The effect of an infusion of esmolol on the incidence of myocardial ischaemia during tracheal extubation following coronary artery surgery

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Summary
The aim of this randomised controlled study was to determine whether an esmolol infusion affected the incidence of ST segment changes during weaning from intermittent positive pressure ventilation and tracheal extubation after coronary artery surgery. Thirty-one patients received an infusion of esmolol 0–300 \( \mu \text{g.kg}^{-1} \text{.min}^{-1} \) and 37 patients comprised the control group. ST segment changes were monitored using a continuous ambulatory surveillance system. The electrocardiogram, direct arterial pressure and pulse oximetry were monitored continuously. The period of analysis was from 120 min before until 180 min after tracheal extubation. Three patients in the esmolol group developed myocardial ischaemia during the study period compared with 12 in the control group (p = 0.05). Heart rate increased with time during the study period (p = 0.002) in the control group but was unchanged in the esmolol group. Mean heart rate was significantly higher in the control group than in the esmolol group from 40 min before until 180 min after tracheal extubation. Seven patients in the esmolol group suffered adverse events related to the esmolol infusion. Although the use of esmolol reduced the incidence of myocardial ischaemia, the incidence of adverse effects makes it unsuitable prophylaxis for patients after coronary artery surgery.

Keywords
Heart: ischaemia. Surgery: cardiovascular. Intubation: tracheal.
Intravenous fentanyl 10–15 mg or metoclopramide 10 mg was used as clinically indicated. An \( \mu g \cdot kg^{-1} \cdot min^{-1} \) dose is used almost routinely at this centre. GTN was used for myocardial protection in 53 patients and ventricular fibrillation with or without arterial cross clamp was used in 15 patients. Four patients had cardiac revascularisation without cardiopulmonary bypass. After surgery, patients were transferred to the cardiothoracic intensive care unit (ICU), where they received IPPV of the lungs.

### Methods

The local research ethics committee at the Northern General Hospital, Sheffield approved this prospective study and patients gave written, informed consent. Assuming that the control group has an incidence of myocardial ischaemia of 25%, a reduction of 80% in the active group can be detected with a power of 80% with 59 patients in each group. Patients were considered for inclusion if they were scheduled for elective coronary artery surgery. Patients were not studied if they had conditions that would make ST segment monitoring unreliable: pre-operative digoxin therapy; left ventricular hypertrophy; left bundle branch block; the presence of a cardiac pacemaker. Patients were also not studied if they had contraindications to \( \beta \)-adrenergic blockade; asthma; a previous intolerance to \( \beta \)-adrenergic blockade; first-degree heart block; \( \beta \)-adrenergic agonist infusion at the time of study entry. A further exclusion criterion was a pre-operative serum creatinine \( \geq 120 \mu mol.l^{-1} \).

All patients received their normal anti-angina medication up to and including the day of surgery. Premedication comprised oral lorazepam 2–3 mg on the night before the operation and intramuscular morphine 10–15 mg with either intramuscular prochlorperazine 12.5 mg or metoclopramide 10 mg 1 h before surgery. Anaesthesia was based on the analgesia provided by intravenous alfentanil 10–15 \( \mu g \cdot kg^{-1} \) and hypnotic provided by either a propofol infusion or the inhalation of isoflurane. Pancuronium 0.1–0.15 mg.kg\(^{-1}\) was used to facilitate tracheal intubation. The patients’ lungs were ventilated with air and oxygen to normocapnia. Of the 72 patients studied, 68 had cardiac revascularisation on cardiopulmonary bypass. Cold cardioplegia solution was used for myocardial protection in 53 patients and ventricular fibrillation with or without arterial cross clamp was used in 15 patients. Four patients had cardiac revascularisation without cardiopulmonary bypass. After surgery, patients were transferred to the cardiothoracic intensive care unit (ICU), where they received IPPV of the lungs.

