Midazolam-sufentanil *vs* sufentanil-enflurane for induction of anaesthesia for CABG surgery

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Purpose: To compare the effects of midazolam-sufentanil (Group I) and sufentanil-enflurane (Group II) anaesthesia on myocardial oxygenation and metabolism in patients with preserved ventricular function undergoing CABG surgery.

Methods: Patients randomized to Group I (n = 16) received midazolam 0.3 $mg \cdot kg^{-1}$ at induction of anaesthesia, 0.15 $mg \cdot kg^{-1}$ after tracheal intubation, followed by an infusion of 2.5-10.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Supplemental sufentanil (cumulative maximum of 5 $\mu g \cdot kg^{-1}$) was given for adverse haemodynamic responses. Group II (n = 16) received 5 $\mu g \cdot kg^{-1}$ sufentanil at induction. Additional sufentanil (maximum 5 $\mu g \cdot kg^{-1}$), and enflurane (0-3% inspired concentration) were administered for adverse haemodynamic responses. Haemodynamics, myocardial oxygen consumption (MVO_2), and lactate extraction were determined at the following times: 1) awake (AWA), 2) after induction (IND), and 3) after tracheal intubation (ETT).

Results: Systemic haemodynamics and myocardial metabolism were similar at AWA. Heart rate response was attenuated and MVO_2 reduced in Group I at IND ($P < 0.05$). Following AWA, myocardial lactate production (MLP) occurred more frequently in Group II *vs* Group I patients (9/16 *vs* 2/16) and at more individual measurement points (Group II: 10/64 *vs* Group I: 3/64). Myocardial lactate flux demonstrated a deleterious trend in Group II at ETT.

Conclusions: Compared with sufentanil-enflurane, midazolam-sufentanil anaesthesia resulted in comparable and acceptable haemodynamics and myocardial oxygenation in CABG patients.

Objectif : Comparer les effets de l'anesthésie produite avec un mélange midazolam-sufentanil (Groupe I) à celle du mélange sufentanil-enflurane (Groupe II) sur le métabolisme et l'oxygénation du myocarde chez des patients dont la fonction ventriculaire est préservée et qui doivent subir un pontage aortocoronarien.

Méthode : Les patients assignés au Groupe I (n = 16) ont reçu 0,3 $mg \cdot kg^{-1}$ de midazolam lors de l'induction de l'anesthésie, 0,15 $mg \cdot kg^{-1}$ après l'intubation endotrachéale et une perfusion de 2,5-10,0 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Du sufentanil supplémentaire a été administré, jusqu'à un maximum cumulatif de 5 $\mu g \cdot kg^{-1}$, pour contrer les réactions hémodynamiques défavorables. Le Groupe II (n = 16) a reçu 5 $\mu g \cdot kg^{-1}$ de sufentanil à l'induction. Du sufentanil additionnel, pour une dose maximale de 5 $\mu g \cdot kg^{-1}$ et de l'enflurane (par inhalation, en concentration de 0-3 %) ont été administrés dans le cas de réactions hémodynamiques indésirables. L'hémodynamique, la consommation d'oxygène du myocarde (MVO_2) et l'extraction de lactate ont été déterminés aux temps suivants : 1) à l'éveil (ÉVE), 2) après l'induction (IND) et 3) après l'intubation endotrachéale (IET).

Résultats : L'hémodynamique générale et le métabolisme du myocarde ont été similaires à l'ÉVE. La réaction de la fréquence cardiaque a été atténuée et MVO_2 réduit dans le Groupe I à l'IND ($P < 0,05$). Après le réveil, la production de lactate myocardique (PLM) est survenue plus souvent chez les patients du Groupe II que chez ceux du Groupe I (9/16 *vs* 2/16) et selon des points de mesure plus individuels (Groupe II : 10/64 *vs* Groupe I : 3/64). Le flux de lactate myocardique a démontré une tendance à la nocivité dans le Groupe II au moment de l'IET.

Conclusion : L'anesthésie à base d'une combinaison de sufentanil et d'enflurane et celle qui utilise du midazolam et du sufentanil présentent une hémodynamique et une oxygénation myocardique comparables et acceptables chez les patients qui subissent un pontage aortocoronarien.

