Laboratory Investigations

Comparison of nifedipine and metoprolol on collateral coronary blood flow in a swine model of chronic coronary obstruction and acute ischaemia during isoflurane anaesthesia

Davy C.H. Cheng MD MSc FRCPC,
Ming Tao Jiang MD PhD,
Buvanendran Asokumar MD, Patty Boylen BSc AHT,
Alan Sandler MB ChB MSC FRCPC

Purpose: This study compared the effects of nifedipine and metoprolol on collateral-dependent myocardial blood flow in a swine model of chronic coronary obstruction and acute ischaemia during isoflurane anaesthesia.

Methods: Collateral coronary circulation was induced in 15 three-week-old piglets by banding of the proximal left anterior descending coronary artery (LAD). After 8–10 wk, the distal LAD was ligated and the open-chest pigs were randomized to

receive infusions of either saline, nifedipine ($5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) or metoprolol ($10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) for 30 min during isoflurane anaesthesia (2%). Transient ischaemia was induced by 30 sec occlusion of the left circumflex artery. Arterial blood pressures, heart rate and regional myocardial blood flow (radio-labelled microspheres technique) were measured at the end of drug infusion (baseline) and one minute after transient ischaemia.

Results: No differences in the blood flow to the collateral-dependent (CD) myocardium or haemodynamic variables were observed at baseline among the three groups. Following transient ischaemia, in the nifedipine but not in the metoprolol group, blood flow to the CD myocardium was reduced by $28 \pm 24\%$ in the epicardium ($P < 0.05$) and $56 \pm 20\%$ in the endocardium ($P < 0.01$), resulting from intercoronary and transmural steal. This was associated with a moderate increase (10% , $P < 0.05$) in the heart rate in the nifedipine group.

Conclusions: In a swine model of chronic coronary obstruction and acute ischaemia during isoflurane anaesthesia, the collateral coronary blood flow was maintained in the presence of metoprolol, but reduced in the presence of nifedipine following transient ischaemia due to intercoronary and transmural steal.

Objectif: Comparer les effets de la nifédipine et du métoprolol sur le débit sanguin à dépendance collatérale sur un modèle porcin d'obstruction coronaire chronique et d'ischémie aiguë pendant l'anesthésie à l'isoflurane.

Méthode: La circulation coronaire collatérale a été initiée

Key Words:

ANAESTHETICS, VOLATILE: isoflurane;

HEART: ischaemia;

PHARMACOLOGY: nifedipine;

SYMPATHETIC NERVOUS SYSTEM, BETA RECEPTOR

ANTAGONIST: metoprolol.

From the Department of Anaesthesia, The Toronto Hospital, University of Toronto, Toronto, Ontario, Canada M5G 2C4.

Address correspondence to: Dr. D.C.H. Cheng, Department of Anaesthesia, BW 4-643, The Toronto Hospital, 200 Elizabeth Street, Toronto, Ontario, Canada M5G 2C4.

This study was supported in part by a grant from the Heart and Stroke Foundation of Ontario (No. AN1925) and The David Sheridan Research Award from the Canadian Anaesthetists' Society.

Phone: (416) 340-3567, Fax: (416) 340-3698.

Email: 75147.1500@compuserve.com

Accepted for publication 12th October, 1995.

chez 15 porcelets par baguage proximal de l'artère descendante antérieure gauche (DAG). Après 8 à 19 semaines, la DAG a été ligaturée distalement et, à thorax ouvert, les porcelets ont été repartis aléatoirement pour recevoir soit du sol. physiologique, de la nifédipine ($5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) ou du métoprolol ($10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) pour 30 min pendant une anesthésie à l'isoflurane (2%). L'ischémie transitoire a été réalisée par obstruction de l'artère circonflexe gauche pendant 30 sec. La pression artérielle, la fréquence cardiaque et le débit sanguin myocardique (technique des microsphères marquées) ont été mesurés à la fin de la perfusion du médicament (ligne de base) et une minute après l'ischémie transitoire.

Résultats: On n'a observé aucune différence tant pour le myocarde à débit sanguin à dépendance collatérale (DC) que pour les variables hémodynamiques entre les trois groupes. Après une ischémie passagère observée dans le groupe nifédipine mais pas dans le groupe métoprolol, le débit sanguin au myocarde DC a été réduit de $28 \pm 24\%$ à l'épicarde ($P < 0,05$) et de $56 \pm 20\%$ à l'endocarde ($P < 0,01$) par vol intercoronaire et transmural. Ceci a été associé à une augmentation modérée de la fréquence cardiaque (10%, $P < 0,05$) dans le groupe nifédipine.

