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# Comparison of lorazepam alone *vs* lorazepam, morphine, and perphenazine for cardiac premedication

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**Purpose:** To compare the effects of two premedication regimens on cardiorespiratory variables, sedation, and anxiety in patients scheduled for coronary artery bypass graft (CABG) surgery.

**Methods:** This was a prospective randomized, double-blind clinical trial. Sixty-eight patients were monitored for 1.5 hr before and 2.0 hr after premedication with lorazepam ( $0.03 \text{ mg}\cdot\text{kg}^{-1} \text{ sl}$ ), morphine ( $0.15 \text{ mg}\cdot\text{kg}^{-1} \text{ im}$ ), and perphenazine ( $0.05 \text{ mg}\cdot\text{kg}^{-1} \text{ im}$ ) [Group 1], or with lorazepam ( $0.03 \text{ mg}\cdot\text{kg}^{-1} \text{ sl}$ ) and saline ( $1.5 \text{ ml im}$ ) [Group 2]. All were continuously monitored with a 12-lead ECG ST monitors, respiratory inductive plethysmography (RIP), digital pulse oximetry, intra-arterial blood pressure, and arterial blood gas analysis. Sedation and anxiety scores were also recorded.

**Results:** The incidence and duration of myocardial ischaemia was low and similar in Groups 1 and 2. Patients in Group 1, but not in Group 2, had a greater number of events ( $P < 0.04$ ) and duration ( $P < 0.02$ ) of  $\text{O}_2$  desaturation; higher  $\text{PaCO}_2$  ( $P < 0.001$ ), and more haemodynamic events ( $P < 0.006$ ) after premedication when compared with baseline. There was no difference in RIP or ECG variables between the two groups. Following premedication, both groups reported reduced anxiety scores and elevated sedation scores ( $P < 0.01$ ), with sedation greater in Group 1 than in Group 2 ( $P < 0.01$ ).

**Conclusion:** In CABG patients, premedication with lorazepam provides adequate anxiolysis and sedation, and the addition of morphine and perphenazine results in elevated  $\text{PaCO}_2$ , arterial haemoglobin desaturation, and potentially adverse haemodynamic changes.

**Objectif :** Comparer les effets de deux régimes de prémédication sur les paramètres cardiorespiratoires, la sédation, et l'anxiété chez des patients programmés pour une chirurgie de revascularisation myocardique (CVRM).

**Méthodes :** Cette étude clinique était aléatoire et à double aveugle. Soixante-huit patients ont été suivis pendant 1,5 h et 2,0 h après une prémédication constituée de lorazepam ( $0,03 \text{ mg}\cdot\text{kg}^{-1} \text{ sl}$ ), de morphine ( $0,15 \text{ mg}\cdot\text{kg}^{-1} \text{ im}$ ) et de perphénazine ( $0,05 \text{ mg}\cdot\text{kg}^{-1} \text{ im}$ ) [groupe 1] ou de lorazepam ( $0,03 \text{ mg}\cdot\text{kg}^{-1} \text{ sl}$ ) avec du sol.phys. ( $1,5 \text{ mg im}$ ) [groupe 2]. Tous ont été surveillés en continu avec un moniteur ECG du segment ST à 12 dérivations, pléthysmographie respiratoire à induction (PRI), oxymétrie de pouls, pression artérielle sanglante et analyse des gaz artériels. Les scores de sédation et d'anxiété étaient aussi enregistrés.

**Résultats :** L'incidence et la durée de l'ischémie myocardique, tout en étant peu élevées, étaient identiques chez les patients du groupe 1 et 2. Après la prémédication, les patients du groupe 1 présentaient comparativement à ceux du groupe 2 un plus grand nombre d'épisodes ( $P < 0,04$ ) de désaturation dont la durée était plus longue ( $P < 0,02$ ) ; des  $\text{PaCO}_2$  plus élevées ( $P < 0,001$ ) et plus d'événements de nature hémodynamique ( $P < 0,005$ ). Il n'y avait pas de différence en ce qui concerne les paramètres enregistrés sur la PRI et sur l'ECG entre les deux groupes. Après la prémédication, les deux groupes ont présenté des scores d'anxiété bas et de sédation élevés ( $P < 0,01$ ), avec une sédation plus importante dans le groupe 1 que dans le groupe 2 ( $P < 0,01$ ).