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Presented in part at Canadian Anaesthetists' Society Annual meeting, Montreal, June 1991.

Accepted for publication September 12, 1998.

ALTHOUGH commonly used in cardiac anaesthesia,[1,2] midazolam is a potent vasodilator[2,3] and may impair coronary vascular autoregulation.[4] Studies employing the ECG[1] and transoesophageal echocardiography[1,5] have not demonstrated increased risk of myocardial ischaemia with midazolam. Myocardial lactate production (MLP) (i.e. coronary venous lactate concentration > systemic arterial lactate concentration) is a sensitive indicator of the development of myocardial ischaemia.[6] Utilizing MLP as a measure of ischaemia, the effect of midazolam-sufentanil anaesthesia (Group I) on myocardial oxygenation, metabolism and systemic haemodynamics was compared with that of sufentanil-enflurane anaesthesia (Group II).

Methods

With IRB approval and written informed consent, 32 patients with preserved ventricular function undergoing primary elective CABG were studied. As premedication, patients received 0.2 $mg \cdot kg^{-1}$ morphine *im* and 0.5 $mg \cdot kg^{-1}$ promethazine *im*. Following placement of a coronary sinus catheter, studies were performed at the following times: 1) awake (AWA); 2) after induction (IND); and 3) after tracheal intubation (ETT). Study measurements, calculations, and coronary sinus blood flow (CSBF) methodology have been described previously.[7] Myocardial lactate production was defined as myocardial lactate extraction (MLE) < 0% and myocardial lactate flux (MLF, $\mu mol \cdot min^{-1}$), as the product of CSBF and the coronary arteriovenous lactate concentration difference.

Baseline heart rate (HR) and mean arterial pressure (MAP) were recorded the day before operation. An adverse haemodynamic response was defined as a HR > 115% of baseline HR or an absolute limit of 115 bpm or a MAP >120% of baseline MAP of >60 sec duration.

Following AWA measurements, Group I received 0.3 $mg \cdot kg^{-1}$ midazolam *iv* over three minutes. Induction measurements were made, followed by tracheal intubation and ETT measurements. Immediately after ETT, 0.15 $mg \cdot kg^{-1}$ midazolam was infused over 15 min, followed by a variable-rate infusion of midazolam (2.5-10.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) adjusted to maintain control of haemodynamic responses. Supplemental sufentanil (maximum 5 $\mu g \cdot kg^{-1}$ cumulative dose) was administered for adverse haemodynamic response. Patients randomized to Group II received 5 $\mu g \cdot kg^{-1}$ sufentanil at induction of anaesthesia. After ETT, adverse haemodynamic responses were treated with sufentanil (maximum 5 $\mu g \cdot kg^{-1}$ cumulative dose) and enflurane (0-3% inspired).

All patients received 0.1 $mg \cdot kg^{-1}$ pancuronium to facilitate tracheal intubation and muscle relaxation.

Statistical analysis

Repeated-measures ANOVA was used to determine between-group differences in haemodynamic, myocardial oxygenation, and metabolism data with post hoc analysis using Student t tests with Bonferroni correction. Power analysis determined that 16 patients per group were required to detect a 30% difference between groups in MLE with $\alpha = 0.05$ and $\beta = 0.80$.

Results

Thirty-two patients were enrolled in the study. Study group demographics were comparable (Table I).

Pharmacological interventions

One Group I patient required sufentanil at IND. Three Group II patients required enflurane at IND and one required nitroglycerine. Total supplemental sufentanil dose was 2.5 $\mu g \cdot kg^{-1}$ (range: 1-5) in Group I and 1.2 $\mu g \cdot kg^{-1}$ (range: 0-5) in Group II. More Group I patients (14/16 *vs* 5/16) received prebypass sufentanil. Five Group II patients required no additional sufentanil supplementation after induction.

Systemic haemodynamics and myocardial oxygenation

Differences were confined to IND (Table II). Compared with Group II, Group I demonstrated lower MAP and Cardiac Index (CI), an attenuated HR response, a reduction in myocardial oxygen extraction (MOE) and myocardial oxygen consumption (MVO_2) without a decrease in CSBF. The LVSWI was lower in Group I than in Group II.

