Left ventricular regional wall motion and haemodynamic changes following bolus administration of pipecuronium or pancuronium to adult patients undergoing coronary artery bypass grafting

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The objective of this study was to compare the haemodynamic and myocardial effects of pipecuronium and pancuronium in patients undergoing coronary artery bypass grafting (CABG) during benzodiazepine/sufentanil anaesthesia. Twenty-seven ASA III–IV patients received lorazepam (1–3 mg) po and midazolam (<0.1 mg · kg^{-1}) iv before induction of anaesthesia with sufentanil (3–8 μg · kg^{-1}). Vecuronium (0.1 mg · kg^{-1}) was administered to facilitate tracheal intubation. According to random allocation, each patient received either pipecuronium (150 μg · kg^{-1}) or pancuronium (120 μg · kg^{-1}) after sternotomy but before heparinization. Mean arterial pressure, central venous pressure (CVP), pulmonary artery pressure (PAP), ST segment position and ECG (leads III, V_5, AVF) were monitored continuously throughout the procedure. Thermodilution determinations of CO in triplicate were made immediately before, and at two and five minutes after muscle relaxant administration. Multiplane transoesophageal echocardiography (TEE, mid-papillary short axis views of the left ventricle) images were continuously recorded from ten minutes before until ten minutes after muscle relaxant administration and graded by two experienced echocardiographic readers. Heart rate, MAP and CO increased after administration of pancuronium (by 13.6 beats · min^{-1}, 10.8 mmHg and 1.0 L · min^{-1} respectively) but not after pipecuronium ($P < 0.05$). Evidence of myocardial ischaemia was not detected in any patients using ECG ST segment analysis or TEE assessment of left ventricular wall motion. We conclude that pancuronium caused increases in HR, MAP and CO but that neither pancuronium nor pipecuronium caused myocardial ischaemia.

Cette étude compare les effets hémodynamiques et myocardiques du pipécuronium et du pancuronium auprès de patients soumis à une revascularisation myocardique sous anesthésie par benzodiazépine/sufentanil. Vingt-sept patients ASA III–IV reçoivent du lorazepam (1–3 mg) per os et du midazolam (<0,1 mg · kg^{-1}) iv avant une induction anesthésique au sufentanil (3–8 μg · kg^{-1}). Du vécuronium (0,1 mg · kg^{-1}) est administré pour permettre l'intubation. Une fois réparti au hasard, chaque patient reçoit du pipécuronium (150 μg · kg^{-1}) ou du pancuronium (120 μg · kg^{-1}) après la sternotomie mais avant l'héparinisation. La pression artérielle moyenne (PAM), la tension veineuse centrale (TVC), la pression artérielle pulmonaire (PAP), la configuration du segment ST et l'ECG (dérivations II, V_5, AVF) sont monitorés pendant l'intervention. Des mesure du débit cardiaque (DC) à trois exemplaires par thermodilution sont effectuées immédiatement avant ainsi qu'à la deuxième

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et cinquième minutes qui suivent l'administration du myorésolutif. Des images échocardiographiques transoesophagiennes (ETE) sur plusieurs plans (médio-papillaires sur l'axe court du ventricule gauche) sont enregistrées continuellement à partir de dix minutes avant jusqu'à dix minutes après l'administration du myorelaxant et évaluées par deux anesthésistes expérimentés. La fréquence cardiaque, la PAM et le DC augmentent après l'administration du pancuronium (respectivement par 13,6 battements · min^{-1}, 10,8 mmHg et 1,0 L · min^{-1}) mais pas après le pipécuronium ($P < 0,05$). On n'a pas détecté d'ischémie myocardique chez aucun patient par l'analyse du segment ST ou par l'évaluation de la motilité ventriculaire gauche par ETE. Nous concluons que le pancuronium produit des augmentations de la Fc, de la PAM et du DC mais ni la pipécuronium ni la pancuronium ne provoque de l'ischémie myocardique.

Pipecuronium and pancuronium are long-acting non-depolarizing muscle relaxants which contain steroid nuclei. Pipecuronium is associated with minimal cardiovascular effects in patients anaesthetized with nitrous oxide/opioid combinations or volatile agents.[1,2] For this reason, it appears suitable for use in patients in whom cardiovascular stability is particularly desirable.