Conclusion: Pendant l'anesthésie à l'isoflurane, sur un modèle porcin d'obstruction coronaire chronique et d'ischémie aiguë, le débit sanguin coronaire collatéral s'est maintenu avec le métoprolol mais a diminué avec la nifédipine à la suite d'une ischémie transitoire due à un vol intercoronaire et transmural.

Perioperative cardiac morbidity is a leading cause of mortality following anaesthesia and surgery. Evidence from clinical and laboratory studies indicates that preoperative administration of β blockers reduces the incidence of perioperative myocardial ischaemia in patients with coronary artery disease.¹⁻⁶ The clinical benefits of Ca^{++} channel blockers are still controversial.⁶⁻¹¹ Nifedipine was ineffective in relieving angina pectoris in some patients with coronary collateral vessels and/or a vasospastic component of angina.⁹ This was postulated to be due to a coronary steal phenomenon. In patients presenting for coronary bypass surgery, a higher incidence of perioperative myocardial ischaemia was observed in those receiving pre-treatment with Ca^{++} channel blockers than in those receiving β blockers.⁶ The effects of blockers and Ca^{++} channel blockers on the collateral coronary blood flow under general anaesthesia remain to be defined. In this study, we have compared the effects of the β -blocker metoprolol and the Ca^{++} channel blocker nifedipine on collateral coronary blood flow in a swine model of chronic coronary obstruction and acute ischaemia during isoflurane anaesthesia.

Methods

Induction of collateral coronary circulation

All experimental work conformed to the guidelines of the Canadian Committee for Animal Care, and was approved by the Animal Care Committee of The Toronto Hospital.

Approximately three week old piglets (6–8 kg) were used for induction of functional coronary collateral vessels, as described by Millard¹² and further detailed in our previous study.¹³ Briefly, the piglets were anaesthetized via mask with isoflurane. After tracheal intubation (5.5 mm ID cuffed tube), the lungs were mechanically ventilated and cefazolin (1 g, iv) was given. Through a left thoracotomy at the third intercostal space under sterile conditions, the pericardium was incised and the left atrium was reflected to expose the proximal left anterior descending coronary artery (LAD). A nonocclusive band of polyethylene tubing (PE-205, ID 1.57 mm, OD 2.08 mm) was secured with a 5-0 silk suture encircling the proximal third of the LAD, avoiding the anterior septal artery. The pericardium and chest were then closed and intercostal nerve blocks were performed with 2–3 ml of bupivacaine (0.25%) at each level. The animals were awakened and maintained for 8–10 wk (body weight 25–30 kg). During this period, collateral vessels were established in a region of myocardium distal to LAD stenosis (collateral dependent area, CD).^{12,13}

Study protocol

INSTRUMENTATION

Animals were fasted overnight with free access to water. On the day of study, general anaesthesia was induced with isoflurane. For ethical considerations, no muscle relaxant was used throughout the study. After tracheal intubation with a 6.0-mm ID cuffed endotracheal tube, mechanical ventilation was employed to maintain PaCO_2 between 35–40 mmHg. The ECG, arterial pressure (left carotid artery with 16-G catheter) and pulmonary arterial pressure (left internal jugular vein with 5 F Swan-Ganz catheter) were continuously monitored with a Gould recorder (Model TDA11, Interfax, Toronto, Ontario). The end tidal isoflurane vapour concentration was monitored continuously via a medical gas analyzer (Datex Instrumentarium Corp, Helsinki). The thorax and pericardium were opened through median sternotomy and a pericardial cradle was established. The constrictive band on the LAD was identified and ligated to ensure total LAD occlusion. Animals with inadequate collateral circulation will develop ventricular fibrillation and die within five to ten minutes ($n = 2$).

Further instrumentation included catheterization of the left atrium with a PE-205 catheter for injection of the microspheres and of bilateral femoral arteries with PE-190 catheters for reference blood flow samples. A transducer-tipped Millar catheter was inserted into the left ventricle via a apical incision for determination of the end diastolic pressure (LVEDP). All catheters were calibrated and checked for zero position drift before each measurement. Coronary perfusion pressure (CPP) was defined as diastolic arterial blood pressure minus LVEDP.

DETERMINATION OF HAEMODYNAMIC VARIABLES AND REGIONAL MYOCARDIAL BLOOD FLOW

Following instrumentation, isoflurane was maintained at about 2% to just prevent body movements (one MAC = 2.04%¹⁴). Animals were allowed to stabilize for 10–15 min and then randomly selected to receive a continuous infusion (via an injection pump) of saline, nifedipine ($5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) or metoprolol ($10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) for 30 min. The doses selected are within ranges of antianginal therapy in patients.^{6,9,15} At the end of drug infusion, baseline variables were recorded, including heart rate (HR), systolic and diastolic pressure, pulmonary arterial pressure, pulmonary capillary wedge pressure, LVEDP and arterial blood gases. For determination of regional myocardial flow, 2×10^6 radiolabelled microspheres (^{141}Ce or ^{113}Sn) were injected into the left atrium over a period of 20 sec. The microspheres were suspended in 1 ml dextran (20%) with Tween-80 (0.01%) and vigorously shaken for two minutes before injection. Withdrawal of blood samples from both femoral arteries was started 15 sec before injection of microspheres and continued for two minutes after injection, at a rate of $2 \text{ ml} \cdot \text{min}^{-1}$ using a Harvard injection pump (Harvard Apparatus, South Natick, MA).

