Sevoflurane or halothane with target-controlled sufentanil infusions for coronary artery bypass surgery

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ABSTRACT

Objectives
Comparison of hemodynamics, circulatory efficiency, myocardial ischemia and recall during and after sevoflurane or halothane (0.6 MAC {Minimum Alveolar Concentration} inspired) combined with a target-controlled sufentanil infusion (2 ng.ml^{-1}) for coronary artery bypass grafting.

Methods
Prospective randomised non-blinded study in a university teaching hospital of 45 patients undergoing on-pump surgery. Inhalation anesthetic agent was delivered before, during and after cardiopulmonary bypass.

Results
Intraoperative hemodynamics were maintained within predetermined limits using vasoactive and cardioactive drugs. Heart rate was unchanged from baseline, however the sevoflurane-sufentanil group required more glycopyrrolate, indicating a tendency towards a slower heart rate. In both groups, similar low incidences of myocardial ischemia were detected. After induction of anesthesia, as well as intraoperatively, oxygen consumption decreased by up to 36.6% compared with the awake values in both groups. Oxygen delivery remained unchanged during all measuring periods. Mixed venous oxygen tensions rose after induction, even in patients with cardiac indices below 2.2 L.min^{-1}.m^{-2}, indicating maintenance of an effective circulation when utilising these techniques. Twelve hours postoperatively, oxygen consumption exceeded awake values by 31%. No explicit recall was reported by any patient on enquiry on the third postoperative day.

Conclusions
Low concentrations of sevoflurane or halothane, supplementing target-controlled sufentanil infusions, were both suitable for providing anesthesia for coronary bypass surgery.

Keywords: Coronary artery bypass grafting, anesthesia, hemodynamics, sevoflurane, halothane, sufentanil, mixed venous oxygen tension, oxygen consumption, balanced anesthesia

Introduction
High dosages of opioids alone do not reliably provide anesthesia or obtund autonomic responses during coronary artery bypass grafting (CABG).[1-3] Failure to achieve these goals may result in awareness, or the development of myocardial ischemia.[4-6] Techniques making use of an opioid in combination with either an inhaled anesthetic agent or infusions of propofol, are used to achieve these goals.[7-9] If the correct combination is employed, the deleterious circulatory effects of any one agent may be avoided, and optimal myocardial oxygen supply-demand balance may be facilitated.

Furthermore, early experimental work on animals[10-12] and more recently in humans[8,13-15] has shown that inhaled anesthetic agents, but not propofol, if administered both before aortic clamping and on reperfusion, reliably limit the degree of myocardial injury after cardiac surgery.[16] This study was designed to compare hemodynamics, circulatory efficiency, myocardial ischemia and explicit recall, when using either sevoflurane or halothane, in combination with sufentanil, for coronary artery bypass graft surgery.

Methods
Informed consent was obtained from 45 patients who were scheduled for on-pump coronary bypass graft surgery. Exclusion criteria were:
- Patients with an intra-aortic balloon pump in situ preoperatively.
- Patients undergoing CABG in addition to other procedures e.g. valve replacement or carotid endarterectomy.
- Patients who had experienced a previous unusual response to a halogenated anesthetic agent.
- Administration of an experimental drug within 28 days prior to the study.
- Suspected or known hepatic dysfunction or adverse reaction to halothane.
- Family or personal history of muscle disease (e.g. malignant hyperthermia).
- History of alcohol or drug abuse within the previous year.

Patients were randomly allocated (blind card draw) to one of two groups to receive either sevoflurane or halothane. The clinician responsible for the patient was not blinded as to which inhalation agent was used.

Premedication comprised oral lorazepam 0.025 mg.kg^{-1} and intramuscular morphine 0.15 mg.kg^{-1}. On arrival in the operating room, intravenous lorazepam (maximal dose 0.05 mg.kg^{-1} if considered necessary) was followed by placement of peripheral cannulae (14 to 16 gauge venous and 20 gauge radial arterial cannulae) and an internal jugular vein 8.5 French gauge introducer sheath. A 4-lumen balloon tipped thermodilution pulmonary artery catheter (Arrow®, Reading, PA, USA) was inserted via the introducer sheath. Radial artery, pulmonary artery and central venous blood pressures were transduced (Medex Medical® MX9504, Rossendale, Lancashire, Great Britain) and displayed on a multichannel monitor (Siemens® Sirecust 1281, Erlangen, Germany). Further monitoring included 5 lead EKG (standard

lead two, chest lead five and automated ST segment analysis), pulmonary artery, rectal and oesophageal temperatures. Cardiac output was measured by thermodilution and was calculated as the average of three measurements randomly spaced during the respiratory cycle. Mixed venous samples were obtained by withdrawing blood from the distal lumen of the pulmonary artery catheter after it had been withdrawn into the right ventricle.

