The Role of an Ultra Short-acting Adrenergic Blocker (Esmolol) in Patients Undergoing Coronary Artery Bypass Surgery

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Despite advances in anesthetic techniques, the reported incidence of prebypass myocardial ischemia is 37–50%.1,2 Both tachycardia and hypertension, which have been shown to be undesirable in patients with coronary artery disease,3,4 may be due to inadequate beta blockade during narcotic-O₂ anesthesia.5

Propranolol has been used during the prebypass period to modify these responses.6 However, any undesirable effects may be persistent because of its elimination half-life of 100 min.

Esmolol, a new intravenous beta, adrenergic antagonist, has a rapid onset and short duration of action (t½ 2₈ = 9 mins.). Its effect on heart rate was absent 5 min after cessation of an infusion, and plasma levels of esmolol were undetectable 15 min after termination of the infusion.7 Tachycardia, in response to elevated endogenous nor-epinephrine plasma concentrations, has been attenuated by esmolol in patients during induction of anesthesia for coronary artery surgery.7

The purpose of this study was twofold. First, we wished to determine if esmolol would reduce the incidence of prebypass myocardial ischemia and arrhythmias in patients undergoing coronary bypass surgery, anesthetized with fentanyl-O₂. Second, we sought to determine if the use of esmolol altered the requirements for additional volatile anesthetic agents.

METHODS

With Ethics Committee approval and informed consent, thirty patients scheduled for elective myocardial revas-

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significan t a or v waves during the prebypass period as a further method of detecting early myocardial ischemia.\textsuperscript{12} A preoperative Holter monitor ECG strip was compared to the ward control ECG in each patient to detect any new ischemic episodes present on arrival in the OR.

The hemodynamic mean values are presented with the standard error of the mean (SEM) as an index of dispersion. The change in HR and SBP was calculated as a percentage of the baseline value. Analysis of variance for repeated measurements was performed on the changes in hemodynamic observations. This analysis included the patient as the random blocking factor and tested for significant differences between treatments, significant differences among events, and significant interactions between treatment and event. Testing for treatment differences at each event was performed using least mean squares.\textsuperscript{11}

The incidence of prebypass ischemia and the occurrence of significant arrhythmias in each group was compared using chi-squared analysis with Yates correction for continuity. The amount of isoflurane administered to each patient was expressed as the product of inspired concentration and time in minutes during which that concentration was administered. The log doses received were compared using the Student's t test. In all analyses, the null hypothesis was rejected when $P < 0.05$.

\section*{RESULTS}

Comparison of the demographic data is shown in table 2. There were no significant differences between the groups. Important hemodynamic data, both measured and derived at the various time intervals during the study, are shown in tables 3 and 4. There were significant changes within groups when comparisons were made between event and baseline in SBP, HR, RPP, CI, PCWP, CVP, PVR, LVSWI, and SV, and between event to previous event in HR, RPP, CI, and SV (P < 0.05). When comparisons were made, using least mean squares, for treatment differences at each event, significant differences between treatment groups were found for the change in HR at sternotomy only with percentage change from baseline (fig. 1). In both groups, the HR rose significantly at induction, compared with baseline values, the maximal increase from baseline occurring at intubation (27\% in the control group and 25\% in the esmolol group). Thereafter, they fell to post-induction level by the time of skin incision, but remained above baseline values throughout the prebypass period (table 5). Significant differences in

\begin{table}
\centering
\caption{Exclusion Criteria}
\begin{tabular}{l}
\hline
Pregnancy  \\
Atrial flutter or atrial fibrillation  \\
Atrio-ventricular conduction block greater than first degree  \\
Conditions that preclude treatment with beta-adrenergic blocker; e.g., congestive heart failure, bronchial asthma, etc.  \\
Myocardial infarction within the previous 3 months  \\
Severe hepatic or renal disease  \\
Systolic blood pressure less than 100 mmHg or cardiogenic shock  \\
Severe electrolyte imbalance  \\
Adrenergic augmenting drugs, e.g., MAO inhibitors, or adrenergic depleting drugs, e.g., reserpine  \\
Long-term beta-adrenergic blocking drugs, e.g., nadolol  \\
Calcium channel antagonists other than nifedipine  \\
\hline
\end{tabular}
\end{table}