After recording of baseline variables, transient myocardial ischaemia was induced by occluding the LCX for 30 sec with a silastic ligature fashioned into a pseudo-Rummel tourniquet. Haemodynamic measurements and regional myocardial blood flow were again determined one minute after release of the occlusion. At the completion of the study, a lethal dosage of KCl was injected to the left atrium to ensure euthanasia and the heart was isolated. Triphenyl tetrazolium chloride (TTC, 1% solution in sodium phosphate buffer) and Evans blue dye were simultaneously infused into the LAD distal to the occlusion and the proximal LCX respectively under equal pressure of 100 mmHg. The myocardium was transversely dissected from the apex into five sections and inspected for myocardial infarction. The red-stained LV myocardium was considered the collateral-

dependent area (CD) and the area stained blue was taken as the control area of normal perfusion (CNT). After removal of fat and fascia, tissue samples (1–2 g) were obtained from the epicardial (outer 1/3) and endocardial (inner 1/3) regions of the CNT and CD zones. Quantitation of radioactivity in the myocardial samples and the reference blood samples was determined for each radioisotope using a γ -counter (Packard Instrument). The radioactivity for each myocardial sample was corrected for background emission and Compton crossover. Regional coronary blood flow was expressed in $\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for CD and CNT regions. Transmural (intracoronary) blood distribution was expressed as the ratio of endocardial and epicardial blood flow for each area. Intercoronary blood flow redistribution was expressed as the ratio of blood flow for CD and CNT.

A total of 19 swine were studied. Two swine died after LAD ligation or torn LAD; one swine developed ventricular fibrillation during instrumentation and nifedipine infusion. One pig was discarded due to mishap in obtaining reference blood samples. Thus data on 15 swine were used for analysis.

Data analysis

Data are presented as mean $\pm$ SD. The haemodynamic variables and myocardial blood flow were compared with two way analysis of variance (ANOVA) for repeated measurements using NCSS software (Kaysville, Utah). Duncan's range test and paired *t* tests were used for *post hoc* inter- and intra-group comparisons respectively. $P < 0.05$ was taken as the level of significance.

Results

Systemic haemodynamic variables

Compared with saline, infusion of nifedipine and metoprolol for 30 min did not induce changes in systemic haemodynamic variables, including the HR, arterial and pulmonary blood pressures, rate pressure product (product of HR and systolic pressure), LVEDP, CPP and pulmonary capillary wedge pressure. The PO_2 , PCO_2 and pH values were similar for all three groups at baseline or after ischaemic insult. One minute after release of the transient coronary occlusion, the HR remained unchanged in the saline group but was slightly increased in the nifedipine group and reduced in the metoprolol group. Thus the rate pressure product was reduced in the metoprolol group. Other haemodynamic variables remained unaltered after transient coronary occlusion (Table).

TABLE Comparison of saline, nifedipine and metoprolol on haemodynamics and blood gas in swine

	Saline (n = 5)		Nifedipine (n = 5)		Metoprolol (n = 5)	
	Baseline	Post	Baseline	Post	Baseline	Post
ISO (%)	2.2 ± 0.2	2.2 ± 0.2	2.0 ± 0.0	2.0 ± 0.6	2.4 ± 0.6	2.2 ± 0.6
HR (bpm)	104 ± 5.6	106 ± 5.8	99 ± 8.9	110 ± 7.1*	107 ± 6.7	86.2 ± 6.1*†
SBP (mmHg)	102 ± 7.9	92 ± 5.8	92 ± 8.9	86.8 ± 7.5	97 ± 10.9	95.6 ± 11.2
DBP (mmHg)	67.6 ± 9.0	63 ± 3.5	60 ± 9.4	56 ± 8.9	60 ± 15.4	63.8 ± 13
PRP (bpm.mmHg)	10678 ± 1317	9797 ± 865	9175 ± 1609	9548 ± 1026	10337 ± 357	8032 ± 719*
LVEDP (mmHg)	13.5 ± 4.6	15 ± 4.1	15.4 ± 3.6	16 ± 4.2	15.4 ± 3.6	15.8 ± 3.6
CPP (mmHg)	53.8 ± 9.1	48.2 ± 5.7	44.6 ± 8.7	40 ± 8.7	49.4 ± 17	48 ± 15
SPAP (mmHg)	21 ± 3.3	23 ± 6.0	27.4 ± 9.6	28.8 ± 12	20.6 ± 4.0	21.8 ± 4.9
DPAP (mmHg)	14 ± 2.9	15.2 ± 5.4	16 ± 5.1	18.2 ± 4.7	13.8 ± 3.9	14.4 ± 4.0
PCWP (mmHg)	12.2 ± 2.7	11 ± 2.4	10.5 ± 6.4	9.5 ± 3.5	11.8 ± 4.8	11.4 ± 5.3
PO ₂ (mmHg)	440 ± 111	423 ± 111	428 ± 116	395 ± 89.3	501 ± 62	540 ± 41
pH	7.45 ± 0.08	7.42 ± 0.02	7.46 ± 0.07	7.46 ± 0.07	7.49 ± 0.09	7.47 ± 0.07
PaCO ₂ (mmHg)	38.9 ± 3.9	38.8 ± 3.8	38.1 ± 2.8	38.8 ± 2.2	37 ± 4.3	38.7 ± 3.8