**Conclusion :** Chez des patients programmés pour une CRVM, la prémédication au lorazepam produit une anxiolyse et un sédation adéquates, alors que l'addition de morphine et de perphénazine augmente la  $\text{PaCO}_2$ , la désaturation de l'hémoglobine et produit des effets hémodynamiques potentiellement néfastes.

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Accepted for publication October 4, 1996.

**P**ATIENTS with critical coronary artery stenosis who develop perioperative myocardial ischaemia may have an associated increased risk of postoperative myocardial infarction following coronary artery bypass graft (CABG) surgery.<sup>1,2</sup> Anxiety related haemodynamic changes may increase myocardial demand and be a causative factor in the development of myocardial ischaemia. Anaesthetic premedication may reduce anxiety levels and thereby reduce the incidence and/or severity of myocardial ischaemia.

The standard preoperative cardiac premedication at the University of Toronto involves the co-administration of a benzodiazepine, an opioid, and an antiemetic/sedative agent (usually perphenazine).<sup>3</sup> This regimen is designed to produce anxiolysis, amnesia, and sedation, thereby reducing myocardial oxygen demand and myocardial ischaemia. However, the precise cardiorespiratory and haemodynamic effects are unknown. Opioid-induced hypoventilation can lead to hypoxaemia<sup>4</sup> and reflex tachycardia,<sup>5</sup> leading to oxygen imbalance and myocardial ischaemia. The relationship between premedication given in patients with critical coronary stenosis and the development of myocardial ischaemia has not been clearly defined.

Using continuous 12-lead ECG monitoring, intra-arterial catheter, digital pulse oximeter, respiratory inductive plethysmography, and sedation/anxiety scales, we studied and compared the effects of two premedication regimens given prior to arrival in the operating room for elective CABG surgery. We aimed to determine if the type of premedication influences the development of myocardial ischaemia, if lorazepam alone provides adequate anxiolysis, and if the addition of morphine and perphenazine to lorazepam confers additional beneficial or adverse cardiorespiratory effects.

## Methodology

### Subjects

After institutional ethics committee approval and completion of written informed consent, 68 elective CABG patients were randomized into one of two different premedication groups and were studied in a double-blind manner. Patients were recruited from those scheduled for the afternoon to ensure that normal sleep patterns did not interfere with the respiratory assessment.

### Inclusion/Exclusion Criteria

All elective CABG patients were eligible for the study with the following exceptions: redo CABG surgery or

other concurrent surgery; active pulmonary disease or requirement for supplemental oxygen therapy; co-existing severe valvular heart disease; artificial cardiac pacemaker; preoperative left bundle branch block; current use of digoxin, opioid, or benzodiazepine therapy; or reported allergy to any of the study medications.

### Protocol

The patients were studied on the morning of the surgery for four hours prior to the scheduled operating time in a quiet secluded room near the operating area to minimize extraneous disturbances and to allow the study to continue until transportation of the patient into the operating room. Patients were continuously supervised by an investigator throughout the study period. All patients received all of their usual cardiac medications on the morning of the study. No supplemental oxygenation was given.

Computer-generated randomisation schedules were seen only by a research nurse who administered the drugs and was otherwise uninvolved with the study. Otherwise, the patient, investigator, and all other personnel were blinded to the medication given.

The study was divided into two consecutive intervals: A [1.5 hr before premedication], and B [2.0 hr after premedication]. Following baseline monitoring for 1.5 hr, patients in Group 1 received 0.03 mg·kg<sup>-1</sup> lorazepam *sl*, 0.15 mg·kg<sup>-1</sup> morphine *im* and 0.05 mg·kg<sup>-1</sup> perphenazine *im*; patients in Group 2 received 0.03 mg·kg<sup>-1</sup> lorazepam *sl* and 1.5 ml saline *im*. All patients were then studied for a further two hours after premedication. Patients in Group 2 received morphine and perphenazine after completion of the study to comply with the current standard of practice at our institution.

### Data Collection and Monitoring

#### DEMOGRAPHIC DATA

Preoperative demographic data collected included age, weight, sex, haemoglobin concentration, and history of cigarette smoking. The severity of cardiac disease was documented using left ventricular function data derived from cardiac catheterization (Grade 1–4) and number of diseased vessels. The presence of recent angina pectoris, defined as characteristic chest pain within the previous 24 hr, was also noted. The use of preoperative beta blockers, calcium channel blockers, and nitrates was noted, as was the presence of hypertension and diabetes mellitus. Baseline systolic, diastolic, and mean arterial blood pressures were determined after the placement of a radial arterial line and were confirmed by blood pressure cuff and auscultation.