CLINICAL REPORTS

**Table 2. Demographic Data***

<table>
<thead>
<tr>
<th></th>
<th>Age (yr)</th>
<th>Weight (Kg)</th>
<th>Height (cm)</th>
<th>Sex</th>
<th>Preop BP (mmHg)</th>
<th>N. Y. H. A. Class</th>
<th>XCT (min)</th>
<th>BPT (min)</th>
<th>No. Grafos/Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group E</td>
<td>56.7 ± 2.06</td>
<td>75.29 ± 2.25</td>
<td>170.53 ± 1.47</td>
<td>M 15</td>
<td>Syst 129.0 ± 4.4</td>
<td>III/IV 15</td>
<td>46.60 ± 4.87</td>
<td>84.73 ± 7.27</td>
<td>3.1 ± 0.3</td>
</tr>
<tr>
<td>Group C</td>
<td>56.0 ± 2.16</td>
<td>76.99 ± 3.42</td>
<td>172.53 ± 1.63</td>
<td>M 14</td>
<td>Syst 129.0 ± 4.7</td>
<td>III/IV 14</td>
<td>51.07 ± 5.96</td>
<td>98.26 ± 8.20</td>
<td>3.5 ± 0.3</td>
</tr>
</tbody>
</table>

XCT = Cross clamp time during CPB; BPT = Total bypass time;
N. Y. H. A. = New York Heart Association; M = Males; F = Females.

* Mean values ± SEM.

**Table 3. Hemodynamic Data 1***

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Preinduction</th>
<th>Preincision</th>
<th>Insulation</th>
<th>Skin Incision</th>
<th>Sternotomy</th>
<th>Aortic Dissection</th>
<th>Prebypass</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>E</td>
<td>54.4 ± 2.1</td>
<td>52.8 ± 1.8</td>
<td>62.3 ± 1.9†</td>
<td>66.8 ± 2.2†</td>
<td>61.8 ± 1.8†</td>
<td>62.1 ± 2.0†</td>
<td>61.3 ± 1.9†</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>50.5 ± 1.4</td>
<td>50.5 ± 1.4</td>
<td>55.8 ± 1.6‡</td>
<td>64.3 ± 2.2†</td>
<td>58.3 ± 2.1†</td>
<td>61.9 ± 1.6†</td>
<td>59.3 ± 2.4†</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>E</td>
<td>145.5 ± 6.0</td>
<td>156.4 ± 5.4</td>
<td>137.7 ± 6.8</td>
<td>134.5 ± 6.9</td>
<td>126.8 ± 2.7†</td>
<td>127.9 ± 3.8†</td>
<td>120.7 ± 3.6†</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>134.5 ± 5.8</td>
<td>135.1 ± 5.3</td>
<td>133.6 ± 6.5</td>
<td>134.3 ± 7.0</td>
<td>127.3 ± 4.5</td>
<td>156.1 ± 6.2</td>
<td>128.3 ± 3.1</td>
</tr>
<tr>
<td>RPP</td>
<td>E</td>
<td>7.9 ± 0.5</td>
<td>7.1 ± 0.3‡</td>
<td>8.6 ± 0.3‡</td>
<td>9.0 ± 0.5†</td>
<td>7.8 ± 0.3</td>
<td>7.9 ± 0.3</td>
<td>7.4 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>6.8 ± 0.3</td>
<td>6.8 ± 0.3</td>
<td>7.5 ± 0.4</td>
<td>6.7 ± 0.4‡</td>
<td>7.4 ± 0.3</td>
<td>8.4 ± 0.4</td>
<td>7.4 ± 0.4</td>
</tr>
</tbody>
</table>

bpm = beats·min⁻¹; E = Esmolol group; C = Control group.
* Mean values ± SEM.
† P < 0.05 from baseline.
‡ P < 0.05 from previous recording.