Baseline hemodynamic measurements were recorded once the monitors had been calibrated. Prior to induction of anesthesia, patients were given sufficient fluid (6 % hydroxyethyl starch 200/0.5; Fresenius Kabi, Bad Homburg, Germany) to raise pulmonary artery wedge pressure (PAWP) by two to four mmHg above baseline values, provided pulmonary artery wedge pressures remained less than 16 mm Hg. While the patients breathed 100 % oxygen via a facemask attached to a circle-absorber breathing circuit (fresh-gas-flow 6L/min), a computer-controlled sufentanil infusion (Stelpump version 1.2 (University of Stellenbosch, South Africa), controlling a Graseby 3400 syringe pump) targeted to achieve and maintain a plasma concentration of 2 ng/ml throughout surgery, was commenced. The pharmacokinetic parameter set employed was that derived by Gepts and colleagues.[17] The k_{e0} value was 0.18 min^{-1} which resulted in a simulated time to peak effect following a bolus dose of 5.5 minutes. At this point an inspired concentration of approximately 0.6 minimum alveolar concentrations (MAC) of the volatile anesthetic agent (sevoflurane 1.2 kPa or halothane 0.5 kPa) was started, and vecuronium 1 mg was administered to prevent opioid-induced muscle rigidity. When the patient became apnoeic or unresponsive to verbal stimuli, etomidate 0.1 to 0.3 $mg.kg^{-1}$ followed by vecuronium 0.15 $mg.kg^{-1}$ was administered intravenously, and manual facemask intermittent positive pressure ventilation was commenced. After the simulated equilibration of the plasma and effect site concentrations of sufentanil occurred, a full hemodynamic study was completed during continued facemask ventilation. Thereafter, nasotracheal intubation was performed and mechanical ventilation commenced, utilising a tidal volume of 8-10 $ml.kg^{-1}$. The fresh gas flow was adjusted to 4 litres per minute (2 litres per minute each of oxygen and air). The rate of ventilation was adjusted to maintain end-tidal carbon dioxide partial pressures ($P_{ET}CO_2$) at 4.5 to 5.0 kPa.

In the period before initiation of cardiopulmonary bypass (CPB), heart rate (HR) was maintained between 45 and 75 beats per minute by administering boluses of esmolol 0.15 to 0.5 $mg.kg^{-1}$ followed by an infusion of 0.1 to 0.5 $mg.kg^{-1}.min^{-1}$ if needed, and/or glycopyrrolate in increments of 0.006 $mg.kg^{-1}$. Mean arterial blood pressure (MAP) was maintained within 20% of the pre-induction values as follows: If the MAP exceeded 120% of the pre-induction value or if myocardial ischemia was evident, esmolol as described above, and/or nitroglycerine (0.25 to 10 µg.kg-1.min-1) was administered.

If hypotension (defined as a MAP of less than 80% of the pre-induction value) occurred, and if the preload was considered inadequate, as judged by a pulmonary artery wedge pressure (PAWP) or central venous pressure (CVP) of less than two to four mmHg above baseline values, patients were given 6% hydroxyethyl starch, sufficient to raise PAWP to these levels, provided that PAWP remained less than 16 mm Hg. If ventricular preload and cardiac output were considered adequate and hypotension persisted, phenylephrine was administered in boluses of 50 to 500 µg and/or an infusion of between 0.1 to 3.0 $\mu g.kg^{-1}.min^{-1}$ was administered. If the cardiac index (CI) was less than 2.2 $L.min^{-1}.m^{-2}$, an adrenaline infusion was started at a dose of 0.02 $\mu g.kg^{-1}.min^{-1}$ and increased as needed.

Throughout hypothermic (30^{O}C) cardiopulmonary bypass (CPB), the infusion of sufentanil was continued, and an inhalational anesthetic agent (minimum 0.6 MAC) was added to the pump gases. A pump flow of 2.4 $L.^{-1}min^{-1}.m^{-2}$ was utilised. Mean arterial pressure was maintained at 70% of the patient's pre-induction values using phenylephrine as described above. If hypertension (defined during hypothermic cardiopulmonary bypass, as a MAP exceeding 80% of the pre-induction pressure) occurred, the concentration of inhaled anesthetic agent could be incrementally increased up to a maximum of 2.5 MAC, after which nitroglycerine, as described above, was administered. Oxygenated St. Thomas' solution passed through an ice bath (initial dose of 15 ml/kg followed by 300 ml every 20 minutes) was employed for cardioplegia.

Serum potassium concentrations were adjusted to values of between 5 to 6 $mmol.litre^{-1}$ prior to unclamping of the aorta. The protocol for internal defibrillation consisted of the following sequence until defibrillation was successful: 10, 10, 15 joules, lignocaine 1 $mg.kg^{-1}$, 15 joules, lignocaine 1 $mg.kg^{-1}$, 15 joules. As an indication of the degree of reperfusion dysrythmias, the number of countershocks, their total dose measured in joules and the total dosages of lignocaine required to facilitate defibrillation of the heart after aortic unclamping, were noted. The inhaled anesthetic agent was discontinued 5 minutes before weaning from CPB, whereupon a benzodiazepine (either midazolam 2 to 12 mg, lorazepam 1 to 2 mg or diazepam 5 to 7 mg) was administered to prevent awareness.

Before weaning from CPB, the patient's heart rate was adjusted to 80 to 110 beats per minute in sinus rhythm, utilising glycopyrrolate titrated to effect; if unsuccessful, a temporary epicardial pacemaker in VVI mode was employed. The serum ionised calcium level was adjusted to within the normal range after rewarming, and prior to weaning from CPB. Weaning from CPB was facilitated, if needed, by an adrenaline infusion as described above. Phenylephrine boluses could be used as a temporary measure if the systolic blood pressure decreased to less than 100 mmHg. A nitroglycerine infusion, as described above, was administered if myocardial ischemia, systemic hypertension or a PAWP greater than 20 mmHg occurred. After successful weaning from CPB, red blood cell concentrate was administered to restore the hematocrit to 30%. The volatile agent (the same one as was used initially) was reintroduced until completion of surgery.

Postoperatively patients received intermittent mandatory ventilation, which was facilitated by 5 mg boluses of diazepam and/or morphine at the discretion of the nurse in the cardiac surgery intensive care unit. Tracheal extubation occurred between 6 and 24 hours after surgery.

Patients were interviewed on the third postoperative day by the anaesthesiologist to establish whether they had experienced explicit recall of any intraoperative event. No specific set of questions was used.

Variables were recorded at the following stages:

Step 1: Prior to induction of anesthesia, before fluid loading,
Step 2: Prior to tracheal intubation whilst ventilating with a facemask,
Step 3: Immediately after tracheal intubation,
Step 4: Before sternotomy,
Step 5: Immediately after sternotomy,
Step 6: 10 minutes after successful weaning from CBP, and
Step 7: 12 Hours after completion of surgery.