Baseline: after infusion of saline, nifedipine or metoprolol for 30 min. Post: one min after release of occlusion of left circumflex artery.

ISO: isoflurane. HR: heart rate. bpm: beat per min. SBP: systolic arterial blood pressure, DBP: diastolic arterial pressure. PRP: pressure rate product, i.e., SBP*HR. LVEDP: left ventricular end diastolic pressure. CPP: coronary perfusion pressure. SPAP: systolic pulmonary arterial pressure; DPAP: diastolic pulmonary arterial pressure. PCWP: pulmonary wedge pressure. PO₂: arterial oxygen tension. PCO₂: arterial carbon dioxide tension.

* $P < 0.05$ – 0.002 compared with baseline.

† $P < 0.05$ compared with saline.

Coronary haemodynamic variables

In the CNT zone (Figure 1), nifedipine increased the baseline coronary blood flow to the epicardium but not to the endocardium ($P < 0.05$), compared with the saline and metoprolol groups. One minute after release of transient LCX occlusion, the myocardial blood flow to both epicardium and endocardium was not altered from baseline within each group.

In the CD zone (Figure 2), nifedipine and metoprolol did not alter the baseline myocardial blood flow to both the epicardium and endocardium compared with that of saline. After release of transient LCX occlusion, however, the myocardial blood flow was reduced by $28 \pm 24\%$ in the epicardium ($P < 0.05$) and $56 \pm 20\%$ in the endocardium ($P < 0.01$) in the nifedipine group; the myocardial blood flow was not altered within the saline or metoprolol groups. As a result, the postischaemic myocardial blood flow was lower in the nifedipine group than the other two groups in both the epicardium and the endocardium. Thus, the regional myocardial perfusion in the CD-dependent myocardium was maintained in the presence of metoprolol following transient coronary occlusion.

Coronary blood flow distribution

The transmural blood flow distribution was represented by the ratio of endocardial to epicardial flow (ENDO/EPI) (Figure 3). In both the CNT and CD zones,

the ENDO/EPI ratios in the metoprolol group was higher than the nifedipine or saline group at baseline. Following transient ischaemia, the ENDO/EPI ratio was reduced in the CD zone within the nifedipine group only. Intercoronary blood flow distribution was represented by the ratio of CD myocardial blood flow to that of CNT zone (CD/CNT) (Figure 4). In the epicardium, the CD/CNT ratio was lower in the nifedipine group than the metoprolol or saline group, at both baseline and following ischaemia ($P < 0.05$). In the endocardium, the CD/CNT ratios were not different between the three groups at baseline. However, after transient coronary occlusion, the CD/CNT ratio was reduced in the nifedipine group only ($P < 0.01$). Thus, the postischaemic CD/CNT ratio was lower ($P < 0.05$) in the nifedipine group than the metoprolol or saline group.

Pathological examination

The tissue slides of the left ventricle were inspected macroscopically. In both CD (stained red) and CNT zones (stained blue) no myocardial infarction was evident in any of the three group.

Discussion

The issue of whether β blockers or Ca⁺⁺ channel blockers offer better perioperative myocardial protection for patients with coronary artery disease during general anaesthesia is of particular interest to anaesthetists. In

FIGURE 1 Comparison of regional myocardial blood flow following saline, nifedipine and metoprolol infusion in the normally perfused myocardium (left circumflex artery-dependent) in swine with chronic coronary obstruction. Data are presented as mean $\pm$ SD. CNT, control myocardium. EPI, epicardium; ENDO, endocardium. BASE: baseline. POST: one min after release of transient coronary occlusion. SAL, NIF and MET represent saline, nifedipine and metoprolol group respectively. #, higher than SAL and MET groups ($P < 0.05$, $n = 5$).

the present study, we have compared the effects of nifedipine and metoprolol on regional coronary collateral blood flow in a swine model of chronic coronary obstruction and acute ischaemia during isoflurane anaesthesia. The results showed that the regional collateral blood flow in both endocardium and epicardium was maintained in the presence of metoprolol regardless of transient ischaemia, but was reduced in both regions of the CD zone due to intercoronary and transmural steal in the presence of nifedipine following transient ischaemia.

