6	14.9 ± 1.1	13.6 ± 1.1	13.6 ± 1.0*	11.9 ± 1.5*	12.1 ± 1.4*
CO ($L \cdot min^{-1}$)	2.5 ± 0.2*	1.9 ± 0.2	2.3 ± 0.4	2.0 ± 0.3	1.7 ± 0.3	1.4 ± 0.3	1.5 ± 0.3
SVR ($dyn \cdot s \cdot cm^{-5}$)	3380 ± 360	3860 ± 440	3110 ± 360	2960 ± 270*	2870 ± 250*	3130 ± 770	3120 ± 530
SV (ml)	32 ± 3*	16 ± 2	16 ± 2	14 ± 2	13 ± 2	11 ± 2*	11 ± 2*
PWI ($ml \cdot min^{-1} \cdot g^{-1}$)	9.1 ± 0.5	8.3 ± 0.7	9.4 ± 1.2	8.1 ± 0.8	7.0 ± 0.8	6.0 ± 0.8*	6.0 ± 0.8*
ΔET (%)	—	—	0.51 ± 0.25	1.55 ± 0.12	1.74 ± 0.10	1.92 ± 0.10	2.11 ± 0.11

Data are mean ± SEM; n = 6.

*Significantly ($P < 0.05$) different from 1.0 MAC isoflurane.

Abbreviations: HR = heart rate; MBP = mean aortic blood pressure; LVSP and LVEDP = left ventricular systolic and end diastolic pressure, respectively; CPP = coronary artery perfusion pressure; SS = segment shortening; CO = cardiac output; SV = stroke volume; SVR = systemic vascular resistance; PWI = pressure-work index; ΔET = change in end-tidal isoflurane concentration from baseline anesthetic.

TABLE II Haemodynamic effects of isoflurane in thiopentone-anaesthetized dogs

		Thiopentone	*Time after beginning isoflurane 5% (sec)*				
	Conscious	*Alone*	*60*	*120*	*180*	*240*	*300*
HR (bpm)	79 ± 4*	120 ± 19	156 ± 16*	164 ± 10*	152 ± 7*	144 ± 6*	139 ± 6
MBP (mmHg)	105 ± 3	109 ± 3	94 ± 4*	81 ± 6*	68 ± 5*	59 ± 5*	52 ± 4*
LVSP (mmHg)	126 ± 3	122 ± 4	113 ± 8*	95 ± 5*	84 ± 5*	70 ± 6*	62 ± 5*
LVEDP (mmHg)	9 ± 2	7 ± 2	6 ± 1	6 ± 1	6 ± 1	6 ± 1	6 ± 1
CPP (mmHg)	83 ± 3	93 ± 3	84 ± 6	72 ± 6*	57 ± 6*	46 ± 4*	40 ± 4*
$+dP/dt_{max}$ ($mmHg \cdot sec^{-1}$)	2388 ± 135*	1865 ± 152	1933 ± 134	1567 ± 104*	1251 ± 69*	1033 ± 32*	902 ± 17*
SS (%)	21.6 ± 0.9	18.1 ± 3.9	17.4 ± 4.5	15.4 ± 4.0	15.1 ± 3.0	14.3 ± 2.9*	13.4 ± 2.9*
CO ($L \cdot min^{-1}$)	2.5 ± 0.1*	1.7 ± 0.2	2.0 ± 0.1	1.8 ± 0.1	1.7 ± 0.2	1.5 ± 0.1	1.3 ± 0.1*
SVR ($dyn \cdot s \cdot cm^{-5}$)	3370 ± 130*	5460 ± 540	3800 ± 170*	3680 ± 440*	3460 ± 510*	3220 ± 270*†	3330 ± 310*
SV (ml)	32 ± 1*	16 ± 3	14 ± 2	11 ± 1*	11 ± 1*	10 ± 1*	9 ± 1*
PWI ($ml \cdot min^{-1} \cdot g^{-1}$)	9.4 ± 0.4	9.8 ± 0.9	10.9 ± 0.8	9.8 ± 0.8	8.1 ± 0.5*	6.7 ± 0.5*	6.0 ± 0.4*
ΔET (%)	—	—	1.10 ± 0.14	1.79 ± 0.11	2.13 ± 0.11	2.58 ± 0.07	2.80 ± 0.06

Data are mean ± SEM; n = 6.