The percentage change in SBP from baseline values were found between groups at preinduction, skin incision, and all events from sternotomy to 5 min after the start of aortic dissection (fig. 2). Mean SBP decreased in the esmolol group from skin incision until the start of CPB, falling to 78% of baseline values. In the control group, mean SBP was virtually unchanged until aortic dissection, and then fell to 84% of baseline value by the start of CPB (fig. 2). The rise in SBP seen in the control group at sternotomy matched the increase in HR, which also occurred at this time. These increases were not seen in the esmolol group.

There were no significant differences between treatment groups for any of the other hemodynamic variables measured. During the prebypass period, there was no significant change in PCWP in the esmolol group, although the PCWP dropped significantly compared with baseline values in the control group from skin incision to the start

**Table 4. Hemodynamic Data II**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Pre-induction</th>
<th>Insulation</th>
<th>Skin Incision</th>
<th>Sternotomy</th>
<th>Aortic Dissection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Index (l·min⁻¹·m⁻²)</td>
<td>E</td>
<td>2.62 ± 0.09</td>
<td>2.46 ± 0.08</td>
<td>2.82 ± 0.14†</td>
<td>2.58 ± 0.17</td>
<td>2.44 ± 0.15</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>2.50 ± 0.06</td>
<td>2.56 ± 0.09</td>
<td>2.99 ± 0.16†</td>
<td>2.67 ± 0.19</td>
<td>2.65 ± 0.29</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>E</td>
<td>13.27 ± 1.2</td>
<td>14.27 ± 1.1</td>
<td>13.6 ± 1.5</td>
<td>11.53 ± 0.9</td>
<td>10.87 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>14.07 ± 0.8</td>
<td>14.67 ± 1.1</td>
<td>12.9 ± 2.0</td>
<td>11.13 ± 1.0*</td>
<td>10.40 ± 0.9*</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>E</td>
<td>8.13 ± 1.0</td>
<td>9.0 ± 1.2</td>
<td>8.5 ± 0.8</td>
<td>7.9 ± 0.9</td>
<td>7.0 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>9.6 ± 0.9</td>
<td>9.0 ± 0.9</td>
<td>8.3 ± 0.9</td>
<td>8.4 ± 0.6</td>
<td>7.3 ± 0.7*</td>
</tr>
<tr>
<td>SVR (dys·s·cm⁻⁵)</td>
<td>E</td>
<td>1462 ± 64</td>
<td>1499 ± 59</td>
<td>1351 ± 71</td>
<td>1476 ± 90</td>
<td>1570 ± 85</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>1372 ± 72</td>
<td>1517 ± 88</td>
<td>1242 ± 95†</td>
<td>1350 ± 112</td>
<td>1520 ± 158</td>
</tr>
<tr>
<td>PVR (dys·s·cm⁻⁵)</td>
<td>E</td>
<td>100 ± 12</td>
<td>98 ± 11</td>
<td>92 ± 6</td>
<td>91 ± 10</td>
<td>92 ± 12</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>124 ± 8</td>
<td>113 ± 12</td>
<td>119 ± 14</td>
<td>89 ± 8*</td>
<td>96 ± 12</td>
</tr>
<tr>
<td>LVSWI (gm·m·m⁻²)</td>
<td>E</td>
<td>55.71 ± 3.8</td>
<td>52.49 ± 3.8</td>
<td>47.43 ± 3.2</td>
<td>46.73 ± 3.2</td>
<td>44.24 ± 3.4*</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>51.84 ± 3.3</td>
<td>50.36 ± 3.5</td>
<td>50.91 ± 3.1</td>
<td>48.92 ± 4.0</td>
<td>47.69 ± 3.6</td>
</tr>
<tr>
<td>SV (mls)</td>
<td>E</td>
<td>91.9 ± 4.7</td>
<td>89.5 ± 4.8</td>
<td>79.2 ± 3.3‡</td>
<td>78.6 ± 4.9*</td>
<td>73.9 ± 4.1*</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>94.7 ± 4.2</td>
<td>89.9 ± 5.2</td>
<td>82.2 ± 3.9</td>
<td>87.3 ± 5.5</td>
<td>80.6 ± 5.9</td>
</tr>
</tbody>
</table>