In contrast, the use of pancuronium, in clinically effective doses, may be associated with increased HR, MAP and CO.[3-5] During high-dose fentanyl anaesthesia after morphine/scopolamine premedication for coronary artery bypass surgery, pancuronium administration has been associated with a greater incidence of myocardial ischaemia, as evidenced by ST segment changes, than the use of either metocurine or a metocurine-pancuronium combination.[6] In one study, electrocardiographic (ECG) evidence of myocardial ischaemia was detected in 50% of patients who were anaesthetised with high-dose fentanyl and pancuronium following atropine/morphine/diazepam premedication.[7] Despite this, pancuronium is widely used in patients undergoing coronary artery bypass grafting (CABG).

We hypothesized that pancuronium administration was not associated with myocardial ischaemia during benzodiazepine/sufentanil anaesthesia for CABG surgery. This study compares the changes in haemodynamic variables and left ventricular regional wall motion detected by transoesophageal echocardiography (TEE) when either pipecuronium or pancuronium are administered to patients undergoing CABG surgery. In order to examine specifically the effects of each muscle relaxant, pancuronium or pipecuronium was administered approximately 30 min after tracheal intubation.

Methods

With institutional ethics approval and having obtained written informed consent, 27 ASA III–IV patients with sympotomatic coronary artery disease, undergoing elective coronary artery bypass grafting were studied. Participating patients were free from neuromuscular disease and receiving no medication known to influence neuromuscular function. Patients in whom rapid-sequence induction of anaesthesia was indicated were excluded.

Anti-anginal medications (beta-adrenergic blocking agents, calcium channel blocking agents and nitrates) were continued through the morning of operation. Patients received lorazepam (1–3 mg) *po* 90 min before planned induction of anaesthesia and increments of midazolam (up to 0.1 mg · kg^{-1}) as clinically indicated during placement of arterial and venous canulae. Anaesthesia was induced with sufentanil (3–8 μg · kg^{-1}). Vecuronium (0.1 mg · kg^{-1}) was administered to facilitate tracheal intubation. Intermittent positive-pressure ventilation with oxygen (100%) was instituted to maintain end-tidal PCO_2 ($PETCO_2$) within normal limits (35–40 mmHg). After sternotomy but prior to heparinization, during a time when the degree of surgical stimulation appeared to be constant (dissection of the left internal mammary artery), either pipecuronium (150 μg · kg^{-1}) or pancuronium (120 μg · kg^{-1}) was administered, according to random allocation, over ten seconds through a fast-running intravenous infusion.

The Merlin System (Hewlett Packard Co., Waltham MA) was used to monitor continuously ECG (leads II, V_5, AVF), MAP, central venous pressure, and pulmonary artery pressures and for ST segment analysis. The ECG diagnosis of myocardial ischaemia was based on depression of the ST segment of at least 1 mm with respect to a point 80 msec after the user-selected J-point. Pulmonary capillary wedge pressure (PCWP) and thermodilution determinations of cardiac output (CO) were recorded in triplicate immediately before administration of pipecuronium or pancuronium and two and five minutes after muscle relaxant administration. The pancuronium and pipecuronium groups were compared in terms of the greatest change in HR, MAP, CO and PCWP which occurred during the ten minutes after muscle relaxant administration relative to the immediate pre-muscle relaxant control values.

Multiplane TEE (Hewlett-Packard Sonos 1500, 64 element, 3.7/5.0 MHz phased array ultrasound transducer, Hewlett-Packard, Andover, MA) was used for cardiac imaging. The transducer was positioned at the level of the mid-papillary muscles to obtain short axis views of the left ventricle. Images were continuously recorded from ten minutes before until ten minutes after muscle relaxant administration. Subsequently, two experienced echocardiographic readers graded left ventricular systolic function before and after administration of the muscle relaxant.

Readers were unaware of patient identity, temporal sequence of images, clinical course and which muscle relaxant had been administered. The analytical method used has been described previously.[8] The short axis left ventricular image was divided into four segments using the papillary muscles as reference. To be considered suitable for analysis, visualization of 70% of the entire endocardial border throughout the cardiac cycle was required. Each wall (anterior, lateral, inferior and septal) was graded as normal (scored as 0), mildly hypokinetic (scored as 1), severely hypokinetic (scored as 2), akinetic (scored as 3), or dyskinetic (scored as 4). A change in wall motion was accepted as indicative of myocardial ischaemia if both readers detected a difference of two or more grades lasting for at least one minute. A difference between grades assigned by the readers of two or more grades for any one segment was considered a discrepancy and that image was assessed by a third reader whose score was accepted.