TABLE I Patient Demographics. All results mean ± SD.

	GROUP I *n = 16*	*GROUP II* *n = 16*
Age (yr)	63 ± 7	61 ± 10
Gender (M/F)	14/2	13/3
Weight (kg)	83 ± 14	83 ± 12
LVEDP (mmHg)	12 ± 4	12 ± 4
Ejection Fraction (%)	68 ± 8	70 ± 8
Beta-Blocker	10	14
Calcium Channel Blocker	12	13
Previous MI	9	7
History of Hypertension	8	4
Diseased Vessels (n)	2.5 ± 0.63	3.0 ± 0.34

Group I = Midazolam - Sufentanil
Group II = Sufentanil - Enflurane

TABLE II Haemodynamics and myocardial oxygenation. Results are mean ± SEM. *$P < 0.05$ *vs* SE.

		STUDY TIMES		
	Group	*AWA*	*IND*	*ETT*
HR (bpm)	I	59 ± 2.1	52 ± 1.9*	72 ± 2.5
	II	59 ± 2.5	68 ± 3.3	69 ± 3.4
MAP (mmHg)	I	95 ± 3.3	69 ± 2.6*	88 ± 3.3
	II	92 ± 2.3	84 ± 4.5	82 ± 3.8
CI ($l \cdot min^{-1} \cdot m^{-2}$)	I	3.06 ± 0.19	2.64 ± 0.11*	3.21 ± 0.12
	II	2.89 ± 0.15	3.31 ± 0.20	3.23 ± 0.19
SVRI (dynes·sec $\cdot cm^{-5} \cdot m^{-2}$)	I	2289 ± 108	1836 ± 80	2022 ± 109
	II	2343 ± 123	1779 ± 100	1812 ± 100
LVSWI ($g \cdot m \cdot m^{-2} \cdot beat^{-1}$)	I	84 ± 4.3	50 ± 3.0*	65 ± 3.5
	II	75 ± 4.3	66 ± 5.4	63 ± 4.6
MVO_2 ($ml \cdot min^{-1}$)	I	15.5 ± 2.3	10.8 ± 1.2*	12.5 ± 1.5
	II	13.2 ± 1.7	13.4 ± 1.5	11.9 ± 1.7
CSBF ($ml \cdot min^{-1}$)	I	151 ± 21	129 ± 14	141 ± 18
	II	124 ± 52	133 ± 14	118 ± 14
MLF ($mol \cdot min^{-1}$)	I	49 ± 12	43 ± 11	55 ± 16*
	II	48 ± 7	47 ± 13	26 ± 10
MOE (%)	I	57 ± 16	48 ± 1.3*	54 ± 1.5
	II	57 ± 2.0	56 ± 2.2	57 ± 1.7
MLP (n)	I	1	0	1
	II	1	2	2

Group I=Midazolam-Sufentanil; Group II=Sufentanil-Enflurane; HR=Heart Rate; MAP=Mean Arterial Pressure; CI=Cardiac Index; SVRI=Systemic Vascular Resistance Index; LVSWI=Left Ventricular Stroke Work Index; MVO_2=Myocardial Oxygen Consumption; CSBF=Coronary Sinus Blood Flow; MLF=Myocardial Lactate Flux; MOE=Myocardial Oxygen Extraction; MLP=Myocardial Lactate Production.

Myocardial ischaemia

One patient in each group exhibited MLP at AWA (Table II). Two myocardia became net lactate producers for the first time at IND (both in Group II). The solitary Group I patient with MLP at AWA ceased production at IND. Individual prebypass MLP incidence was 12.5% (2/16) in Group I patients and 57% (9/16) in Group II patients (P = NSD). Excluding the AWA study, MLP prevalence was 4.7% in Group I patients and 16% in Group II patients (3/64 *vs* 10/64 measurements) (P = NSD). The MLF showed a trend to myocardial ischaemia at ETT in Group II.

For comparison, ECG changes indicative of ischaemia were detected in 6/12 Group I and 4/12 Group II patients.