### Patient management

On entry to the ICU, 72 patients fulfilled the entry criteria, of whom 38 were randomly allocated to the control group and 34 to the esmolol group. The randomised sequence was provided by the hospital pharmacy clinical trials department and was in numbered, sealed envelopes. While in the ICU, all patients received intravenous morphine analgesia in 2-mg boluses and intravenous propofol sedation as clinically indicated. An intravenous infusion of glyceryl trinitrate (GTN) in a low dose is used almost routinely at this centre. GTN was also used in higher doses to decrease arterial pressure if necessary. In addition, patients in the esmolol group received intravenous esmolol from entry into the ICU until 180 min after tracheal extubation with the aim of maintaining heart rate in the range 55–75 beat.min\(^{-1}\). A ‘sliding scale’ esmolol infusion scheme based on heart rate was devised and is shown in Table 1. A loading dose of intravenous esmolol 500 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) for 1 min could be given at the discretion of the investigating clinician at the beginning or during the esmolol infusion in order to gain or regain control of the heart rate. Weaning patients from IPPV and tracheal extubation was conducted by the nursing staff in accordance with departmental protocol. In outline, spontaneous ventilation via the tracheal tube was established when the patient was warm (36–37°C core and peripheral temperatures), awake and comfortable. The patient’s trachea was extubated within 30 min of the start of spontaneous ventilation, providing the patient then had good respiratory effort, was maintaining \( S_{\text{p}}O_2 > 95% \), \( P_{\text{a}}O_2 > 12 \) kPa on an \( F_{\text{I}}O_2 \leq 0.6 \) and \( P_{\text{E}}CO_2 < 6.5 \) kPa.

### Equipment and monitoring

The study period was from 120 min before until 180 min after tracheal extubation. Myocardial ischaemia was detected using the Compass computerised ambulatory ECG surveillance system (S-space Medical, Sheffield, UK). This is a four-lead, microprocessor-based, solid-state system with algorithms for the accurate detection and analysis of myocardial ischaemia. Leads V\(_2\), V\(_3\) and AVF were monitored for ST segment changes. Significant myocardial ischaemia was defined as reversible ST segment depression \( \geq 2 \) mm or elevation \( \geq 3 \) mm relative to the baseline taken at 60 ms after the J point, and lasting for at least 1 min. The ECG, direct arterial pressure and pulse oximetry were monitored continuously using Datex AS/3 (Datex Engstrom, Denmark) monitors and heart rate, systolic, mean and diastolic arterial pressures were recorded every 10 min during the study period.

### Statistical analysis

The groups were analysed on an intention to treat basis. Statistical analysis was performed using statsdirect.
version 1.617 running on Windows 98. Patient characteristics were compared using Student's t-test, Mann–Whitney U-test, Chi-squared test or Fisher's exact test as appropriate. Chi-squared analysis was used to compare the incidence of myocardial ischaemia between the two groups. The 'ischaemic load' was calculated as being the ischaemic time (in min h\(^{-1}\)) during two periods: the 120 min before and the 180 min after tracheal extubation. One-way analysis of variance was used to detect changes in the heart rate and arterial pressures over time, and Student’s t-test was used to determine differences in heart rate between the two groups. Significance was set at the 5% level.

**Results**

Four patients were withdrawn from analysis. One patient from the control group and one from the esmolol group had insufficient monitoring time because of faults in the leads of the Compas monitor. Two patients from the esmolol group suffered hypotension, so the esmolol infusion was stopped. One of these was given a β-adrenergic agonist. Analysis was performed on 37 patients in the control group and 31 patients in the esmolol group.

**Patient characteristics**

Patient characteristics are presented in Table 2. There were no differences between the groups in patient pre-operative characteristics, duration of cardiopulmonary bypass or aortic cross-clamping, or the time from entry into ICU to tracheal extubation. Details of pre-operative anti-angina therapy and infusions of GTN and propofol during the study period are presented in Table 3. There were no differences between the two groups in the types of pre-operative anti-angina therapy or in the number of patients who received propofol sedation before tracheal extubation. Thirty-six patients in the control group received a GTN infusion during the study period compared with 23 in the esmolol group (p < 0.05). The mean (SD) total dose of GTN during the study period in those who received it was not significantly different between the groups: control group = 13.44 (13.06) mg, esmolol group = 9.12 (7.84) mg (p = 0.125).

**Myocardial ischaemia**

The incidence of myocardial ischaemia and the ischaemic load in those patients with myocardial ischaemia are presented in Table 4. Patients in the esmolol group had a lower incidence of myocardial ischaemia than the control group (3/31 vs. 12/37, p = 0.05). The incidence of myocardial ischaemia in the esmolol group was too small to make comparisons of the ischaemic load between the two groups meaningful, so only the mean and range ischaemic load are presented. There was no difference in the ischaemic load before and after tracheal extubation in the patients in the control group who experienced myocardial ischaemia. Eight of 15 patients (53%) who developed myocardial ischaemia had been taking β-adrenoceptor blockers, compared with 40 of 53 patients (75%) without myocardial ischaemia (p = 0.117). All patients who