FIGURE 2 Comparison of regional myocardial blood flow in the collateral-dependent myocardium following saline, nifedipine and metoprolol infusion in swine with chronic coronary obstruction. CD, collateral-dependent myocardium. EPI, epicardium. ENDO, endocardium. SAL, NIF and MET represent saline, nifedipine and metoprolol group respectively. #, different from SAL and MET groups ($P < 0.05$). *, different from baseline ($P < 0.05-0.01$, $n = 5$).

Animal model and critique of methods

Similar to the human heart, the swine heart possess few pre-existing collateral vessels.¹² By creating a fixed stenosis of the LAD in the piglet, collateral vessels are induced to supply the myocardium distal to the LAD constriction during natural growth over 8–10 wk.^{12,13} In the present study, pathological examination revealed no myocardial infarction in any of the animals studied and collateral coronary flow was well established in the CD zone as demonstrated in the saline group (Figure 2).

FIGURE 3 Comparison of transmural distribution of myocardial blood flow (ENDO/EPI ratio) following saline, nifedipine and metoprolol infusion in open-chest swine with chronic coronary obstruction under isoflurane anaesthesia. CNT, control myocardium. CD, collateral-dependent myocardium. EPI, epicardium. ENDO, endocardium. BASE: baseline. POST, one min after release of transient coronary occlusion. SAL, NIF and MET represent saline, nifedipine and metoprolol group respectively. #, different from SAL and NIF groups ($P < 0.05$). *, different from baseline ($P < 0.05$). $n = 5$.

Our previous study¹³ showed that isoflurane, which is commonly used clinically, does not cause intercoronary or transmural steal in the same swine model. Therefore we chose to examine the effects of metoprolol and nifedipine on collateral myocardial blood flow in this

FIGURE 4 Comparison of intercoronary distribution of myocardial blood flow (CD/CNT ratio) following saline, nifedipine and metoprolol infusion in open-chest swine with chronic coronary obstruction under isoflurane anaesthesia. CD, collateral-dependent myocardium. CNT, control myocardium. EPI, epicardium. ENDO, endocardium. BASE, baseline. POST, one min after release of transient coronary occlusion. SAL, NIF and MET represent saline, nifedipine and metoprolol group respectively. #, different from SAL and MET group respectively ($P < 0.05$). *, different from baseline ($P < 0.01$). $n = 5$.

swine model during isoflurane general anaesthesia. Although nifedipine has been used clinically to treat coronary arterial spasm, Schulz *et al.*⁹ noted that patients with obstructed but collateralized coronary diseases responded poorly to nifedipine therapy, especially

those with vasospastic angina. Its underlying mechanisms were not clearly defined. In our study, transient ischaemia induced by coronary spasm was simulated by occluding the circumflex artery (which also supplies the collateral vessels) for 30 sec. In swine, the hyperaemic response following transient LAD occlusion during isoflurane anaesthesia was shown to be preserved up to 1.75 MAC,¹⁶ thus the coronary reactivity was likely preserved under 1 MAC used in the present study. As the reactive hyperaemia usually lasts twice the duration of flow arrest,^{16,17} we chose to measure regional blood flow at one min after release of LCX occlusion to obtain steady-state myocardial blood flow. The lack of any increase in the regional myocardial blood flow after transient LCX occlusion in the CNT myocardium confirmed the cessation of reactive hyperaemia. The use of a β blocker (propranolol¹⁸) or a Ca^{++} channel blocker (nifedipine or diltiazem¹⁹) is known to abbreviate reactive hyperaemia. Therefore, in the present study, the measurements of myocardial flow were likely minimally affected by reactive hyperaemia at one minute after flow arrest in all three groups.