*Significantly ($P < 0.05$) different from thiopental alone.

†Significantly ($P < 0.05$) different from dogs receiving isoflurane alone (Table 1).

Abbreviations: See Table 1.

index, systemic vascular resistance, and stroke volume during administration of propofol. However, isoflurane-induced decreases in mean arterial, LV systolic, and coronary perfusion pressures observed in propofol-anaesthetized dogs were greater than those observed in dogs receiving isoflurane in the presence or absence of thiopentone. Isoflurane increased both diastolic and mean coronary blood flow velocity in propofol-anaesthetized dogs (Figures 1,2). As was observed during administration of isoflurane to dogs receiving thiopentone, reductions in diastolic and mean coronary vascular resistance were greater in dogs receiving propofol and isoflurane than in those receiving isoflurane alone. In addition, increases in the ratios of diastolic coronary blood flow velocity to pressure-work index in response to abrupt administration of isoflurane were greater in propofol-anaesthetized dogs than in those receiving isoflurane alone (e.g., +109 ± 19 during isoflurane alone versus +182 ± 27% change from baseline during propofol and isoflurane 210 sec after beginning 5% isoflurane; Figure 3).

Etomidate decreased $+dP/dt_{max}$, cardiac output, and stroke volume and increased systemic vascular resistance (Table IV). No other changes in systemic haemodynam-

TABLE III Haemodynamic effects of isoflurane in propofol-anaesthetized dogs

		Propofol	*Time after beginning isoflurane 5% (sec)*				
	Conscious	*Alone*	*60*	*120*	*180*	*240*	*300*
HR (bpm)	81 ± 2*	118 ± 13	133 ± 8	137 ± 7*	133 ± 6	129 ± 6	128 ± 5
MBP (mmHg)	110 ± 5*	89 ± 7	69 ± 5*†	57 ± 4*†	50 ± 4*†	45 ± 4*	45 ± 4*
LVSP (mmHg)	131 ± 5*	102 ± 7	90 ± 11*	77 ± 9*	68 ± 8*	59 ± 7*	57 ± 8*
LVEDP (mmHg)	8 ± 2	6 ± 2	5 ± 1	5 ± 2	5 ± 2	6 ± 2	5 ± 2
CPP (mmHg)	89 ± 3*	76 ± 7	59 ± 5*†	47 ± 5*†	40 ± 5*†	33 ± 4*	34 ± 4*
$+dP/dt_{max}$ ($mmHg \cdot sec^{-1}$)	2373 ± 187*	1760 ± 160	1650 ± 153	1349 ± 114*	1136 ± 107*	966 ± 77*	985 ± 89*
SS (%)	20.1 ± 1.8	18.3 ± 2.7	17.5 ± 2.6	17.7 ± 2.9	16.4 ± 2.7	15.1 ± 2.0*	15.1 ± 2.8*
CO ($L \cdot min^{-1}$)	2.1 ± 0.2*	1.9 ± 0.2	2.0 ± 0.2	1.7 ± 0.2*	1.6 ± 0.1*	1.4 ± 0.2*	1.4 ± 0.2*
SVR ($dyn \cdot s \cdot cm^{-5}$)	4430 ± 560	3960 ± 600	2740 ± 730*	2870 ± 440*	2670 ± 390*	2710 ± 430*	2750 ± 450*
SV (ml)	26 ± 2	18 ± 3	17 ± 2	13 ± 2	12 ± 2*	11 ± 2*	11 ± 2*
PWI ($ml \cdot min^{-1} \cdot g^{-1}$)	8.9 ± 0.3	8.5 ± 0.8	8.2 ± 0.7	6.6 ± 0.5	5.9 ± 0.5*	5.2 ± 0.4*	5.1 ± 0.4*
ΔET (%)	—	—	0.80 ± 0.21	1.77 ± 0.13	2.10 ± 0.23	2.29 ± 0.27	2.71 ± 0.07

Data are mean ± SEM; n = 6.
*Significantly ($P < 0.05$) different from propofol alone.
†Significantly ($P < 0.05$) different from dogs receiving isoflurane alone (Table 1).
Abbreviations: See Table 1.