These variables included: inspired oxygen concentration, arterial and pulmonary arterial blood pressures, pulmonary artery wedge and central venous pressures, cardiac output, arterial and mixed venous blood gases, hematocrit, blood temperature as measured by the distal thermistor of the pulmonary artery catheter, ST segment trending, heart rate, the total dosage of drugs used before, during and after CPB. Derived indices were calculated using standard formulae[18] and included body surface area, cardiac index, stroke volume and stroke index, left and

right ventricular stroke work indices (LVSWI and RVSWI), systemic and pulmonary vascular resistance (SVR), oxygen delivery (DO_2), oxygen consumption (VO_2) and oxygen extraction ratio (OER). Myocardial ischemia was considered to be present if 1 mm or more ST segment depression was present 60 milliseconds after the J point.

Intergroup comparisons were made at each step, using unpaired Student t-tests, after testing for normality of distribution and equal variances. Within-group analysis was performed using analysis of variance for repeated measures. The post hoc test employed if differences were detected, was the Student Newman Keuls test. Proportional data were compared using two-tailed Fisher's exact tests. An alpha value of 0.05 or less was regarded as indicating a significant difference.

Calculation of sample size: If a decrease in LVSWI of 20% from 50 $g.m.m^{-2}$ to 40 $g.m.m^{-2}$ (standard deviation of 12) is regarded as a clinically important difference, then group sample sizes of 23 each achieve a power of 81% to detect a difference with a significance level (alpha) of 0.05, using a two-sided two-sample t test.

Results:

Demographics (Table 1):

Twenty-four patients were enrolled in the halothane group and 21 in the sevoflurane group. The two groups were similar with respect to age, sex-distribution, mass, length and body surface area (Table 1). In addition, similar numbers had unstable angina and had suffered a previous myocardial infarction. Preoperatively however, more patients were categorised as New York Heart Association (NYHA) Class 3 for exercise tolerance in the halothane than in the sevoflurane group and there were more patients with NYHA Class 2 for angina in the sevoflurane than the halothane group. Pre-operative medications were comparable. The durations of cardiopulmonary bypass and of aortic cross-clamping were similar for the two groups.

Table 1: Patient demographics and pre-operative details:

Variable	**Halothane Mean (SD)** n = 24	**Sevoflurane Mean (SD)** n = 21	**CI-diff**
Age (Years)	56.1 (8.9)	60.0 (10.7)	-9.8 tot 2.1
Body Mass (kg)	76.0 (14.6)	80.0 (12.5)	-12.3 to 4.2
Height (cm)	166.4 (10.9)	167.5 (9.8)	-7.3 to 5.3
BSA (m^2)	1.84 (0.21)	1.89 (0.18)	-0.17 to 0.06
CPB-Time (min)	120 (45)	105 (25)	-7 to 37
Aortic clamp Time (min)	60 (21)	54 (16)	-5 to 18
Pre-operative details	**Halothane**	**Sevoflurane**	**P Fisher exact test (2-tailed)**
Male sex (n)	16	16	0.50
Unstable angina (n)	12	8	0.64
NYHA classification for angina (n)			
Class I	2	2	1.0
Class II	4	11	0.025
Class III	14	6	0.07
Class IV	4	2	0.67
NYHA classification for exercise tolerance (n)			
Class I	3	6	0.27
Class II	8	12	0.14
Class III	13	3	0.01
Previous myocardial infarction (n)	14	8	0.24
Pre-op chronic medication: (n)			
Beta-blocking drugs	17	15	1.00
Aspirin	18	18	0.47
Nitrate	21	17	0.69
Calcium channel blockers	4	8	0.18
Heparin	5	8	0.32
ACE inhibitor	10	5	0.34
Diuretic	5	6	0.73
Anti-diabetic drugs	6	4	0.73

Quantitative data are presented as mean (standard deviation). Haltothane = Halothane group; Sevoflurane = Sevoflurane group; CI Diff = 95% Confidence interval of the difference between means; BSA = body surface area; CPB-Time = duration of time on cardiopulmonary bypass; NYHA = New York Heart Association.

The period from before induction of anesthesia to before CPB (Tables 2-4):
Both groups underwent no significant changes in mean HR, MAP, CI, SVR, CVP, PAWP, DO_2 and OER. In the Halothane group, immediately after sternotomy, LVSWI was greater than all previous measurements and this value was also greater than that of the Sevoflurane group.

Ten minutes after CPB (Tables 2-4):
In both groups, MAP and SVR were less, while HR and CI were greater than all pre-bypass measurements. In the Halothane group, LVSWI was less than the post-intubation and the post-sternotomy measurements, but no different from the values obtained before and after induction of anesthesia. In the Sevoflurane group, LVSWI was unchanged and no different from that of the Halothane group. CVP, PAWP, DO_2 and OER remained unchanged in both groups.

***Twelve hours after surgery (Tables 2-4)*:**
Both groups exhibited increased temperature, VO_2, HR, CI and OER. These values were greater than those of all previous measurements, including those obtained before induction of anesthesia. HR was greater in the Halothane group than in the Sevoflurane group. In both groups, MAP and SVR had returned to values that were no different from the pre-CPB period, including the pre-induction measurements. P_vO_2 decreased to values similar to those obtained before anesthetic induction. LVSWI remained less than pre-induction values. In the Halothane group, although LVSWI was at its lowest, it was not different from that of the Sevoflurane group. In the Sevoflurane group, PAWP was at its lowest, but it was not different from that of the Halothane group. CVP and DO_2 remained unchanged in both groups

***Drug usage (Table 5)*:**
The Sevoflurane group received greater doses of glycopyrrolate during the pre-CPB period. A greater proportion of patients in the Halothane group required nitroglycerine to lower blood pressure during CPB. After CPB, ten of 24 patients in the halothane group compared with only one of 21 sevoflurane patients required phenylephrine to maintain blood pressure (p = 0.011). Apart from the foregoing exceptions, the dosage and proportions of patients needing cardio- and vasoactive drugs (esmolol, nitroglycerine, lignocaine and adrenaline) were similar in both groups throughout the pre-, intra-, and post-bypass periods.