Effects of nifedipine and metoprolol on collateral coronary blood flow

Nifedipine is a negative inotropic and vasodilatory agent blocking Ca^{++} entry through the dihydropyridine-sensitive Ca^{++} channels.^{10,11} Its clinical benefits in treating ischaemic heart disease and its effect on collateral coronary blood flow remain controversial in animal and human studies.⁷⁻¹¹ Schulz *et al.*⁹ failed to detect a beneficial effect of steady-state administration of nifedipine in patients with single coronary artery occlusion and collateral circulation. Pupita *et al.*²⁰ found recently that in patients with complete coronary artery occlusion with collateral circulation, acute administration of nifedipine (10 mg sublingually) increased time to ischaemic threshold and maintained rate pressure product in an exercise test; nitroglycerin increased both. Thus the nifedipine effect was postulated to be due to reduction of myocardial oxygen consumption rather than increasing blood flow to the collateral-dependent myocardium. In animal studies, nifedipine was shown to increase blood flow to the acutely ischaemic myocardium in dogs⁷ but not in baboons.⁸ In the present study, the blood flow to the CD zone was not altered although epicardial blood flow was increased in the CNT zone before ischaemic insult. Therefore, nifedipine induced intercoronary redistribution in the epicardium. Following transient LCX occlusion, however, the regional blood flow to the CD zone was reduced. This reduction was due to transmural and intercoronary steal (Figures 3 and 4). The redistribution of blood flow in the epicardi-

um at baseline and the intercoronary steal after transient ischaemia were likely due to a decline in CPP at the origin of the collateral circulation,²¹⁻²⁴ subsequent to differential coronary vasodilation between the CD and CNT zone.

To mimic the clinical situation, we did not intentionally control the CPP and HR. The results of our study indicate that the CPP (as well as diastolic pressure) was similar among the three groups, but tended to be lower in the nifedipine group than the saline or metoprolol group. We could not exclude the possibility that this nonsignificant decline in CPP (10-15%) in the nifedipine group might be due to the relatively small number of observations. However, it probably did not markedly affect the global myocardial blood flow due to coronary autoregulation. Further, it is also highly unlikely to account for the differential reduction in the myocardial blood flow in the CD zone following coronary flow arrest.

As the HR was not altered in the saline group following release of coronary occlusion, the moderate increase in the HR (11 bpm) in the nifedipine group may have resulted from the sympathetic reflex due to myocardial ischaemia. This change in the HR probably exerted minimal effect on the absolute coronary blood flow, but may have contributed to the change in the transmural flow distribution.²⁵⁻²⁷ It was shown that, in swine anaesthetized with sodium pentobarbitone,²⁷ an increase of heart rate by 40 beats per min caused a moderate reduction (10%) in total coronary flow, but markedly reduced (60%) the ENDO/EPI ratio. The reduction of collateral myocardial blood flow in the presence of nifedipine following transient ischaemia may provide an explanation to the clinical observation that nifedipine is ineffective in relieving angina pectoris in some patients with vasospastic components of angina.⁹

The negative inotropic and chronotropic effects of β -blockers reduce myocardial oxygen demand and are beneficial in the treatment of ischaemic heart diseases.¹⁻⁶ In conscious humans,²⁸ blockade caused coronary vasoconstriction but did not alter maximum coronary blood flow. Using a canine model of chronic coronary obstruction, Traverse *et al.*²⁹ showed that, during exercise, propranolol reduced myocardial blood flow in collateral-dependent and normal myocardium but increased the ENDO/EPI ratio. In acute ischaemia in conscious dogs, β blockade was shown to redistribute blood flow to endocardium.³⁰ The results of our study showed that metoprolol did not appreciably alter regional myocardial blood flow in either the CNT and CD zones during isoflurane anaesthesia, but improved the transmural blood flow ratio compared with that of saline and nifedipine. This increase in ENDO/EPI ratio was proba-

bly due to improved endocardial perfusion, as a result of the negative chronotropic effect of metoprolol. Thus, compared with nifedipine, myocardial perfusion is better preserved by metoprolol during isoflurane anaesthesia, especially after transient coronary occlusion. Metoprolol also decreased myocardial oxygen demand by decreasing the pressure rate product following transient myocardial ischaemia. Our data may explain, partly, the clinical observation that patients treated with β blockers have a lower incidence of perioperative ischaemic changes than with Ca^{++} channel blockers.⁶

Interaction between nifedipine, metoprolol and isoflurane

Isoflurane is considered a direct myocardial depressant and systemic vasodilator in both animals (including swine) and humans,^{13,31,32} which may be related to its interference with the intracellular Ca^{++} kinetics.³³ Recent studies in chronically instrumented dogs with a single or multiple vessel disease model^{34,35} or swine¹³ with enhanced collateral development failed to detect coronary steal with isoflurane. Results from the present study showing no transmural and intercoronary steal in the saline group at baseline confirmed our previous observation using the same swine model.¹³

In humans with coronary artery disease, moderate haemodynamic interaction was observed between Ca^{++} channel blockers and volatile anaesthetic agents,^{36–38} including verapamil and isoflurane,³⁶ halothane and nifedipine³⁷ or verapamil.³⁸ Interpretation of these clinical data, however, may be complicated by the presence of other medications including β blockers.³⁸ In dogs, isoflurane and halothane suppressed the reflex tachycardia induced by nicardipine and nifedipine respectively in a dose-dependent manner, while the hypotensive effect of the calcium channel blockers appeared to be additive to that of the anaesthetics.^{39,40} Similarly, β blockade is known to maintain perioperative haemodynamic stability and reduce perioperative myocardial ischaemia.^{1,6} In the present study, haemodynamic changes in both nifedipine and metoprolol groups were moderate. Isoflurane anaesthesia was thus likely responsible for the blunted haemodynamic changes with administration of nifedipine and metoprolol.