#### MYOCARDIAL ISCHAEMIA

Myocardial ischaemia was defined as >1 mm depression of the ST segment for >60 msec in a regional pattern of leads,<sup>3</sup> and was diagnosed using a continuous 12-lead ECG real time ST segment monitor (Mortara Instruments Eli 100s). This monitor compares the ST segment at the J point + 60 msec with the initial reference ECG on an individual and regional lead basis and its accuracy has been previously validated.<sup>6,7</sup> In this study, the ST segment was analyzed every 20 sec and recorded every five minutes. Additional ECGs were automatically recorded if alarm parameters were violated. At the end of the study, summary statistics of all ischaemic ECGs were printed with both the graphic ECG and the numerical recordings of the depth of the ST segment at the J-point across the 12-leads. The pre- and post-ischaemic ECGs were also provided by the monitor, thus allowing the determination of duration and depth of ST-segment depression. The area under the curve [duration-degree] for myocardial ischaemia was then determined.

#### ARTERIAL HAEMOGLOBIN SATURATION

Arterial saturation of haemoglobin ( $\text{SpO}_2$ ) was continuously measured by pulse oximetry (Novamatrix 515A, Medical Systems Inc). This was connected to the central computer programme used to collect all respiratory data in the study on a real time breath-by-breath basis. A desaturation event was defined as an  $\text{SpO}_2$  reading >90% for >15 sec.<sup>3</sup> The duration and minimum saturation were then recorded and the hypoxaemic burden was determined by calculating the area under the curve  $\text{SpO}_2 < 90\%$ .

#### RESPIRATORY MONITORING

Respiratory patterns were continually assessed using a non-invasive respiratory inductive plethysmography (RIP) system (NIMS Respirace Inc).<sup>8-9</sup> The monitor automatically calibrates over a five minute period of quiet breathing, and was additionally calibrated for this study using known preset tidal volumes. All patients were studied in a semi-recumbent position and the plethysmograph inductance coil bands were taped in place to ensure continuity of the measurements taken. The breath-by-breath data were recorded. Central apneas were defined by prolonged expiratory time ( $T_e$ ) >10 sec and by tidal volume ( $V_T$ ) <100 ml for >10 sec.<sup>8</sup> Obstructive apneas were determined by chest wall and abdominal movements being persistently out of phase such that the Laboured Breath Index (LBI) was >1.6 for >10 sec (rib cage + abdominal breathing/ $V_T$ ).<sup>4</sup> Low respiratory rate was

defined as a breath rate <6 per minute for >10 sec. The severity of respiratory abnormalities was quantified by the calculation of the area under the curve for each variable [duration-degree], using the computer programme previously described, where possible.

#### ARTERIAL BLOOD GASES

Arterial blood gas samples were withdrawn from an indwelling radial artery catheter inserted in a sterile manner under local anaesthesia before the start of the study. Samples were taken for analysis in Interval A as a baseline: 30 min before cardiac premedication (Sample 1), and at one and two hours after premedication in Interval B (Samples 2 and 3). Each sample was analyzed in a standardised fashion.

#### HAEMODYNAMICS

These were assessed by the previously described indwelling arterial catheter, which was transduced and monitored throughout the study (Propaq). Heart rate and blood pressure were recorded as a baseline at the start of the study and confirmed by auscultation and blood pressure cuff readings. In addition, during the study they were continually assessed, recorded every 30 min, and additionally recorded if defined parameters were exceeded. A haemodynamic event was defined as a variation of >20% above or below the baseline readings for heart rate or blood pressure.<sup>10</sup> Data were recorded for incidence, number, and duration of events.