TABLE IV Haemodynamic effects of isoflurane in etomidate-anaesthetized dogs

		Etomidate	*Time after beginning isoflurane 5% (sec)*				
	Conscious	*Alone*	*60*	*120*	*180*	*240*	*300*
HR (bpm)	80 ± 3	77 ± 10	98 ± 14*	129 ± 14*	134 ± 8*†	134 ± 5*†	133 ± 3*†
MBP (mmHg)	106 ± 7	106 ± 5	105 ± 8	97 ± 6*†	86 ± 8*†	79 ± 8*†	71 ± 8*
LVSP (mmHg)	124 ± 8	122 ± 6	124 ± 8	115 ± 9	101 ± 9*	90 ± 9*	83 ± 10*
LVEDP (mmHg)	8 ± 1	10 ± 1	9 ± 2	8 ± 2	8 ± 2	8 ± 2	8 ± 2
CPP (mmHg)	83 ± 6	81 ± 5	83 ± 8	78 ± 7†	70 ± 7*	62 ± 7*	57 ± 7*
$+dP/dt_{max}$ ($mmHg \cdot sec^{-1}$)	2294 ± 142*	1929 ± 117	2128 ± 151	2075 ± 175†	1642 ± 115†	1454 ± 129*	1321 ± 154*
SS (%)	24.6 ± 3.6	22.2 ± 3.1	22.1 ± 3.6	20.9 ± 3.8	19.2 ± 2.8	18.6 ± 2.6*	17.9 ± 2.8*
CO ($L \cdot min^{-1}$)	2.2 ± 0.2*	1.5 ± 0.1	1.9 ± 0.2	2.0 ± 0.3	1.9 ± 0.3	1.8 ± 0.3†	1.6 ± 0.3
SVR ($dyn \cdot s \cdot cm^{-5}$)	4020 ± 430*	5700 ± 340	4540 ± 490	4200 ± 470*	4110 ± 660*	4100 ± 780*	4450 ± 750
SV (ml)	28 ± 3*	21 ± 3	21 ± 2	16 ± 2*	14 ± 2*	13 ± 2*	12 ± 2*
PWI ($ml \cdot min^{-1} \cdot g^{-1}$)	8.9 ± 0.6	7.7 ± 0.6	9.3 ± 0.9*	10.0 ± 0.9*	9.3 ± 0.9*†	8.5 ± 0.9†	7.9 ± 1.0†
ΔET (%)	—	—	0.46 ± 0.19	1.75 ± 0.30	2.16 ± 0.23	2.39 ± 0.28	2.74 ± 0.31

Data are mean ± SEM; n = 6.
*Significantly ($P < 0.05$) different from etomidate alone.
†Significantly ($P < 0.05$) different from dogs receiving isoflurane alone (Table 1).
Abbreviations: See Table 1.