Temperature (Table 4) decreased in both groups by approximately one degree Celsius during the period before CPB, those recorded immediately before and after bypass being similar. After induction of anesthesia, VO_2 decreased and P_vO_2 increased (by as much as 36% and 40% respectively) in both groups and these changes were sustained throughout the intraoperative period (Table 4). P_vO_2 in the Halothane group was greater than that of the Sevoflurane group only after tracheal intubation.

Hematocrit was slightly greater in the Sevoflurane group prior to surgery (Table 3). Thereafter it decreased progressively in both groups, reaching the lowest values immediately after CPB. Twelve hours postoperatively hematocrit increased to approximately 33%, values that were still lower than the pre-CPB measurements.

Two patients in each group exhibited myocardial ischemia during the pre-bypass period. There were no intergroup differences between the number of patients requiring defibrillation, the total amount of joules administered and the total dose of lignocaine needed to facilitate defibrillation (Table 6).

Table 2: Hemodynamic data (1)

Step	HR (beats per min)			MAP (mmHg)			CVP (mm Hg)			PAWP (mm Hg)		
	Halo	Sevo	CI-diff	Halo	Sevo	CI-diff	Halo	Sevo	CI-diff	Halo	Sevo	CI-diff
1. Before induction of anesthesia	69 (14)	62 (13)	-0.5 to 16	94.5 (13.1)	97.8 (17.0)	-12.4 to 5.7	7.3 (3.4)	9.1 (3.8)	-4 to 0.4	11.6 (5.3)	13.7 (3.7)	-4.9 to 0.7
2. Pre-intubation	62 (12)	59 (13)	-5 to 10	86.5 (13.7)	92.8	-16.5 to 3.8	9.7 (2.5)	10.2 (2.8)	-2.1 to 1.1	13.2 (2.9)	14.1 (3.3)	-2.7 to 1.0
3. Post-intubation	66 (13)	62 (13)	-4 to 12	96.2 (20.0)	88.0 (17.9)	-3.3 to 19.7	10.5 (3.0)	9.6 (2.0)	-0.7 to 2.4	14.2 (3.7)	13.8 (3.4)	-1.8 to 2.6
4. Pre-sternotomy	59 (10)	57 (7)	-5 to 7	87.2 (20.3)	82.8 (10.9)	-3.8 to 13.6	10.2 (3.5)	9.3 (2.6)	-1.0 to 2.9	14.0 (3.8)	13.1 (3.7)	-1.4 to 3.2
5. Post-sternotomy	62 (11)	66 (17)	-13 to 5	99.9 (19.0)	90.1 (14.1)	-0.4 to 20.0	10.2 (3.0)	9.7 (2.6)	-1.2 to 2.2	14.6 (3.8)	14.5 (5.1)	-2.6 to 2.8
6. 10' after weaning from CPB	* 97 (18)	* 95 (18)	-18 to 13	* 81.2 (9.1)	* 78.4 (8.7)	-2.6 to 8.1	10.0 (3.4)	9.8 (4.4)	-2.1 to 2.5	13.5 (4.6)	15.6 (6.3)	-5.4 to 1.2
7. 12 hours after surgery	* 99 (50)	* 89 (50)	# 0.2 to 19	84.7 (11.4)	87.3 (11.9)	-9.8 to 4.7	12.5 (4.8)	10.3 (3.8)	-0.5 to 4.9	12.6 (3.2)	11.0 (4.4)	-0.7 to 4.0

Data are presented as mean (standard deviation). Halo = Halothane group; Sevo = Sevoflurane group; CI Diff = 95% Confidence interval of the difference between means; MAP = Mean arterial pressure; CVP = central venous pressure; PAWP = pulmonary artery wedge pressure.
= HR at Step 7: Halothane and Sevoflurane groups differ (t-test, p = 0.046).
RM-ANOVA:
* = HR, Steps 6 & 7 differ from steps 1-5, but not from each other; MAP, Step 6 differs from steps 1-5;
9 = PAWP, (Sevoflurane group) Step 7 differs from steps 2, 5 & 6.

Table 3: Hemodynamic data (2)