In summary, we have demonstrated that, in a swine model of chronic coronary obstruction and acute ischaemia during isoflurane anaesthesia, collateral-dependent myocardial blood flow was maintained with β blockade with metoprolol, but reduced with Ca^{++} channel blockade with nifedipine following transient coronary occlusion due to intercoronary and transmural steal.

References

- 1 Slogoff S, Keats AS, Ott E. Preoperative propranolol therapy and aortocoronary bypass operation. *JAMA* 1978; 240: 1487–90.
- 2 Hjalmarson A. International beta-blocker review in acute and postmyocardial infarction. *Am J Cardiol* 1988; 61: 26B–9B.
- 3 Sidi A, Davis RF. Esmolol decreases the adverse effects of acute coronary artery occlusion on myocardial metabolism and regional myocardial blood flow in dogs. *Anesth Analg* 1988; 67: 124–30.
- 4 Leone BL, Lehot J-J, Francis CM, Cutfield GR, Foex P. Beta-blockade reverses regional dysfunction in ischaemic myocardium. *Anesth Analg* 1987; 66: 607–14.
- 5 Sill JC, Nugent M, Moyer TP, Torres LE, Schaff HV, Tinker JH. Influence of propranolol plasma levels on hemodynamics during coronary artery bypass surgery. *Anesthesiology* 1984; 60: 455–63.
- 6 Chung F, Houston PL, Cheng DC, *et al.* Calcium channel blockade does not offer adequate protection from perioperative myocardial ischaemia. *Anesthesiology* 1988; 69: 343–7.
- 7 Henry PD, Shuchleib R, Borda LJ, Roberts R, Williamson JR, Sobel BE. Effects of nifedipine on myocardial perfusion and ischaemic injury in dogs. *Circ Res* 1978; 43: 372–80.
- 8 Geary GG, Smith GT, Suehiro GT, McNamara JJ. Failure of nifedipine therapy to reduce myocardial infarct size in the baboon. *Am J Cardiol* 1982; 49: 331–8.
- 9 Schulz W, Jost S, Kober G, Kaltenbach M. Relation of antianginal efficacy of nifedipine to degree of coronary arterial narrowing and to presence of coronary collateral vessels. *Am J Cardiol* 1985; 55: 26–32.
- 10 Weiner DA. Calcium antagonists in the treatment of ischemic heart disease: angina pectoris. *Coron Artery Dis* 1994; 5: 14–20.
- 11 Held PH, Yusuf S. Calcium antagonists in the treatment of ischemic heart disease: myocardial infarction. *Coron Artery Dis* 1994; 5: 21–6.
- 12 Millard RW. Induction of functional coronary collaterals in the swine heart. *Basic Res Cardiol* 1981; 76: 468–73.
- 13 Cheng DC, Moyers JR, Knutson RM, Gomez MN, Tinker JH. Dose-response relationship of isoflurane and halothane versus coronary perfusion pressures. Effects on flow redistribution in a collateralized chronic swine model. *Anesthesiology* 1992; 76: 113–22.
- 14 Eger EI II, Johnson BH, Weiskopf RB, *et al.* Minimum alveolar concentration of I-653 and isoflurane in pigs: definition of a supramaximal stimulus. *Anesth Analg* 1988; 67: 1174–6.
- 15 Åblad B, Carlsson E, Johnsson G, Regårdh C-G. Metoprolol. In: Scriabine A (Ed.). *Pharmacology of*