ics were observed during etomidate anaesthesia. Diastolic and mean coronary blood flow velocity (68 ± 11 and 41 ± 6 during control to 62 ± 7 and 41 ± 4 $Hz \cdot 10^2$ during etomidate alone, respectively) and coronary vascular resistances (1.51 ± 0.24 and 2.89 ± 0.47 during control to 1.61 ± 0.29 and 2.76 ± 0.43 $mmHg \cdot Hz^{-1} \cdot 10^{-2}$ during etomidate alone, respectively) were also unaffected. Isoflurane increased heart rate and decreased mean arterial, LV systolic, and coronary perfusion pressures and $+dP/dt_{max}$ in the presence of etomidate. Pressure-work index increased early after beginning administration of isoflurane but returned to control values later as mean arterial pressure decreased. However, reductions in systemic and coronary perfusion pressures were less pronounced in dogs receiving etomidate and isoflurane than those observed in dogs receiving isoflurane with or without thiopentone or propofol. Isoflurane-induced increases in diastolic and mean coronary blood flow velocity were greater in the presence than the absence of etomidate (Figures 1,2). In contrast, isoflurane-induced reductions in diastolic and mean coronary vascular resistance and increases in the ratio of coronary blood flow velocity to pressure-work index were similar with and without etomidate as the baseline anaesthetic (Figures 1,2,3).

Discussion

The present results indicate that acute increases in inspired isoflurane concentration caused coronary vascular effects that were similar to those previously reported by our laboratory during mask induction with this volatile anaesthetic in dogs.[18] Diastolic coronary blood flow velocity increased by 63 ± 17 % 150 sec after beginning isoflurane 5% inspired in dogs previously anaesthetized with 1.0 MAC isoflurane. Corresponding reductions in diastolic and mean coronary vascular resistance observed with isoflurane alone in the present study were similar to those previously reported as well.[18] In addition, the abrupt increase in isoflurane concentration was also accompanied by an increase in the ratio of mean or diastolic coronary blood flow velocity to pressure-work index (Figure 3). These findings also agree with our previous results[18] and suggest that isoflurane-induced coronary vasodilatation exceeded the requirements of myocardial oxygen consumption during abrupt increases in isoflurane concentration. Although the coronary vasculature was equilibrated with 1.0 MAC isoflurane for 30 min in the present investigation, the coronary vascular actions of isoflurane were nearly identical when isoflurane 5% inspired was administered to conscious compared with isoflurane-anaesthetized dogs in the previous[18] and present studies, respectively. Thus, the potential influence of time-dependent, coronary vascular adaptation to the coronary vasodilating effects of isoflurane in the present results was probably minimal. The present findings confirm the results of Crystal *et al.*[1] who reported large increases in coronary blood flow despite concomitant decreases in myocardial oxygen consumption consistent with enhanced luxury perfusion during abrupt increases in intracoronary isoflurane concentration in blood-perfused canine hearts *in situ*. These authors[1] reported increases in coronary blood flow and decreases in coronary vascular resistance that were substantially greater in magnitude than those observed in the present investigation, however. It is likely that differences in the route of administration of isoflurane (i.e., inhalation *vs* intracoronary isoflurane-equilibrated blood) played an important role in the differences in coronary haemodynamics observed between the present and previous[1] studies.

The present results also indicate that thiopentone, propofol, and etomidate produce systemic and coronary haemodynamic effects that were very similar to those previously reported in chronically instrumented[19,20] and open-chest dogs.[7,9] The doses of thiopentone, propofol, and etomidate were chosen because we[19,20] have demonstrated that these doses provide stable anaesthesia in dogs and do not produce important alterations in coronary haemodynamics *in vivo*. The present results agree with the findings of several previous investigations in a variety of experimental models[2–7,19] demonstrating that thiopentone, propofol, and etomidate possess little direct coronary vasodilating properties.

Despite the lack of direct alteration in coronary haemodynamics produced by the intravenous anaesthetics, the present results demonstrate that dogs anaesthetized with thiopentone, propofol, and etomidate had different coronary vascular responses to the abrupt administration of high inspired concentrations of isoflurane compared to those initially anaesthetized with 1.0 MAC isoflurane alone. Increases in diastolic and mean coronary blood flow velocity caused by isoflurane in dogs anaesthetized with thiopentone were similar to those observed in isoflurane-anaesthetized dogs. However, isoflurane reduced diastolic and mean coronary vascular resistance to a greater extent in the presence *vs* the absence of thiopentone despite similar declines in coronary perfusion pressure between groups. These findings suggest that rapid administration of isoflurane during thiopentone anaesthesia may cause more pronounced coronary vasodilatation than isoflurane alone. However, isoflurane produced equivalent increases in the ratio of diastolic or mean coronary blood flow velocity to pressure-work index between experimental groups. These data suggest that baseline thiopentone anaesthesia does not substantially affect the increase in coronary blood flow produced by abrupt administration of isoflurane above that required to meet myocardial oxygen demand.