	CI (L.min^{-1}.m^{-2})			LVSWI (g.cm.m^{-2})			SVR (dynes^{-5}.sec)			Hematocrit (%)		
Step	**Halo**	**Sevo**	**CI-diff**	**Halo**	**Sevo**	**CI-diff**	**Halo**	**Sevo**	**CI-diff**	**Halo**	**Sevo**	**CI-diff**
1. Before induction of anesthesia	2.88 (0.67)	2.81 (0.80)	-0.37 to 0.51	60.8 (14.4)	⊕69.0 (16.5)	-17.5 to 1.1	1406 (503)	1400 (3040)	-249 to 260	⊕44.1 (4.6)	⊕40.7 (3.6)	# 0.8 to 6.0
2. Pre-intubation	2.62 (0.60)	2.44 (0.67)	-0.20 to 0.55	57.5 (11.9)	60.0 (16.9)	-11.0 to 5.9	1391 (623)	1528 (523)	-486 to 212	40.4 (4.7)	37.9 (3.3)	# 0.1 to 5.0
3. Post-intubation	2.75 (0.59)	2.64 (0.75)	-0.30 to 0.50	62.3 (12.0)	58.6 (13.1)	-3.9 to 11.2	1495 (777)	1330 (392)	-213 to 543	38.9 (4.7)	37.0 (3.5)	-0.6 to 4.4
4. Pre-sternotomy	2.46 (0.47)	2.51 (0.68)	-0.43 to 0.27	58.2 (12.2)	57.3 (15.2)	-7.6 to 9.3	1472 (663)	1327 (450)	-214 to 505	36.3 (3.8)	35.9 (3.2)	-1.9 to 2.6
5. Post-sternotomy	2.68 (0.64)	2.53 (0.72)	-0.26 to 0.56	+ 68.1 (19.6)	56.2 (16.7)	# 0.8 to 22.9	1567 (560)	1452 (464)	-197 to 427	36.0 (3.9)	35.0 (3.5)	-1.3 to 3.3
6. 10' after weaning from CPB	* 3.84 (1.19)	* 3.81 (1.05)	-0.64 to 0.71	@ 51.9 (18.3)	51.9 (13.1)	-9.7 to 9.7	* 943 (537)	* 836 (287)	-158 to 371	⊕ 27.8 (4.6)	⊕ 26.1 (3.4)	-0.8 to 4.1
7. 12 hours after surgery	* 3.41 (0.78)	* 3.39 (0.90)	-0.50 to 0.55	* 46.6 (12.7)	51.3 (14.3)	-13.2 to 3.7	$ 972 (322)	$ 1026 (296)	-247 to 139	⊕ 32.6 (4.8)	x33.1 (3.7)	-3.2 to 2.1

Data are presented as mean (standard deviation). Halo = Halothane group; Sevo = Sevoflurane group; CI Diff = 95% Confidence interval of the difference between means;
CI = cardiac index; LVSWI = left ventricular stroke work index; SVR = systemic vascular resistance;
# = Halo and Sevo groups differ (t-tests $p < 0.05$): LVSWI at Step 5; Hematocrit at Steps 1 & 2.
RM-ANOVA:
* = CI, Steps 6 & 7 differ from steps 1 to 5, but not from each other; SVR, Step 6 differs from steps 1 to 5; LVSWI, (Halo group), Step 7 differs from all other steps.
⊕ = Differs from all other steps: LVSWI (Sevo group) Step 1, Hematocrit (both groups) Steps 1 & 6, Hematocrit (Halo group) Step 7.
+ = LWSWI (Halo group) Step 5 differs from Steps 2, 4, 6, 7
@ = LWSWI (Halo group) Step 6 differs from steps 3, 5
$ = SVR (both groups) Step 7 differs from step 5
x = Hematocrit (Sevo group) Step 7 differs from steps 1 to 4, 6

Table 4: Hemodynamic data (3)

	VO_2 (m/min)			DO_2 (m/minute)			P_vO_2 (kPa)			OER			Temperature (°C)		
Step	**Halo**	**Sevo**	**CI-diff**	**Halo**	**Sevo**	**CI-diff**	**Halo**	**Sevo**	**CI-diff**	**Halo**	**Sevo**	**CI-diff**	**Halo**	**Sevo**	**CI-diff**
1. Before induction of anaesthesia	⊕ 254 (62)	⊕ 242 (81)	-31 to 56	1033 (298)	984 (307)	-133 to 231	x 5.2 (0.6)	x 5.4 (1.0)	-0.8 to 0.2	0.25 (0.05)	0.26 (0.08)	-0.04 to 0.04	x 36.3 (0.6)	ψ 36.3 (0.5)	-0.4 to 0.4
2. Pre-intubation	183 (78)	177 (57)	-36 to 47	963 (307)	868 (292)	-85 to 277	7.3 (1.0)	6.9 (1.0)	-0.3 to 1.0	0.19 (0.05)	0.21 (0.05)	-0.05 to 0.01	36.0 (0.6)	35.9 (0.4)	-0.3 to 0
3. Post-intubation	163 (58)	183 (70)	-58 to 19	966 (274)	907 (287)	-109 to 229	@ 7.6 (1.0)	7.0 (1.1)	#0.02 to 1.3	0.17 (0.05)	0.21 (0.08)	-0.07 to 0.01	35.9 (0.6)	35.7 (0.5)	-0.2 to 0.5
4. Pre-sternotomy	161 (48)	166 (62)	-39 to 29	792 (192)	831 (262)	-179 to 100	6.3 (1.0)	6.2 (0.6)	-0.4 to 0.7	0.21 (0.06)	0.22 (0.05)	-0.03 to 0.04	35.5 (0.6)	35.1 (0.7)	-0.04 to 0.8
5. Post-sternotomy	173 (63)	169 (49)	-30 to 38	865 (288)	802 (229)	-95 to 221	6.4 (1.2)	6.1 (0.7)	-0.3 to 0.9	0.21 (0.06)	0.22 (0.06)	-0.05 to 0.03	35.4 (0.6)	35.1 (0.7)	-0.1 to 0.7
6. 10' after weaning from CPB	⊕ 206 (68)	205 (72)	-41 to 44	965 (364)	908 (276)	-140 to 253	7.4 (3.2)	6.3 (0.9)	-0.4 to 2.5	0.23 (0.09)	0.23 (0.06)	-0.04 to 0.05	35.2 (0.7)	35.2 (0.9)	-0.5 to 0.5
7. 12 hours after surgery	⊕ 319 (70)	⊕ 318 (107)	-55 to 57	978 (324)	988 (300)	-206 to 185	x 4.8 (1.1)	x 4.8 (0.9)	-0.6 to 0.6	* 0.35 (0.12)	* 0.34 (0.13)	-0.06 to 0.09	x 37.8 (1.0)	x 37.7 (1.0)	-0.4 to 0.8