Discussion

Systemic haemodynamics and myocardial oxygenation

The reduction in MAP (-27%) at IND in Group I (*vs* -9% in Group II) was associated with a decrease in cardiac work (CI and LVSWI), MOE, and MVO_2, beneficial changes prior to myocardial revascularization. The HR decrease in Group I at IND was unexpected. A moderate increase in HR with midazolam has been documented in other studies.[4,8] The use of an opioid-phenothiazine premedicant may explain this difference in the current study.[9]

Myocardial lactate production and myocardial lactate flux

The MLF at ETT in Group I was more than twice that of Group II (55 *vs* 26 $\mu mol \cdot min^{-1}$), suggesting that Group II hearts were metabolizing less lactate, indicative of the development of myocardial ischaemia. The MLP, a well-accepted method for the detection of global myocardial ischaemia,[6] was not different between groups. The absence of MLP does not exclude ischaemia, but its presence in the context of this investigation assures it.

Sufentanil interventions

Eighty-eight percent of Group I patients (14/16) required prebypass sufentanil interventions to treat adverse haemodynamic responses, suggesting that the doses of midazolam employed in this study would be incapable of controlling autonomic responses if used alone in patients with preserved ventricular function.

Limitations

We chose MLP as the criterion for the diagnosis of myocardial ischaemia. While MLP may underestimate the incidence of *regional* ischaemia, when present MLP provides conclusive proof of clinically important burdens of myocardial ischaemia.[6] The MLP was defined stringently with MLE <0%, rather than a more positive value (e.g. 10%) in order to eliminate false-positives.

We chose to concentrate our report and discussion on the period surrounding induction of anaesthesia and tracheal intubation to avoid the confounding effects of surgical stimulation, cardiopulmonary bypass, and surgical revascularization on interpretation of the results. Our findings may be only applicable to patients with preserved ventricular function.

In conclusion, utilizing MLP as a measure of the development of myocardial ischaemia, our study suggests that, when combined with sufentanil, midazolam is a safe and effective induction agent for coronary patients with preserved ventricular function.

References

1 *Jain U, Body SC, Bellows W, et al.* Multicenter study of target-controlled infusion of propofol-sufentanil or sufentanil-midazolam for coronary artery bypass graft surgery. Anesthesiology 1996; 85: 522–35.

2 *Heikkilä H, Jalonen, J, Arola M, Kanto J, Laaksonen V.* Midazolam as adjunct to high-dose fentanyl anaesthesia for coronary artery bypass grafting operation. Acta Anaesthesiol Scand 1984; 28: 683–9.
3 *Raza SMA, Masters RW, Zsigmond EK.* Comparison of the hemodynamic effects of midazolam and diazepam in patients with coronary occlusion. Int J Clin Pharmacol Ther Toxicol 1989; 27: 1–6.
4 *Marty J, Nitenberg A, Blanchet F, Zouioueche S, Desmonts JM.* Effects of midazolam on the coronary circulation in patients with the coronary artery disease. Anesthesiology 1986; 64: 206–10.
5 *Messina AG, Paranicas M, Yao F-S, et al.* The effect of midazolam on left ventricular pump performance and contractility in anesthetized patients with coronary artery disease: effect of preoperative ejection fraction. Anesth Analg 1995; 81: 793–9.
6 *Hall RI, Moffitt EA.* Monitoring the coronary circulation. Anesthesiology Clinics of North America 1988; 6: 839–50.
7 *Hall RI, Murphy JT, Moffitt EA, Landymore R, Pollak PT, Poole L.* A comparison of the myocardial metabolic and haemodynamic changes produced by propofol-sufentanil and enflurane-sufentanil anaesthesia for patients having coronary artery bypass graft surgery. Can J Anaesth 1991; 38: 996–1004.
8 *Al-Khudhairi D, Whitwam JG, Chakrabarti MK, Askitopoulou H, Grundy EM, Powrie S.* Haemodynamic effects of midazolam and thiopentone during induction of anaesthesia for coronary artery surgery. Br J Anaesth 1982; 54: 831–5.
9 *Hug CC Jr, Hall RI, Angert KC, Reeder DA, Moldenhauer CC.* Alfentanil plasma concentration *v.* effect relationships in cardiac surgical patients. Br J Anaesth 1988; 61: 435–40.