Similar to the findings during baseline thiopentone anaesthesia, isoflurane caused equivalent increases in diastolic and mean coronary blood flow velocity in dogs in the presence and absence of propofol. However, these findings occurred despite the fact that coronary perfusion pressure was lower during administration of isoflurane to propofol- than to isoflurane-anaesthetized dogs. As a result, decreases in diastolic and mean coronary vascular resistance were greater in dogs receiving propofol and isoflurane than in those receiving isoflurane alone. Increases in the ratios of diastolic or mean coronary blood flow velocity to pressure-work index caused by rapid administration of isoflurane were greater in the presence than in the absence of propofol. These findings indicate that the combination of baseline propofol anaesthesia and abruptly administered isoflurane causes more pronounced coronary vasodilatation and luxury perfusion than those observed during rapid increases in inspired isoflurane concentration alone. Although the degree of coronary vasodilatation produced by steady-state concentrations of isoflurane has been shown to be insufficient to redistribute coronary collateral blood

flow away from ischaemic myocardium[21,22] and does not appreciably exceed the requirements of metabolic demand,[23] the alterations in coronary haemodynamics produced by rapid increases in isoflurane concentration during propofol anaesthesia in the present investigation may be of sufficient magnitude to cause coronary steal in experimental models of or susceptible patients with coronary artery disease. This intriguing hypothesis remains to be tested in a laboratory or clinical setting, however.

In contrast to the findings during abrupt administration of isoflurane to dogs anaesthetized with thiopentone and propofol, isoflurane caused more pronounced increases in diastolic and mean coronary blood flow velocity in dogs receiving etomidate as the baseline anaesthetic than in those initially anaesthetized with 1.0 MAC isoflurane. However, coronary perfusion pressure and pressure-work index were higher in dogs receiving isoflurane in the presence of etomidate than in dogs receiving isoflurane alone. Although diastolic and mean coronary vascular resistance decreased during the abrupt administration of high inspired concentrations of isoflurane to etomidate-anaesthetized dogs, the reductions in coronary vascular resistance under these conditions were similar to those observed in dogs receiving isoflurane alone. In addition, increases in the ratios of diastolic or mean coronary blood flow velocity to pressure-work index produced by rapid administration of isoflurane were nearly identical in the presence and absence of etomidate. Thus, the present findings suggest that etomidate modifies the coronary haemodynamic effects of abruptly administered isoflurane primarily by preserving coronary perfusion pressure and not by producing direct actions on the coronary vasculature itself.

The results of the present investigation must be interpreted within the constraints of several potential limitations. Mathematical indices of myocardial oxygen consumption that incorporate stroke work or stroke volume into their calculation have been shown to be closely correlated to directly measured oxygen consumption in the intact heart.[24] The pressure-work index used in the present investigation has been previously demonstrated to provide a reliable estimate of myocardial oxygen consumption under a variety of loading conditions and contractile states when stroke volume can be accurately measured.[25] Recording of continuous proximal aortic blood flow using an ultrasonic flow transducer has been shown to quantify cardiac output and stroke volume precisely *in vivo*.[26] The pressure-work index has also been validated in the presence of volatile anaesthetics.[27,28] Nevertheless, the estimation of myocardial oxygen consumption with the pressure-work index requires qualification because coronary venous oxygen saturation was not measured and oxygen extraction and consumption were not directly calculated in the present investigation. The induction and maintenance doses of thiopentone, propofol, and etomidate were chosen because we[19,20] have previously demonstrated that these doses do not produce significant alterations in coronary haemodynamics in dogs. Continuous infusions of intravenous anaesthetics were used to establish steady-state pharmacological conditions because rapidly fluctuating plasma concentrations associated with a single bolus injection would have made study of the time course of the coronary vascular actions of abruptly administered isoflurane impossible to perform and interpret. Nevertheless, the present results should be qualified because thiopentone and etomidate are very rarely used for total intravenous anaesthesia. Increases in end-tidal isoflurane concentration were modestly less pronounced in dogs anaesthetized with isoflurane than those anaesthetized with thiopentone, propofol, or etomidate. This discrepancy in end-tidal isoflurane concentrations between dogs receiving isoflurane alone and those receiving isoflurane in the presence of intravenous anaesthetics may have also affected the results.