Data are presented as mean (standard deviation). Halo = Halothane group; Sevo = Sevoflurane group; CI Diff = 95% Confidence interval of the difference between means; VO_2 = Oxygen consumption; DO_2 = oxygen delivery; P_vO_2 = Mixed venous venous oxygen partial pressure; OER = oxygen extraction ratio.
= P_vO_2 at step3: halothane and sevoflurane groups differ (t-test $p = 0.044$).
RM ANOVA:
* = OER (both groups), step 7 differs from all other steps.
⊕ = O_2 (both groups), steps 1 & 7 differ from all other groups, as well as from each other.
x = P_vO_2 (both groups), Steps 1, 7 differ from steps 2 t o 6, but not from each other: Temperature (Halo group), Steps 1, 7 differ from steps 2 t o 6, but not from each other:
@ = P_vO_2 (Halo group) differs from steps 1, 4, 5, 7.
ψ = Temperature at step 1 (Sevo group) differs from steps 3 to 6.

Table 5: Doses administered

		Dose			Numbers of patients who received drugs	
Variable	**Step**	**Halo**	**Sevo**	**p M-W**	**Halo n=24**	**Sevo n=21**
Glycopyrollate (mg)	# Pre	0.1 (0 – 0)	0.3 (0.02 - 0.4)	0.047	2/21	5/19
	During	0 0 - 0	0 (0 - 0.2)	0.25	2/21	6/19
	Post	0 (0 - 0.25)	0 (0 - 0.45)	0.54	4/21	8/19
	# Total	0.25 (0 – 0.6)	0.8 (0.4 – 0.8)	0.024	162/4	17/20
Phenylephrine (µg)	Pre	650 (225 –2300)	500 (150 – 2300)	0.98	16/21	17/19
	During	4750 (2181 – 8750)	5750 (3250 – 10700)	0.57	19/21	19/19
	# Post	0 (0 – 1575)	0 (0 – 0)	0.005	10/21	*1/18
	Total	6125 (3075 – 12200)	8200 (4175 – 11600)	0.70	24/24	21/21
Esmolol (mg)	Pre	60 (25 – 100)	40 (6 – 80)	0.60	17/21	15/19
	During	0 (0 – 0)	0 (0 – 0)	0.38	3/21	1/19
	Post	20 (0 – 0)	0 (0 – 25)	0.34	6/20	3/19
	Total	60 (8 – 169)	35 (5 – 140)	0.97	17/21	15/20
Nitroglycerine (µg)	Pre	2500 (625 – 5000)	875 (0-2250)	0.06	18/21	11/18
	#During	0 (0 – 5563)	0 (0 – 0)	0.03	10/21	3/18
	Post	4625 (1875 – 10800)	2500 (1437 – 6975)	0.24	20/20	16/17
	Total	10800 (4063 – 19800)	5500 (1750 – 10300)	0.08	23/23	17/18
Adrenaline (µg)	Pre	0 (0 – 6)	0 (0 - 0)	0.68	5/21	3/18
	During	0 (0 – 0)	0 (0 - 0)	0.26	2/21	0/18
	Post	425 (237 – 787)	400 (175 – 525)	0.73	18/19	17/17
	Total	475 (275 – 875)	475 (175 – 525)	0.52	21/22	18/18
Lignocaine (mg/kg)	Total	0 (0 – 0)	0 (0 – 1)	0.53	5/23	7/20
Defibrillation (Joules)	Total	10 (0 – 35)	0 (0 – 27)	0.36	13/21	9/20

Halo = Halothane Group; Sevo = Sevoflurane Group. n = number of patients in each group.
Doses are presented as median and 25^{th} – 75^{th} percentiles.
M-W = Wilcoxon rank sum test (Mann-Whitney); # = significant difference for M-W test ($p < 0.05$)
Pre = before cardiopulmonary bypass (CPB); During = during CPB; Post = after CPB;
Total = total amount of drug administered.
* = Significant difference (2- sided Fisher exact test p 0.05).

Table 6: Number of patients who required defibrillation, total Joules required and lignocaine dosage.

	Halo (n = 24)	**Sevo** (n = 21)	**p**
Defibrillation (Number of patients)	13	9	0.28 (Chi^2-test)
Defib: Joules	17 (21)	13 (18)	0.45 (t-test)
Lignocaine: mg/kg	0.39 (0.78)	0.45 (0.69)	0.80 (t-test)

Halo = Halothane Group; Sevo = Sevoflurane Group. n = number of patients in each group.
Data for Joules and lignocaine dose are presented as mean (standard deviation).

Awareness
After enquiry, no patient in either group reported that they had experienced explicit recall.

Discussion

Demographics
A greater number of patients classified as NYHA 3 for exercise were enrolled in the halothane group while the sevoflurane group contained more patients classified as NYHA 2 for angina. It is unlikely that this is important, as no differences in either hemodynamic measurements during the awake step, or the numbers of patients with cardiac indices less than 2.2 $L.min^{-1}.m^{-2}$, were found between the two groups.

Pre cardiopulmonary bypass period
Identical target concentrations of opioid were utilised in both groups, hence the different inhalation agents would account for any differences observed in hemodynamics. Furthermore, as in similar studies,[19-22] hemodynamic parameters were specified to be maintained within certain boundaries utilising standardised drug regimens. The dosages of vasoactive drug needed to maintain stable hemodynamics can therefore be used as a comparative indicator of the hemodynamic effects of the two anesthetic techniques.