The minimum acceptable sample size (11/group) was calculated based on $\alpha = 0.05$ (one-tail) and $\beta = 0.20$ for proportion comparison of dichotomous variables. The smaller (pipecuronium-related) expected proportion of patients demonstrating myocardial ischaemia was 0.05 and the difference between expected proportions was 0.45.[7] The haemodynamic data obtained were compared using analysis of variance (ANOVA). Changes in myocardial regional wall motion were compared using Fisher's exact test. $P < 0.05$ was required to indicate significance. Correlation between the grades assigned by the two TEE readers was measured using the Spearman correlation coefficient.

Results

Patients in the two groups were similar in terms of age, sex, weight and preoperative left ventricular ejection fraction (LVEF) (Table I). Similar proportions in each group were receiving preoperative beta adrenergic blockers, calcium channel blocking agents, and nitrates (Table II).

Preoperative values for heart rate (HR), mean arterial pressure (MAP), PCWP and CO were similar in the two groups (Table III). Values for HR, MAP, PCWP and CO obtained prior to administration of pipecuronium and pancuronium were similar in the two groups (Table III). The HR, MAP and CO increased after administration of pancuronium but not after pipecuronium ($P < 0.05$) (Table IV). In three patients (two pipecuronium, one pancuronium), ST segment data were not analysed because the reference point (J point) was not manually pre-set before induction of anaesthesia. Changes consistent with the criteria of myocardial ischaemia were not detected in any patient after muscle relaxant administration (Table III). The greatest ECG ST segment change in any patient in either of the two groups was less than 0.2 mm during the study period.

Each of two assessors made 192 independent evaluations of video taped echocardiographic images of myo-

TABLE I Patient demographics and preoperative LVEF

Group	*Age (yr)*	*Sex (M/F)*	*Weight (kg)*	*LVEF (%)*
Pip. $n = 13$	64.8 (10.9)	11:2	75.0 (9.6)	48.7 (11.8)
Panc. $n = 14$	65.6 (9.9)	10:4	79.2 (7.9)	53.1 (10.9)

Data are mean (SD). Pip: Pipecuronium; Panc: Pancuronium.

TABLE II Number of patients receiving preoperative anti-anginal medication

Group	*β-blockers*	*Ca^{++} channel antagonists*	*Nitrates*
Pipecuronium ($n = 13$)	6	3	3
Pancuronium ($n = 14$)	9	4	6

TABLE III Haemodynamic variables measured prior to induction of anaesthesia (PI) and prior to administration of pipecuronium or pancuronium (PMR)

Group	*Pip. (PI; n = 13)*	*Panc. (PI; n = 14)*	*Pip. (PMR; n = 13)*	*Panc. (PMR; n = 14)*
HR beats · min^{-1}	55.1(16.7)	52.0(11.7)	52.0(14.2)	54.3(11.9)
MAP mmHg	77.4(6.5)	73.8(11.3)	76.9(5.9)	74.0(11.0)
PCWP mmHg	15.7(4.3)	12.6(2.5)	15.2(5.1)	12.9(3.4)
CO L · min^{-1}	3.6(0.78)	3.8(0.70)	3.7(0.73)	3.9(0.64)

Data are mean (SD). Pip: Pipecuronium; Panc: Pancuronium. No differences between groups or within groups (comparing pre-induction with pre-muscle relaxant values).

TABLE IV Haemodynamic data: greatest change from immediately pre- to ten minutes post-muscle relaxant administration

Group	*HR beats · min^{-1}*	*MAP mmHg*	*PCWP mmHg*	*CO L · min^{-1}*
Pip. $n = 13$	−3.4 (15.7)	−2.4 (12.1)	−0.08 (3.2)	0.11 (0.54)
Panc. $n = 14$	13.6* (12.2)	10.8* (11.2)	0.43 (3.2)	1.0* (1.2)

Data are mean (SD). Pip: Pipecuronium; Panc: Pancuronium.
*$P < 0.05$.

cardial wall segments. In 82% of evaluations, the grades allocated by the two assessors were the same. Positive correlations existed between the grades assigned by the two echocardiographic assessors (Spearman rank correlation coefficient = 0.87; 95% confidence intervals: 0.83–0.90; $P < 0.0001$). The images obtained in three patients (one pipecuronium, two pancuronium) were unsuitable for evaluation. In no patient did the grade of regional wall motion change by two or more grades after muscle relaxant administration (Tables V and VI).