### Table 2: Patient characteristics and other operation data. Values are mean (SD) where appropriate.

|                     | Control \(n = 37\) | Esmolol \(n = 31\) |
|---------------------|-------------------|-------------------|
| Sex; male/female    | 33/4              | 25/6              |
| Age; years          | 61.1 (7.47)       | 60.2 (6.69)       |
| Height; cm          | 173.1 (7.77)      | 170.7 (7.96)      |
| Weight; kg          | 86.0 (14.1)       | 82.5 (13.8)       |
| Surface area; m\(^2\)| 1.99 (0.2)       | 1.93 (0.18)       |
| Drug used for maintenance; propofol/isoflurane | 30/7 | 23/8 |
| Cardiopulmonary bypass; on-pump/off-pump | 35/2 | 29/2 |
| Cardiopulmonary bypass time; min | 59.8 (27.3) | 55.3 (23.1) |
| Cross clamp time; min | 27.9 (20.6) | 30.5 (22.0) |
| Time to tracheal extubation; h | 5.95 (2.81) | 5.73 (2.23) |

### Table 3: Number of patients receiving pre-operative anti-angina therapy, and the number receiving glyceryl trinitrate and propofol infusions during the study period.

| Pre-operative medication | Control \(n = 37\) | Esmolol \(n = 31\) | p     |
|-------------------------|-------------------|-------------------|-------|
| Long acting nitrate     | 18                | 20                | 0.244 |
| β-blocker               | 24                | 24                | 0.310 |
| Calcium channel blocker | 19                | 14                | 0.82  |
| Angiotensin converting enzyme inhibitor | 9 | 5 | 0.608 |
| Potassium channel blocker | 9               | 6                 | 0.86  |

| Infusions during the study period | Control \(n = 37\) | Esmolol \(n = 31\) | p     |
|----------------------------------|-------------------|-------------------|-------|
| Glycerol trinitrate              | 36                | 23                | 0.009 |
| Propofol sedation               | 15                | 10                | 0.651 |
developed myocardial ischaemia were receiving an infusion of GTN.

**Haemodynamics**

Changes in heart rate in the two groups are shown in Fig. 1. Mean heart rate in the control group increased during the study period (p \( \leq 0.002 \)). Heart rate in the esmolol group did not change during the study period (p \( \leq 0.7 \)). Heart rate in the control group was significantly higher than that of the esmolol group from 40 min before until 180 min after tracheal extubation. Systolic arterial pressure is presented in Fig. 2. Systolic arterial pressure in the control group increased until tracheal extubation and decreased thereafter (p \( \leq 0.021 \)). There was no change in systolic arterial pressure in the esmolol group during the study (p \( \leq 0.104 \)). There was no change in mean arterial pressure in the control group during the study (p \( \leq 0.075 \)). Mean arterial pressure in the esmolol

|                           | Control | Esmolol | p    |
|---------------------------|---------|---------|------|
| Incidence of myocardial ischaemia | 12/37   | 3/31    | 0.05 |
| Ischaemic load before tracheal extubation; min.h\(^{-1}\) | 17.04 [0–50.5] | 6.83 [0–20.5] |      |
| Ischaemic load after tracheal extubation; min.h\(^{-1}\) | 24.86 [4–57.3] | 21.67 [1–58] |      |

Table 4 Incidence of myocardial ischaemia during the study period and mean [range] myocardial load for those patients with myocardial ischaemia.

**Figure 1** Mean heart rate during the study period. Error bars indicate SD. Open symbols: control group. Closed symbols: esmolol group.

**Figure 2** Mean systolic arterial pressure during the study period. Error bars indicate SD. Open symbols: control group. Closed symbols: esmolol group.
group increased before and decreased after tracheal extubation \( (p = 0.033) \). Diastolic arterial pressure did not change significantly during the study in either of the groups (control group: \( p = 0.776 \), esmolol group: \( p = 0.27 \)).