#### ANXIETY SCORE

This was subjectively scored by the patient at the start and at the end of the study on a linear scale from 0 to 10; where 0 reflects no anxiety and 10 reflects maximal anxiety.<sup>11</sup>

#### SEDATION SCORE

This was objectively assessed by the investigator prior to taking the arterial blood gas samples, in order that the patient was not disturbed before sedation was assessed. It was assessed on a six point scale as follows:<sup>12</sup>

1. agitated and restless
2. awake, cooperative, tranquil
3. drowsy, responds to commands
4. asleep, rouses rapidly to name call
5. asleep, rouses sluggishly to voice or touch
6. no response to voice or touch

#### Data Analysis

Data are presented as mean  $\pm$  standard error of mean (SEM), as ratios, or as percents (%). Data were analyzed using unpaired t-tests for between-group parametric

demographic data; Kruskal-Wallis and Mann-Whitney-U tests for between-group non-parametric ordinal data; Friedmann's test for within-group non-parametric ordinal data; and Fisher's Exact test for categorical data. Outcome data for intervals A and B are expressed as events per hour.  $P < 0.05$  was considered statistically significant.

## Results

Sixty-eight patients were recruited: 39 in Group 1 and 29 in Group 2. One patient was removed from each group because of technical problems on the day of the study. All other patients completed the four hour study period. There was no differences in the demographic data between the two groups for age, weight, haemoglobin concentration, severity of cardiac disease (LV function, number of diseased vessels, recent angina, or medical therapy), and number of patients who smoked cigarettes, or pre-study haemodynamics (Table I). The number of female patients was higher in Group 1.

## Ischaemia

Sixteen of 66 patients (24.2%) developed one or more episodes of regional myocardial ischaemia. There was no difference in the development or duration of ischaemia between the two groups (Table II), nor were there within group differences following pre-medication. In addition, from the raw data, there was no temporal association between the development of myocardial ischaemia and haemodynamic events.

## Arterial Haemoglobin Desaturations

The number of patients demonstrating haemoglobin desaturation increased following premedication in both groups (Table III). No difference was found in the incidence, duration, or hypoxaemic burden in Group 2 between Interval A and Interval B. In Group 1, however, there was an increase in the number of haemoglobin desaturation events, the duration of these events, and the hypoxaemic burden ( $P < 0.02$ ) occurring in Interval B compared with Interval A. There were no differences between the two groups for any of these parameters in either Interval A or Interval B (Table III).

## Respiratory Events

There were no differences in either the within-group or between-group analyses of the respiratory mechanics by RIP in central apneas, as defined by: prolonged expiratory time ( $T_e$ ), low respiratory rates, low tidal volume ( $V_T$ ), labored breath index (LBI), or obstructive apneas (Table IV).

TABLE I Demographic Data

|                         | Group 1        | Group 2        |
|-------------------------|----------------|----------------|
| Age (yr)                | 60.9 $\pm$ 1.4 | 60.1 $\pm$ 1.9 |
| Male/Female             | 26/12          | 26/2*          |
| Weight (kg)             | 76.7 $\pm$ 2.5 | 81.7 $\pm$ 2.3 |
| Hb                      | 13.9 $\pm$ 0.3 | 14.4 $\pm$ 2.6 |
| LV Grade                | 1.8 $\pm$ 0.2  | 1.7 $\pm$ 0.2  |
| No. of Diseased Vessels | 3.1 $\pm$ 0.1  | 3.0 $\pm$ 0.1  |
| SBP                     | 142 $\pm$ 2.9  | 147 $\pm$ 3.9  |
| MABP                    | 95 $\pm$ 1.9   | 98 $\pm$ 2.9   |
| DBP                     | 70 $\pm$ 1.8   | 73 $\pm$ 2.5   |
| Recent Angina Pectoris  | 29/38 (76.3%)  | 23/28 (82.1%)  |
| Hypertension            | 21/38 (55.3%)  | 14/28 (50.0%)  |
| Diabetes                | 29/38 (76.3%)  | 21/28 (75.0%)  |
| Beta Blockers           | 23/38 (39.5%)  | 15/28 (53.6%)  |
| Calcium Channel Block   | 29/38 (76.3%)  | 22/28 (78.6%)  |
| Nitroglycerin           | 29/38 (76.3%)  | 19/28 (67.9%)  |
| Cigarette Smokers       | 28/38 (73.7%)  | 17/28 (60.7%)  |

Hb haemoglobin, LV left ventricular, SBP systolic blood pressure, MABP mean arterial blood pressure, DBP diastolic blood pressure, \* $P < 0.05$