Heart rate
To maintain the heart rate within the predetermined range during the period prior to the initiation of CPB necessitated administration of a twofold greater dose of glycopyrrollate in the sevoflurane group. This suggests that sevoflurane–sufentanil anesthesia has a greater propensity to produce a slower heart rate than halothane–sufentanil anesthesia, a factor that may benefit myocardial oxygen supply in the presence of coronary artery disease.[22]

The simultaneous administration of sufentanil, etomidate and vecuronium is well-known for its propensity to elicit bradycardia,[23] nevertheless no episodes of precipitous bradycardia were observed in this study. It is also interesting that the 31 patients who received pre-operative beta-blockers did not require a greater glycopyrrollate dose to maintain heart rate within the predetermined range (0.45 mg (SD 0.40) versus 0.49 mg (SD 0.48) in the patients receiving and not receiving beta blockers respectively).

Halothane administration is usually associated with an unchanged heart rate[24,25] which has been attributed to the drug's obtundation of baroreceptor reflexes,[26] slowing of sino-atrial node phase 4 depolarisation[27] and little vasodilatation, even when used at concentrations greater than one MAC.[24] Sevoflurane has been demonstrated to induce few changes in heart rate in patients concomitantly administered sevoflurane and fentanyl during CABG,[21,28] in healthy human volunteers or when 0.4 to 1.5 MAC sevoflurane was administered to animals.[31,32]

Hemodynamics
Cardiac index did not differ between the awake and anesthetized states; furthermore, cardiac index did not differ between the two groups before bypass. This may be attributed to maintenance of similar loading conditions (preload, systemic vascular resistance) before and after induction of anesthesia in each group and secondly, the low concentrations of inhaled anesthetic agent causing minimal myocardial depression.

Similar dosages of vasoactive drugs were used in the two groups, therefore we conclude that the dosages of sevoflurane and halothane administered to patients in this study elicited similar hemodynamic effects. Other studies using a combination of opioid and inhalation agent have come to similar conclusions. Searle and colleagues compared 0.58 MAC isoflurane-fentanyl to 0.63 MAC sevoflurane-fentanyl anesthesia during the pre-bypass period in low risk patients undergoing coronary bypass grafting.[21] They found no differences in the cardiovascular effects of equipotent dosages of sevoflurane and isoflurane.[33] Rooke and colleagues found no differences in the hemodynamic effects of either sevoflurane or isoflurane combined with fentanyl and nitrous oxide in patients with coronary artery disease and hypertension.[19]

The efficiency of the global circulation
The efficiency of the global circulation, as judged by the P_vO_2, as far as we can determine, has not been previously described during sufentanil-sevoflurane or sufentanil-halothane anesthesia. The decrease in VO_2, unchanged DO_2 and resultant increase in P_vO_2 after induction of anesthesia and throughout the intraoperative period indicates that this balanced anesthetic technique improves circulatory efficiency.

Seven patients (four in the sevoflurane and three in the halothane group) exhibited resting cardiac indices less than 2.2 $l.min^{-1}.m^{-2}$ on admission to theatre. It is noteworthy that these subjects demonstrated similar increases in P_vO_2 after induction of anesthesia compared to those with better NYHA classifications. These increases in P_vO_2 and the ability to maintain hemodynamics within acceptable limits, indicates that a significant margin of safety exists when using these anesthetic techniques even in NYHA class 4 patients undergoing CABG.

Myocardial ischemia
Our patients exhibited an 8.3% and 9.5% incidence of ECG detected myocardial ischemia in the halothane and sevoflurane groups during the pre-bypass period. These represent relatively low incidences of myocardial ischemia in spite of the presence of relatively severe coronary artery disease and the 50% incidence of unstable angina in the patients enrolled in this study. Similar incidences of myocardial ischemia were observed by Searle and colleagues which compared sevoflurane (7%) or isoflurane (11%) in combination with fentanyl.

Inhaled anesthetic agents, including halothane and more recently sevoflurane, exert beneficial effects on the myocardial oxygen supply - demand relationship and the (potentially) ischemic myocardium.[31,34-37] Because of their negative inotropic effects, both halothane and sevoflurane reduce myocardial oxygen demand in a dose dependent manner.[34] These reductions in demand would be expected to lead to decreases in coronary blood flow.[31,36] While such decreases are readily demonstrated with halothane,[38] coronary blood flow is maintained at baseline levels during sevoflurane administration[39] suggesting that sevoflurane possesses coronary vasodilatory properties.[39] This raises concerns about inducing coronary steal, especially in the 25% of patients with coronary artery disease in whom steal prone anatomy exists.[22,40] However, sevoflurane is a much less potent dilator of epicardial arteries than isoflurane and has never been demonstrated to cause coronary steal.[35,36,39] It is also noteworthy that whereas halothane causes less decrease in blood flow to ischemic collateral-dependent areas than to normal myocardium,[31] sevoflurane has the advantage of doubling flow to collateral dependent myocardium provided that mean arterial pressure is maintained at pre-anesthetic levels.[31,35,41] This is a property unique amongst the inhaled anesthetic agents and potentially confers advantages to sevoflurane under circumstances where the risk of coronary steal exists.[35]

In the presence of ruptured plaque or ulcerated endothelium, maintenance of hemodynamics will not necessarily guard against thrombus formation and subsequent myocardial ischemia.[42] It is therefore understandable that less than 50% of intraoperative myocardial ischemia is associated with hemodynamic abnormalities. Halothane's inhibition of platelet adhesion has been shown to abolish the cyclical blood flow pattern that occurs in the coronary circulation of dogs with coronary artery stenoses.[43] Sevoflurane has recently also been shown to inhibit platelet aggregation[44] and potentially offers similar advantages as halothane in this regard.

The immediate post cardiopulmonary bypass period

Hemodynamics
The halothane group required greater doses of phenylephrine immediately after cardiopulmonary bypass. We speculate that

this could be explained by the fact that because halothane is more soluble in blood than sevoflurane, terminating the inhaled anesthetic agent only 5 minutes before the end of bypass may have resulted in relatively greater residual blood concentrations of halothane and a lower blood pressure after weaning from CPB. The ability to monitor end-tidal partial pressures of inhalation agent would have clarified this issue.