In summary, the present results indicate that high inspired concentrations of isoflurane rapidly administered cause greater reductions in coronary vascular resistance in thiopentone-or propofol- than in isoflurane-anaesthetized dogs. Isoflurane also produced larger increases in the ratio of coronary blood flow velocity to pressure-work index despite lower coronary perfusion pressure consistent with enhanced luxury perfusion during propofol than during isoflurane baseline anaesthesia. Isoflurane caused larger increases in coronary blood flow velocity concomitant with higher coronary perfusion pressure and myocardial oxygen consumption in dogs anaesthetized with etomidate than in those anaesthetized with isoflurane alone. Thus, the results suggest that thiopentone, propofol, and etomidate each uniquely modify the coronary vascular responses to abrupt administration of isoflurane in chronically instrumented dogs.

Acknowledgments

The authors thank Mr. John Tessmer and Mr. Todd Schmeling for technical assistance.

References

1 *Crystal GJ, Czinn EA, Silver JM, Salem MR.* Coronary vasodilation by isoflurane. Abrupt *versus* gradual administration. Anesthesiology 1995; 82: 542–9.

2 *Coughlan MG, Flynn NM, Kenny D, Warltier DC, Kampine JP.* Differential relaxant effect of high concen-

trations of intravenous anesthetics on endothelin-constricted proximal and distal canine coronary arteries. Anesth Analg 1992; 74: 378–83.

3 *Yamanoue T, Brum JM, Estafanous FG.* Vasodilation and mechanism of action of propofol in porcine coronary artery. Anesthesiology 1994; 81: 443–51.

4 *Stowe DF, Bosnjak ZJ, Kampine JP.* Comparison of etomidate, ketamine, midazolam, propofol, and thiopental on function and metabolism of isolated hearts. Anesth Analg 1992; 74: 547–58.

5 *Mouren S, Baron J-F, Albo C, Szekely B, Arthaud M, Viars P.* Effects of propofol and thiopental on coronary blood flow and myocardial performance in isolated rabbit heart. Anesthesiology 1994; 80: 634–41.

6 *Ismail EF, Kim S-J, Salem MR, Crystal GJ.* Direct effects of propofol on myocardial contractility in *in situ* canine hearts. Anesthesiology 1992; 77: 964–72.

7 *Moore PG, Kien ND, Boldy RM, Reitan JA.* Comparative effects of nitric oxide inhibition on the coronary vasomotor responses to etomidate, propofol, and thiopental in anesthetized dogs. Anesth Analg 1994; 79: 439–46.

8 *Feigl EO.* Coronary physiology. Physiol Rev 1983; 63: 1–205.

9 *Nakaigawa Y, Akazawa S, Shimizu R, Ishii R, Yamato R.* Effects of graded infusion rates of propofol on cardiovascular haemodynamics, coronary circulation and myocardial metabolism in dogs. Br J Anaesth 1995; 75: 616–21.

10 *Reiz S, Bålfors E, Friedman A, Häggmark S, Peter T.* Effects of thiopentone on cardiac performance, coronary hemodynamics and myocardial oxygen consumption in chronic ischemic heart disease. Acta Anaesthesiol Scand 1981; 25: 103–10.