TABLE II Myocardial Ischaemia

|                                   | Group 1        | Group 2        |
|-----------------------------------|----------------|----------------|
| Ischaemia incidence in Interval A | 6/38 (15.8%)   | 3/28 (10.7%)   |
| Ischaemia incidence in Interval B | 4/38 (10.5%)   | 3/28 (10.7%)   |
| Duration of ischaemia in A (sec)  | 72.6 $\pm$ 5.0 | 66.4 $\pm$ 3.6 |
| Duration of ischaemia in B (sec)  | 67.9 $\pm$ 3.9 | 65.9 $\pm$ 5.1 |

TABLE III Arterial Haemoglobin Desaturation

|                                              | Group 1          | Group 2         |
|----------------------------------------------|------------------|-----------------|
| Patients with desaturation in Interval A     | 2/38 (5.3%)      | 1/28 (3.6%)     |
| Patients with desaturation in Interval B     | 20/38 (52.6%)**  | 10/28 (35.7%)** |
| Number of desaturation events in Interval A  | 0.04 $\pm$ 0.03  | 0.02 $\pm$ 0.02 |
| Number of desaturation events in Interval B  | 3.10 $\pm$ 1.0*  | 0.60 $\pm$ 0.3  |
| Duration of desaturation in Interval A (sec) | 22.4 $\pm$ 14.1  | 3.1 $\pm$ 2.1   |
| Duration of desaturation in Interval B (sec) | 94.1 $\pm$ 34.5† | 16.9 $\pm$ 8.5  |
| Hypoxaemic burden in Interval A              | 70.7 $\pm$ 46.2  | 5.5 $\pm$ 4.6   |
| Hypoxaemic burden in Interval B              | 284 $\pm$ 144.6‡ | 29.7 $\pm$ 14.6 |

\* $P < 0.04$ ; † $P < 0.02$ ; ‡ $P < 0.05$ ; \*\* $P < 0.005$ ; Interval A vs B

TABLE IV Respiratory Inductive Plethysmography

|                                         | Group 1       | Group 2       |
|-----------------------------------------|---------------|---------------|
| <b>Prolonged Exp Time</b>               |               |               |
| Number of events per hour in Interval A | 9.6 ± 2.1     | 7.5 ± 1.4     |
| Number of events per hour in Interval B | 11.9 ± 3.0    | 7.2 ± 1.6     |
| Duration in Interval A (sec)            | 159 ± 39.9    | 105.5 ± 19.9  |
| Duration in Interval B (sec)            | 250.3 ± 80.3  | 113.0 ± 28.6  |
| <b>Low Respiratory Rate</b>             |               |               |
| Number of events per hour in Interval A | 5.2 ± 1.8     | 2.8 ± 0.9     |
| Number of events per hour in Interval B | 7.3 ± 2.3     | 3.2 ± 1.3     |
| Duration in Interval A (sec)            | 64.5 ± 24.4   | 46.2 ± 14.0   |
| Duration in Interval B (sec)            | 118.1 ± 39.2  | 57.0 ± 26.7   |
| AUC in Interval A                       | 54.1 ± 22.5   | 60.5 ± 21.0   |
| AUC in Interval B                       | 147.3 ± 63.1  | 106.3 ± 58.1  |
| <b>Low Tidal Volumes</b>                |               |               |
| Number of events per hour in Interval A | 0.9 ± 0.5     | 0.6 ± 0.5     |
| Number of events per hour in Interval B | 1.3 ± 0.8     | 1.9 ± 1.0     |
| Duration in Interval A (sec)            | 14.0 ± 7.4    | 8.5 ± 6.0     |
| Duration in Interval B (sec)            | 19.0 ± 12.2   | 33.0 ± 17.9   |
| AUC in Interval A                       | 284.8 ± 185.5 | 70.1 ± 37.8   |
| AUC in Interval B                       | 158.6 ± 2.1   | 451.6 ± 366.8 |
| <b>Labored Breath Index (LBI)</b>       |               |               |
| No. of patients with LBI in Interval A  | 13/38 (34.2%) | 10/28 (35.7%) |
| No. of patients with LBI in Interval B  | 10/38 (26.3%) | 11/28 (39.3%) |
| Duration of LBI in Interval A (sec)     | 17.3 ± 13.3   | 84.3 ± 78.7   |
| Duration of LBI in Interval B (sec)     | 79.8 ± 51.1   | 16.0 ± 9.0    |

AUC area under curve

*Arterial Blood Gases*

Within group comparisons of arterial blood gases in Group 1 showed that pH decreased following premedication in Times 2 ( $P < 0.001$ ) and 3 ( $P < 0.0001$ ) compared with Time 1. Associated with this were increases in  $\text{PaCO}_2$  at Time 2 and 3 ( $P < 0.001$ ), and a decrease in  $\text{PaO}_2$  at Time 3 ( $P < 0.05$ ). Group 2 did not demonstrate any changes in the three time periods (Table V).