Discussion

The most important finding of this study is that neither pancuronium nor pipecuronium administration was associated with electrocardiographic or left ventricular wall motion changes suggestive of myocardial ischaemia. This was true despite differing haemodynamic effects. Pancuronium administration was associated with increases in HR, MAP and CO under the study conditions described whereas no changes were observed in patients who received pipecuronium.

Pancuronium is associated with increases in HR, MAP and CO.[3–5] The cardiovascular response to pancuronium is greater in patients who have received premedication with scopolamine than with lorazepam.[9] Plasma epinephrine, norepinephrine and dopamine concentrations increase when pancuronium is administered to facilitate tracheal intubation.[10] Plasma epinephrine and norepinephrine concentrations increase after administration of pancuronium to ill neonates.[11] The mechanisms of action of these effects of pancuronium include inhibition of muscarinic receptors at the sino-atrial node,[12] inhibition of interneurones which normally inhibit ganglionic transmission[13] and increased release of, and decreased reuptake of, catecholamines at the adrenergic nerve terminal.[14]

Intraoperative myocardial ischaemia can be precipitated in patients with coronary artery disease by tachycardia, hypertension and administration of sympathomimetic drugs. Because of the ischaemic consequences of pancuronium outlined above, we examined the effects of this muscle relaxant on indices of myocardial oxygen balance in patients with coronary artery disease. Our results are compatible with those of Morris *et al.*[15] who found that pancuronium produced 22% and 24% increase in HR and MAP respectively, with no ECG evidence of myocardial ischaemia. However, neither ST analysis of the MCL5 lead (employed by Morris *et al.*[15]) nor the combination of leads II, AvF and V_5 (used in our study) guarantees detection of myocardial ischaemia if it is present.

Electrocardiographic evidence of myocardial ischaemia was detected in 50% of patients undergoing elective CABG who received morphine/atropine/diazepam premedication and subsequently were anaesthetised with high-dose fentanyl and pancuronium.[7] During high-dose fentanyl anaesthesia for CABG, Thompson *et al.* found the use of pancuronium to be associated with a greater incidence of myocardial ischaemia, as evidenced by ST segment changes than the use of either metocurine or a metocurine-pancuronium combination.[6] Three of twelve patients who received pancuronium developed ischaemic ST segment changes.

Our study differs in three important respects from those of Thompson *et al.*[6,7,9]:

1 The patients in our study received a lorazepam premedicant and midazolam *iv* prior to induction of anaesthesia. In Thompson's study, patients received

TABLE V Grades of echocardiographic evaluation of myocardial regional wall motion: Pipecuronium

Pt	*A pre*	*A post*	*L pre*	*L post*	*I pre*	*I post*	*S pre*	*S post*
1	1/2	1/1	1/1	1/1	3/2	3/2	2/2	2/2
2	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
3	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
4	1/2	1/2	0/1	0/1	3/3	3/3	0/1	0/1
5	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
6	0/0	0/0	1/1	1/0	3/2	2/2	0/0	0/0
7	2/3	2/2	0/0	0/0	0/1	0/0	3/4	4/4
8	2/2	2/2	4/4	4/3	2/3	3/3	2/2	2/2
9	0/0	0/0	0/0	0/0	1/3	1/3	0/0	0/0
10	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
11	0/0	0/0	2/2	2/1	3/3	3/3	1/1	1/0
12	0/0	0/1	0/0	0/0	0/1	0/0	0/1	1/1

Data expressed as a/b, i.e., grade assigned by assessor 1/grade assigned by assessor 2. A: anterior wall; L: lateral wall; I: inferior; S: septum. Pre: Prior to muscle relaxant administration. Post: After muscle relaxant administration. See text for grade definition.

TABLE VI Grades of echocardiographic evaluation of myocardial regional wall motion: Pancuronium

Pt	*A pre*	*A post*	*L pre*	*L post*	*I pre*	*I post*	*S pre*	*S post*
1	0/0	0/0	0/1	0/1	2/3	3/3	0/1	1/1
2	1/1	2/2	2/2	2/2	1/1	1/1	3/3	2/2
3	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
4	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
5	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
6	0/0	0/0	0/0	1/1	1/1	1/1	0/1	0/0
7	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
8	0/0	0/0	−/3*	3/3	1/1	1/2	0/0	0/0
9	0/0	0/0	1/1	1/1	3/3	3/3	2/3	2/2
10	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
11	0/0	0/0	0/0	0/0	0/1	0/1	0/0	0/0
12	0/0	0/0	0/1	0/0	0/0	0/1	0/0	0/0