**Esmolol infusion and adverse events**

The mean (SD) infusion rate of esmolol was 155.2 (104) \( \mu \text{g.kg}^{-1}.\text{min}^{-1} \). Four patients in the esmolol group had a low heart rate and received no esmolol. Four patients in the esmolol group were reported as having a heart rate that was difficult to control with esmolol. Three patients in the esmolol group were reported as having hypotension, defined as a systolic arterial pressure \(< 85 \text{ mmHg for } > 20 \text{ min despite an adequate central venous pressure, that was not considered severe enough to warrant discontinuation of the esmolol. A further two patients were withdrawn from the study because hypotension led to the stopping of the esmolol infusion.**

**Discussion**

We had hoped to study at least 100 patients. However, seven of 31 patients in the esmolol group had adverse events and a further two were withdrawn from the study because of hypotension. The study was terminated early because of these adverse events and difficulties with patient recruitment. There was no attempt to blind the study. It was expected that a decrease in heart rate in response to an esmolol infusion would readily identify those patients in the esmolol group. The difficulty in blinding investigators to an infusion of esmolol has been confirmed by Raby et al. [6]. In our study, the definition of myocardial ischaemia using ambulatory monitoring was more demanding than that used by others [6–8], in order to decrease the possibility of false positive results. In practice, this stratagem did not affect the incidence of myocardial ischaemia but may have led to an underestimation of the ischaemic load. Others from this centre have shown that tracheal extubation is associated with myocardial ischaemia [1, 2], but these studies did not examine outcome. The same is true of this study. The rationale for trying to modulate ST segment changes at this time is based on the known association between postoperative myocardial ischaemia and adverse outcome [4, 5]. A \( \beta \)-adrenoceptor antagonist was chosen because this group of drugs is well-established in the prevention of postoperative myocardial ischaemia [9, 10], and esmolol was chosen for its rapid onset and offset, and therefore quick response to changes in infusion rate.

This investigation has shown that an esmolol infusion can decrease the incidence of ST segment changes detected using continuous ambulatory monitoring during the weaning from intermittent positive pressure ventilation and tracheal extubation after coronary artery surgery. Since this study was started, two other groups, Raby et al. [6] and Harwood et al. [8], have reported their experience with esmolol infusions in patients after major vascular surgery. The finding that esmolol can decrease the incidence of myocardial ischaemia confirms that of Raby et al. [6], who showed that esmolol significantly decreased the incidence of postoperative ST segment changes in patients who had myocardial ischaemia detected by ambulatory monitoring after aortic surgery.

We experienced difficulty in controlling the heart rate of four patients in the esmolol group. In practice, esmolol was not good at controlling the heart rate of patients after cardiac surgery. In order to examine heart rate control, the heart rate for each patient in the esmolol group at each time interval was summed and a mean heart rate for each patient over the study period was calculated. Eight patients had a mean heart rate \( > 90 \text{ beat.min}^{-1} \) over the study period and only 12 patients achieved a mean heart rate less than the target of 75 beat.min\(^{-1}\). Five patients had an infusion rate of esmolol 300 \( \mu \text{g.kg}^{-1}.\text{min}^{-1} \), the maximum recommended dose, throughout the study period, and a further seven had a mean infusion rate \( > 200 \mu \text{g.kg}^{-1}.\text{min}^{-1} \). Harwood et al. [8] also experienced difficulty in controlling heart rate \( < 80 \text{ beat.min}^{-1} \) using esmolol after surgery. However, they did demonstrate that esmolol provided good heart rate control in anaesthetised patients during surgery.

This study provides additional information specific to patients undergoing coronary artery surgery and raises some questions. Seventy per cent of the all the study patients, and 53% of those who developed ST segment changes, were receiving \( \beta \)-adrenoceptor antagonist treatment before their operation. This suggests that this treatment provides little protection against myocardial ischaemia in the early postoperative period. Most of the patients who were receiving \( \beta \)-adrenoceptor antagonists were taking atenolol. The authors are not aware of any data relating to the drug disposition of atenolol during and after cardiopulmonary bypass. Many patients resume taking \( \beta \)-adrenoceptor blocking drugs for a limited period after coronary artery surgery. It may be that those who develop ST segment changes in the postoperative period are more likely to develop recurrent angina or myocardial ischaemia and should be considered for long-term \( \beta \)-adrenoceptor blockade.

Of the patients who were randomly allocated to the esmolol group, seven of 31 had either hypotension or a heart rate that was difficult to control, and a further two were withdrawn from the study because of hypotension. This study was open and this makes evaluation of adverse events subject to bias. Nevertheless, the high incidence of
adverse events and the difficulty in the titration of esmolol to heart rate in these patients have convinced us that it is an unsuitable drug for routine prophylactic use against myocardial ischaemia in patients after cardiac surgery. However, the authors will continue to use esmolol in their practice whenever there are specific clinical indications.

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