TABLE V Arterial Blood Gases

|                 | Sample Time | Group 1       | Group 2     |
|-----------------|-------------|---------------|-------------|
| pH              | 1           | 7.40 ± 0.01   | 7.40 ± 0.01 |
|                 | 2           | 7.37 ± 0.01*  | 7.40 ± 0.01 |
|                 | 3           | 7.36 ± 0.01** | 7.40 ± 0.01 |
| $\text{PaCO}_2$ | 1           | 34.5 ± 1.8    | 34.3 ± 2.0  |
|                 | 2           | 36.8 ± 1.9*   | 34.6 ± 1.9  |
|                 | 3           | 37.5 ± 2.2*   | 33.1 ± 2.4  |
| $\text{PO}_2$   | 1           | 88.5 ± 2.4    | 95.1 ± 3.1  |
|                 | 2           | 83.7 ± 2.3    | 88.4 ± 2.3  |
|                 | 3           | 81.7 ± 4.4†   | 88.8 ± 2.5  |

Time 2,3 vs 1; Group 1 vs Group 2;

\*  $P < 0.001$ ;\*\*  $P < 0.0001$ ;†  $P < 0.05$ *Haemodynamic Data*

Within Group 1, there was a higher number and duration of low blood pressure events following premedication. When compared with Group 2, patients in Group 1 showed a higher incidence, number, and duration of haemodynamic events following premedication (Table VI). There were no differences between the two groups during Interval A, but more patients with

TABLE VI Low Blood Pressure

|                                           | Group 1         | Group 2        |
|-------------------------------------------|-----------------|----------------|
| Incidence (no. of patients) in Interval A | 2/38 (5.3%)     | 1.28 (3.6%)    |
| Incidence (no. of patients) in Interval B | 28/38 (73.7%)   | 11.28 (39.3%)* |
| No. of events per hour in Interval A      | 0.05 ± 0.04     | 0.02 ± 0.02    |
| No. of events per hour in Interval B      | 1.63 ± 0.30**   | 0.75 ± 0.30*   |
| Duration of events in Interval A (sec)    | 8.4 ± 6.1       | 1.4 ± 1.4      |
| Duration of events in Interval B (sec)    | 979.0 ± 173.4** | 152 ± 81.9*    |

\*  $P < 0.006$  Group 1 vs Group 2; \*\*  $P < 0.001$  A vs B

haemodynamic events in Group 1 than in Group 2 during Interval B ( $P < 0.006$ ). There were no differences between the two groups during Interval A, but more episodes of haemodynamic events occurred in Group 1 than in Group 2 during Interval B ( $P < 0.006$ ); more haemodynamic events following morphine ( $P < 0.001$ ) but not following placebo. There were no differences between the two groups during Interval A, but a greater duration of haemodynamic events in the morphine group than in the placebo group during Interval B ( $P < 0.001$ ); greater duration of haemodynamic events following morphine ( $P < 0.001$ ) but not following placebo.

#### Anxiolysis and Sedation

Anxiety scores were similar in both groups in Intervals A and B, but within groups at end of Interval B, both Group 1 ( $P < 0.003$ ) and Group 2 ( $P < 0.01$ ) were associated with lowered anxiety scores (Table VII). Sedation scores were similar in the two groups in Periods 1 and 2, and were greater in the morphine group than in the lorazepam group only in Period 3 ( $P < 0.01$ ). Sedation scores in the morphine group were greater in Periods 2 ( $P < 0.0001$ ) and 3 ( $P < 0.0001$ ), than in Period 1. Scores in the lorazepam only group were also greater in Periods 2 ( $P < 0.0002$ ) and 3 ( $P < 0.008$ ), than in Period 1 (Table VII).

#### Discussion

From the current study, we suggest that there are no beneficial effects associated with the addition of morphine and perphenazine to lorazepam in terms of the adequacy of anxiolysis. Furthermore, the data suggest potential adverse effects with the addition of morphine and perphenazine, in terms of arterial haemoglobin desaturation, potential for respiratory acidosis, and adverse haemodynamic events.