- Antihypertensive Drugs. New York: Raven Press, 1980: 247-62.
- 16 Gilbert M, Roberts SL, Mori M, Blomberg R, Tinker JH. Comparative coronary vascular reactivity and hemodynamics during halothane and isoflurane anesthesia in swine. *Anesthesiology* 1988; 68: 243-53.
 - 17 Cutfield GR, Francis CM, Foex P, Jones LA, Ryder WA. Isoflurane and large coronary artery haemodynamics. A study in dogs. *Br J Anaesth* 1988; 60: 784-90.
 - 18 Pauly TJ, Bittar N. Myocardial reactive hyperaemia responses in the dog after beta receptor block with propranolol. *Cardiovasc Res* 1971; 5: 440-3.
 - 19 Dymek DJ, Bache RJ. Effects of nifedipine and diltiazem on coronary reactive hyperaemia. *Cardiovasc Res* 1984; 18: 249-56.
 - 20 Pupita G, Mazzara D, Centanni M, et al. Ischaemia in collateral-dependent myocardium: effects of nifedipine and diltiazem in man. *Am Heart J* 1993; 126: 86-94.
 - 21 Becker LC. Conditions for vasodilator-induced coronary steal in experimental myocardial ischaemia. *Circulation* 1978; 57: 1103-10.
 - 22 Gross GJ, Warltier DC. Coronary steal in four models of single or multiple vessel obstruction in dogs. *Am J Cardiol* 1981; 48: 84-92.
 - 23 Patterson RE, Kirk ES. Coronary steal mechanisms in dogs with one-vessel occlusion and other arteries normal. *Circulation* 1983; 67: 1009-15.
 - 24 Kattus AA, Gregg DE. Some determinants of coronary collateral flow in the open-chest dog. *Circ Res* 1959; 7: 628-42.
 - 25 Feigl EO. Coronary physiology. *Physiol Rev* 1983; 63: 1-205.
 - 26 Bache RJ, Cobb FR. Effect of maximal coronary vasodilation on transmural myocardial perfusion during tachycardia in the awake dog. *Circ Res* 1977; 41: 648-53.
 - 27 McFalls EO, Duncker DJ, Sassen LM, Gho BC, Verdouw PD. Effect of antiischaemic therapy on coronary flow reserve and the pressure-maximal coronary flow relationship in anesthetized swine. *J Cardiovasc Pharmacol* 1991; 18: 827-36.
 - 28 Hodgson JM, Cohen MD, Szentpetery S, Thames MD. Effects of regional alpha- and beta-blockade on resting and hyperemic coronary blood flow in conscious, unstressed humans. *Circulation* 1989; 79: 797-809.
 - 29 Traverse JH, Altman JD, Kinn J, Dunker DJ, Bache RJ. Effect of β -adrenergic receptor blockade on blood flow to collateral-dependent myocardium during exercise. *Circulation* 1995; 91: 1560-7.
 - 30 Vatner SF, Baig H, Manders WT, Ochs H, Pagani M. Effects of propranolol on regional myocardial function, electrograms, and blood flow in conscious dogs with myocardial ischaemia. *J Clin Invest* 1977; 60: 353-60.
 - 31 Eger EI II. The pharmacology of isoflurane. *Br J Anaesth* 1984; 56: 71S-99S.
 - 32 Reiz S, Balfors E, Sorensen MB, Ariola S Jr, Friedman A, Truedsson H. Isoflurane - a powerful coronary vasodilator in patients with coronary artery disease. *Anesthesiology* 1983; 59: 91-7.
 - 33 Lynch C III. Differential depression of myocardial contractility by halothane and isoflurane in vitro. *Anesthesiology* 1986; 64: 620-31.
 - 34 Hartman JC, Kampine JP, Schmeling WT, Warltier DC. Steal-prone coronary circulation in chronically instrumented dogs: isoflurane versus adenosine. *Anesthesiology* 1991; 74: 744-56.
 - 35 Hartman JC, Kampine JP, Schmeling WT, Warltier DC. Alterations in collateral blood flow produced by isoflurane in a chronically instrumented canine model of multivessel coronary artery disease. *Anesthesiology* 1991; 74: 120-33.
 - 36 Kates RA, Kaplan JA, Guyton RA, Dorsey L, Hug CC Jr, Hatcher CR. Hemodynamic interactions of verapamil and isoflurane. *Anesthesiology* 1983; 59: 132-8.
 - 37 Schulte-Sasse U, Hess W, Marksches-Hornung A, Tarnow J. Cardiovascular interactions of halothane anesthesia and nifedipine in patients subjected to elective coronary artery bypass surgery. *Thorac Cardiovasc Surg* 1983; 31: 261-5.
 - 38 Schulte-Sasse U, Hess W, Marksches-Hornung A, Tarnow J. Combined effects of halothane anaesthesia and verapamil on systemic hemodynamics and left ventricular myocardial contractility in patients with ischaemic heart disease. *Anesth Analg* 1984; 63: 791-8.
 - 39 Tosone SR, Reves JG, Kissin I, Smith LR, Fournier SE. Hemodynamic responses to nifedipine in dogs anesthetized with halothane. *Anesth Analg* 1983; 62: 903-8.
 - 40 Hysing ES, Chelly JE, Doursout MF, Hartley C, Merin RG. Cardiovascular effects of and interaction between calcium blocking drugs and anesthetics in chronically instrumented dogs. III. Nicardipine and isoflurane. *Anesthesiology* 1986; 65: 385-91.