A: anterior wall; L: lateral wall; I: inferior; S: septum. Pre: Prior to muscle relaxant administration. Post: After muscle relaxant administration. See text for grade definition.
*One assessor judged the images to be uninterpretable.

scopolamine (0.006 mg · kg^{-1}) and morphine for premedication.[6] The greater incidence of myocardial ischaemia may be due to the *combination* of two vagolytic agents (scopolamine and pancuronium).[9]

2 In our study, vecuronium, a non-depolarizing muscle relaxant of well-established cardiovascular neutrality in cardiac surgical patients[16] was used to facilitate tracheal intubation. Pancuronium administration was separated by 20 to 40 min from two factors which can cause catecholamine release, namely tracheal intubation and fentanyl administration.[17] Thus, changes observed during our designated study period (from ten minutes before to ten minutes after muscle relaxant administration) are more likely to be due to the effects of the muscle relaxant, than to a combination of factors. The disadvantage of choosing to administer the muscle relaxants after intubation is that the data obtained cannot be used to guide the choice of muscle relaxant to facilitate tracheal intubation.

3 In addition to continuous ECG ST segment analysis, TEE was employed as a monitor of myocardial ischaemia. The method of analysis of TEE images used in this study has previously been used by Leung *et al.*,[18] and others[8] for evaluation of regional wall motion abnormalities. Compared with continuous ECG monitoring and measurement of pulmonary artery pressures or PCWP, echocardiographically identified segmental wall motion abnormalities may be an earlier and more sensitive indicator of myocardial ischaemia.[8,19,20] Maximum ventricular excursion is seen in this study.[21] This view also demonstrates areas of myocardium in the distribution of the three coronary arteries. One source of error associated with the exclusive use of this view is that apical or basal myocardial ischaemia may not be detected.

Recently, Neidhart *et al.*[22] compared the changes in plasma catecholamine concentration and haemodynamic variables following pipecuronium and pancuronium in patients anaesthetised with a combination of benzodiazepine and fentanyl. Electrocardiographic changes suggestive of myocardial ischaemia occurred in four patients who received pancuronium and in none who received pipecuronium. The possiblity of misinterpreting these results has been discussed elsewhere.[23] One episode of ischaemia occurred before administration of pipecuronium; one was diagnosed based on T wave changes without ST segment changes. Two occurred during periods of haemodynamic stability suggesting that pancuronium-associated haemodynamic changes were not causative. The alternative hypothesis, that pancuronium caused an increase in coronary vascular resistance, is not supported by the documented decrease in plasma norepinephrine concentration following induction of anaesthesia and tracheal intubation in the patients who received pancuronium.

Pipecuronium was selected for comparison with pancuronium because, within the effective dose range, it is reported to have minimal cardiovascular effects.[24] In patients with coronary artery disease, doses of pipecuronium as large as 3 × ED_{95} did not alter haemodynamic variables.[1] This is consistent with our findings. Bradycardia has been reported following administration of pipecuronium to halothane-anaesthetised patients with coronary artery disease.[25] Although six of the 13 patients in the pipecuronium group were receiving preoperative beta blocking agents, no episode of bradycardia occurred after pipecuronium administration during the high-dose sufentanil anaesthetic used in this study. Nevertheless, awareness of this possibility is important and preparation for immediate treatment should be available.

Haemodynamic changes in patients undergoing CABG surgery are influenced by the degree of surgical stimulation, the response to laryngoscopy and intubation as well as the anaesthetic and muscle relaxant drugs administered. We are unaware of any convincing evidence that, during benzodiazepine/high-dose opioid anaesthesia, pancuronium causes myocardial ischaemia. The findings of the present study indicate that, when other confounding variables (changing degree of surgical stimulation, laryngoscopy and intubation) are excluded, the haemodynamic response to pancuronium is unlikely to be associated with myocardial ischaemia. It should be emphasised that these findings were obtained in patients who received benzodiazepine as an integral part of their anaesthetic, who received sufentanil in "high dose" and who had not received another vagolytic agent such as scopolamine.

We conclude that, in patients with clinically important coronary artery disease anaesthetized with the benzodiazepine/high-dose opioid combination described, intraoperative bolus administration of pancuronium (0.12 mg · kg^{-1}) is unlikely to be associated with myocardial ischaemia. This does not support the safety of pancuronium when used to facilitate tracheal intubation in patients undergoing CABG. Furthermore, the risk of bradycardia associated with the use of a combination of high-dose opioid and either vecuronium or pipecuronium is avoided.

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