Myocardial ischaemia which occurs prior to CABG surgery is of potential clinical importance because of the association with postoperative myocardial infar-

tion.<sup>1,2</sup> In previous studies, however, there has been disagreement as to how often this preoperative ischaemia occurs, with figures ranging from 1.9% up to 48%.<sup>1,3</sup> This variability may be due to the use of different anaesthetic premedication, lack of consistently administering anti-anginal medications preoperatively, and the use of non-standardised cardiac monitoring techniques. Problems can arise with each method because of "missed" ischaemia, which is either not recorded, occurs in leads other than those monitored, or because monitoring is programmed in an inappropriate mode. In the current study, all 12 ECG leads were monitored, with continual computer ST segment analysis, making it unlikely that any episodes of ischaemia were missed in the preoperative monitoring period. Therefore, our figure of 24.2% incidence of preoperative myocardial ischaemia probably reflects the true time incidence. In addition, we did not include single lead ischaemia in our analysis (with the exception of ischaemia in V1), as it is not clear whether this has any clinical importance. Despite randomisation, the study population had a higher % of women in group I. However, a previous report from our centre demonstrated that female sex was associated with a slightly greater incidence of arterial haemoglobin desaturation but not myocardial ischaemia, in this population.<sup>3</sup>

Myocardial ischaemia occurs as a consequence of inadequate myocardial oxygenation due to an imbalance of myocardial oxygen demand and supply. Myocardial ischaemia may be associated with increased demand – determined clinically by increased heart rate and increased systolic arterial blood pressure. However, studies have shown no association between these factors,<sup>13,14</sup> suggesting that myocardial ischaemia results from decreased oxygen supply rather than increased demand. Although only 50% of our patients who developed myocardial ischaemia were treated with beta blockers, we did not record any episodes of tachycardia or hypertension either at rest, or during ischaemic, respiratory, or haemodynamic events in either of the two study groups. However, our definitions of haemodynamic events (>20% change in heart rate or blood pressure compared with baseline measurements) were stringent. Identification of statistically significant haemodynamic changes may not have clinical relevance. In a previous report by our group, these episodes where the heart rate increased were associated with arterial haemoglobin oxygen desaturations, but not with myocardial ischaemia.<sup>3</sup> However, the definition of tachycardia was only a 6% rise in the heart rate.

TABLE VII Anxiety and Sedation Scores

|          |                       | Group 1     | Group 2     |
|----------|-----------------------|-------------|-------------|
| Anxiety  | at start (Interval A) | 4.6 ± 0.4   | 4.8 ± 0.3   |
| Anxiety  | at end (Interval B)   | 3.5 ± 0.3*  | 3.9 ± 0.3** |
| Sedation | Period 1              | 2.5 ± 0.1   | 2.4 ± 0.1   |
|          | Period 2              | 3.7 ± 0.1*  | 3.4 ± 0.1*  |
|          | Period 3              | 4.2 ± 0.1†* | 3.5 ± 0.2*  |

Within group comparison: \* $P < 0.005$ , \*\*  $P < 0.01$ , vs Interval A, vs Period 1; Between group comparison: † $P < 0.01$ , Group 1 vs Group 2

Animal studies have suggested that myocardial ischaemia is more likely to result from reduced myocardial oxygen supply due to a reduction in coronary artery blood flow than to reduced oxygen content of the delivered blood.<sup>15</sup> Previous work from our group suggests that myocardial ischaemia was not related to the pre-study haemoglobin concentration, or to the addition of supplemental oxygen to patients.<sup>3</sup> The current study did not show any temporal association between the hypotensive episodes and the development of myocardial ischaemia. Therefore, the reduction in coronary artery perfusion pressure is unlikely to have produced ischaemia. However, there was a low incidence of myocardial ischaemia in our study, so this lack of relationship may be a function of small numbers of ischemic episodes.

Stress and anxiety may be frequent causes of tachycardia and hypertension, and may lead to the development of myocardial ischaemia. Indeed, the avoidance of this stress and anxiety is one of the main reasons for giving a combined cardiac premedication. We found no difference in the anxiety scores or the incidence of myocardial ischaemia in either group of patients, while the sedation scores were only slightly higher in the combined premedication group at the end of the study. This suggests that the use of lorazepam alone provides sufficient anxiolysis and sedation preoperatively, while the increased level of sedation in the patients receiving additional morphine and perphenazine was not necessary for the prevention of myocardial ischaemia.