The effectiveness of the global circulation after bypass
Immediately after bypass, although cardiac output was higher than at all previous steps, the decrease in hematocrit to its lowest recorded levels resulted in an unchanged delivery of oxygen. Despite a small increase in oxygen consumption compared to prior intraoperative measurements, circulatory efficacy as judged by the P_vO_2, was as effective as in the pre-bypass period.

Twelve hours postoperatively, the increase in body temperature (Table 4) was accompanied by an up to 31% increase in oxygen consumption compared to the awake period. Similar increases in the postoperative demand for oxygen have previously been described after CPB, and may be due to the systemic inflammatory response and repayment of an oxygen debt accumulated both during and after cardiopulmonary bypass.[45] This observation emphasises that meticulous attention needs to be paid to the oxygen delivery-consumption balance *after*, as well as during. surgery for coronary artery bypass grafting.[46]

Pre and post conditioning effected by the inhalation agents
LVSWI was used as a measure of how the anesthetic techniques influenced myocardial performance before and after aortic cross clamping. LVSWI was similar in both groups immediately after bypass and also twelve hours after surgery, suggesting that myocardial protection after global myocardial ischemia is at least as good with sevoflurane as with halothane.

Twelve hours postoperatively, LVSWI was unchanged compared to other intraoperative sevoflurane measurement epochs. However, in the halothane group, LVSWI decreased to its lowest level twelve hours postoperatively compared to all other pre-bypass steps. Whether this statistically significant decrease in LVSWI in the halothane group really represents a clinically important difference, is unknown. If it is important, it may indicate that sevoflurane has advantages over halothane as a cardioprotective agent. Supporting evidence for this contention may well include both the faster heart rate measured after surgery in the halothane group as well as the lower pulmonary artery wedge pressure in the sevoflurane group.

Halothane[10,47-49] and other inhaled anesthetic agents have been shown to produce cardioprotection that resembles ischemic preconditioning. Preconditioning limits myocardial damage and results in better myocardial performance, fewer days in the intensive care unit[8,51] as well as improved one year survival rates.[52] However, inhaled anesthetic agents appear to do this reliably only if administered before, during and after aortic clamping, similar to the protocol used in this study.[53] We believe that the currently available evidence indicating the superiority of inhalation agents for myocardial protection, militates against inclusion of a control group that does not employ inhaled anesthetic agents during coronary artery bypass grafting.[53]

Awareness
The issue of awareness is of particular concern especially during rewarming and weaning from CPB.[3] Opioids act synergistically to reduce the concentration of other agents needed to produce anesthesia.[54] The predicted plasma and brain sufentanil concentration of 2 $ng.ml^{-1}$ in our patients would be expected to reduce MAC by 60 to 70%.[1,2,3] The combination of opioid with low concentrations of halothane or sevoflurane and also the benzodiazepenes administered pre- and intraoperatively, were sufficient to ensure that none of the patients in this study experienced explicit recall of intra-operative events.[55] While it is reassuring that no patient in this study reported intraoperative recall, this study has limitations in its ability to detect awareness. Firstly, this study is significantly underpowered to detect awareness. The incidence of recall varies between 0.1% and 0.2% in the general surgical population,[54] but the reported incidence during cardiac surgery varies between 0 and 23% and averages between 1 to 1.5%.[56] Secondly, we tested for intraoperative awareness only on Day 3. Sandin and colleagues[57] demonstrated that the highest incidence (39%) of awareness was detected between day 1 and 3 preoperatively, 33% and 28% of patients reported awareness in the recovery room and between 7 to 14 days postoperatively. The immediate postoperative investigation is not of relevance in this study, but we may have missed a certain percentage of recall by not performing a late interview. Thirdly, the Sandin study suggested that a structured interview technique be employed. Unfortunately, this study and its accompanying recommendations were only published after our study was underway.

Different benzodiazepines were administered during CPB. The reason included problems with the availability of lorazepam. This represents a shortcoming, albeit minor, of the study.

Depth of anaesthesia
Responses to stressful stimuli, namely increases in P_vO_2, and LVSWI after intubation and sternotomy respectively, occurred in the halothane group. This possibly indicates that depth of anesthesia was lower in the halothane than in the sevoflurane group. For the purposes of this study, sevoflurane MAC was accepted to be 2.05% and that of halothane 0.75%.[58] An F_A/F_I of 0.8 has reportedly been achieved after only 8.2 minutes at a fresh gas flow of 6 litres per minute utilising a circle absorber system with sevoflurane.[59] However, with the more soluble agent halothane, an F_A/F_I of 0.7 may be reached only after 20 to 30 minutes.[60] In this study, the inhaled concentrations of inhaled anesthetic agent may have represented alveolar concentrations of 0.4 MAC for halothane versus 0.46 MAC for sevoflurane. Unlike current practice, at the time this study was conducted, we did not have the facilities to routinely monitor either end-tidal volatile anesthetic partial pressures or depth of anesthesia.

This study focused on hemodynamics, circulatory efficiency, incidence of myocardial ischemia and awareness while administering two different balanced anesthesia techniques to patients undergoing CABG. We conclude that a target-controlled infusion of sufentanil of 2 $ng.ml^{-1}$, supplemented by small concentrations of either sevoflurane or halothane had equivalent hemodynamic effects, improved circulatory efficiency, and similar low incidences of myocardial ischemia in patients undergoing coronary artery bypass grafting. Both techniques were equally effective in preventing explicit recall of intraoperative events.
Acknowledgement

Informed consent
Recommendations Guiding Medical Physicians in Biomedical Research Involving Human Subjects: Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964 and most recently amended by the 41st World Medical Assembly, Hong Kong in September 1989. SAJAA

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