11 *Stephan H, Sonntag H, Schenk HD, Kettler D, Khambatta HJ.* Effects of propofol on cardiovascular dynamics, myocardial blood flow and myocardial metabolism in patients with coronary artery disease. Br J Anaesth 1986; 58: 969–75.

12 *Larsen R, Rathgeber J, Bagdahn A, Lange H, Rieke H.* Effects of propofol on cardiovascular dynamics and coronary blood flow in geriatric patients. A comparison with etomidate. Anaesthesia 1988; 43 (Suppll): 25–31.

13 *Pagel PS, Kampine JP, Schmeling WT, Warltier DC.* Comparison of the systemic and coronary hemodynamic actions of desflurane, isoflurane, halothane, and enflurane in the chronically instrumented dog. Anesthesiology 1991; 74: 539–51.

14 *Theroux P, Franklin D, Ross J Jr, Kemper WS.* Regional myocardial function during acute coronary artery occlusion and its modification by pharmacologic agents in the dog. Circ Res 1974; 35: 896–908.

15 *Rooke GA, Feigl EO.* Work as a correlate of canine left ventricular oxygen consumption, and the problem of catecholamine oxygen wasting. Circ Res 1982; 50: 273–86.

16 *Steffey EP, Howland D Jr.* Isoflurane potency in the dog and cat. Am J Vet Res 1977; 38: 1833–6.

17 *Wallenstein S, Zucker CL, Fleiss JL.* Some statistical methods useful in circulation research. Circ Res 1980; 47: 1–9.

18 *Kenny D, Proctor LT, Schmeling WT, Kampine JP, Warltier DC.* Isoflurane causes only minimal increases in coronary blood flow independent of oxygen demand. Anesthesiology 1991; 75: 640–9.

19 *Pagel PS, Warltier DC.* Negative inotropic effects of propofol as evaluated by the regional preload recruitable stroke work relationship in chronically instrumented dogs. Anesthesiology 1993; 78: 100–8.

20 *Proctor LT, Schmeling WT, Warltier DC.* Premedication with oral dexmedetomidine alters hemodynamic actions of intravenous anesthetic agents in chronically instrumented dogs. Anesthesiology 1992; 77: 554–62.

21 *Cason BA, Verrier ED, London MJ, Mangano DT, Hickey RF.* Effects of isoflurane and halothane on coronary vascular resistance and collateral myocardial blood flow: their capacity to induce coronary steal. Anesthesiology 1987; 67: 665–75.

22 *Hartman JC, Kampine JP, Schmeling WT, Warltier DC.* Steal-prone coronary circulation in chronically instrumented dogs: isoflurane versus adenosine. Anesthesiology 1991; 74: 744–56.

23 *Abdel-Latif M, Kim S-J, Salem MR, Crystal GJ.* Phenylephrine does not limit myocardial blood flow or oxygen delivery during isoflurane-induced hypotension in dogs. Anesth Analg 1992; 74: 870–6.

24 *Braunwald E, Sobel BE.* Coronary blood flow and myocardial ischemia. *In:* Braunwald E (Ed.). Heart Disease. A Textbook of Cardiovascular Medicine, 3rd ed. Philadelphia: W.B. Saunders Company, 1988: 1191–221.

25 *Schipke JD, Burkhoff D, Kass DA, Alexander Jr A, Schaefer J, Sagawa K.* Hemodynamic dependence of myocardial oxygen consumption indexes. Am J Physiol 1990; 258: H1281–91.

26 *Hartman JC, Olszanski DA, Hullinger TG, Brunden MN.* In vivo validation of a transit-time ultrasonic volume flow meter. J Pharmacol Toxicol Methods 1994; 31: 153–60.

27 *Rooke GA.* Low-dose halothane anesthesia does not affect the hemodynamic estimation of myocardial oxygen consumption in dogs. Anesthesiology 1990; 72: 682–93.

28 *Priebe H-J.* Isoflurane and coronary hemodynamics. Anesthesiology 1989; 71: 960–76.