It has been clearly shown that opioids can induce hypoventilation which can lead to hypoxaemia.<sup>4</sup> Hypoxaemia may produce haemodynamic changes which, in turn, may reduce myocardial oxygen supply and increase myocardial oxygen demand, leading to myocardial ischaemia. In this study we carefully and comprehensively studied the respiratory patterns of each group throughout the study period using respiratory inductive plethysmography. We were not able to demonstrate a difference in the development of central or obstructive apneas, or low respiratory rates between the two groups. Our blood gas results did, however, show that the patients who received morphine and perphenazine, in addition to lorazepam, developed a lower arterial pH and higher PaCO<sub>2</sub> following premedication. This mild respiratory acidosis was not seen in the patients receiving lorazepam alone. It is, therefore, likely that the blood gas measurements are more sensitive in detecting the respiratory effects of the combined cardiac premedication.

In previous studies there has been disagreement as to the effects of benzodiazepines on the respiratory

system. Some studies have shown that benzodiazepines result in reduction in the tidal volume, minute ventilation, and the abdominal contribution to respiration<sup>16</sup> and also reduce resting PaO<sub>2</sub> level.<sup>17</sup> Others, however, have found little respiratory change with their use.<sup>18</sup> None of these studies assessed lorazepam specifically. In the current study, which examined lorazepam with more detailed respiratory function analysis, we did not detect alteration in arterial blood gases following administration of lorazepam alone.

The development of arterial haemoglobin desaturation has been associated with premedication<sup>19</sup> and with sleep in the context of systemic opioids.<sup>4</sup> Previous studies have reported low SpO<sub>2</sub> before surgery as having an incidence of 56.9%<sup>3</sup> to 80%.<sup>19</sup> The wide variation in these incidences can be explained by different populations of patients, different premedication regimens, and different definitions of arterial haemoglobin desaturation. Benzodiazepines alone have been reported to reduce the PaO<sub>2</sub>,<sup>17</sup> but the current study did not confirm that. In our study, 45% of patients overall developed low SpO<sub>2</sub> following premedication. However, even before premedication, 15% of patients developed low SpO<sub>2</sub>, perhaps reflecting the age and underlying lung disease of this population of patients. Following premedication, 30% of patients in Group 1 and 15% of patients in Group 2 developed low SpO<sub>2</sub> by our definition. Thus, while the incidence of desaturation doubled in the group receiving morphine, perphenazine and lorazepam, it did not change in the group receiving lorazepam alone. This supports the findings of our previous study<sup>3</sup> where there was no increase in arterial haemoglobin desaturation following lorazepam alone, but there was an increase following morphine and perphenazine without supplemental oxygen.

In the current study, we found that lorazepam alone caused a reduction in the subjective anxiety score, confirming a previous study by Male *et al.*<sup>20</sup> However, Russell *et al.*<sup>21</sup> showed no anxiolytic action of lorazepam in a dose range of 2.5–5.0 mg. Morphine has been described as providing sedation without anxiolysis.<sup>22</sup> Both of our groups received lorazepam, and both groups had similar degrees of anxiolysis suggesting that anxiolysis in our study was due to the lorazepam with no additional anxiolysis being provided by the morphine.

The level of sedation in our study was found to increase with each group following premedication. However, in addition, the patients in Group 1 had a higher level of sedation at the end of the study than those in Group 2. This suggests that the level of sedation is adequate with lorazepam alone, and the addition of morphine and perphenazine results in

additional sedation without conferring any advantage in terms of anxiolysis or prevention of myocardial ischaemia. Furthermore, lorazepam premedication alone did not delay postoperative early extubation in our "fast track" cardiac programme.<sup>23</sup>

In conclusion, we suggest that lorazepam alone can be used safely as a premedication in patients with critical coronary artery stenosis for elective CABG surgery. It provides adequate preoperative anxiolysis and sedation, with no serious adverse respiratory or haemodynamic events. In contrast, the addition of morphine and perphenazine to lorazepam, while providing the same degree of anxiolysis, also provides deeper than necessary levels of sedation, and may result in preoperative adverse respiratory and haemodynamic events and potential painful *im* injections. As a result of this study, the current cardiac premedication practise in our cardiac surgical patients consists of lorazepam *sl* only.<sup>23</sup>

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