Mean values ± SEM.
E = Esmolol group; C = Control group.
* P < 0.05 from baseline.
† P < 0.05 from previous recording.
of CPB. Similarly, there was little change seen in the CVP in the esmolol group until aortic dissection, when it decreased significantly. In the control group, changes in the CVP tended to follow changes in the PCWP, and were significantly lower than baseline measurements from sternotomy to the start of CPB.

Four patients (13.3%) developed ischemia during the prebypass period. Three patients were in the control group, and one was in the esmolol group. The periods of ischemia ranged from 15 s to 5 min. Two of these four patients required cardiac support to wean from bypass (with ischemia times of 15 s and 5 min, respectively), and one of the two required insertion of an intraaortic counterpulsation balloon. Five of the remaining 26 patients with no prebypass ischemia required inotropic support at termination of CPB. All recorded episodes of ischemia occurred around the time of aortic dissection and cannulation. The incidence of "complex ventricular arrhythmias" that occurred during this period was 73.3% in the control group and 26.7% in the esmolol group \( p < 0.05 \).

Eleven patients in each group required additional volatile anesthetic. The total amount received as measured by the number of minutes of 1% inspired concentration of isoflurane was significantly less in the esmolol group (table 5). When all patients who required additional volatile anesthetic to lower their SBP for aortic cannulation were also removed (three from each group), the difference becomes even more significant \( p < 0.02 \). There was no significant difference between the two groups in the mean time of the infusion or the amount of solution infused.

**DISCUSSION**

Despite anesthetic techniques designed to maintain hemodynamic stability during the prebypass period, recent studies\(^1\) continue to show the incidence of myocardial ischemic episodes during this time to range from 37–50%. The incidence of 13% (20%) in the control group and 6.7% in the esmolol group in our study is lower than those reported in other studies. Although the incidence of 6.7% in the esmolol group was not significantly different from control, perhaps due to the small number of patients in each group (Type 2 statistical error), to our knowledge, it is the lowest reported incidence of prebypass ischemia detected by Holter monitoring in patients undergoing CABG surgery. We believe that significant factors in this low incidence (13%) of prebypass ischemia are the preoperative management and preparation of the patient, the anesthetic technique used, and, probably, the intraoperative use of an infusion of a short-acting beta adrenergic blocking drug.

We use a standard premedication of morphine and scopolamine, which produces a well-sedated and cooperative patient prior to induction of anesthesia. De Lange et al. showed a marked reduction in cardiovascular response in patients in whom beta adrenergic blocking drugs
were continued up to the day of surgery. Our practice is also to continue beta blockers, calcium channel blockers, and nitrates up to the time of premedication, which is in contrast to Thomson's study, where beta blockade therapy was discontinued the evening prior to surgery, while, in Slogoff's study, the decision to continue beta blockade therapy up to the day of surgery was not consistent. Therefore, it is possible that there was not a clinically significant degree of beta blockade present in some of their patients at the time of surgery. None of our patients developed new ischemic changes prior to induction of anesthesia, when their Holter baseline tapes were compared to their ward control ECG. This is in contrast to Slogoff's findings of an incidence of 50% of new changes in those patients who subsequently developed further bypass ischemia.

The anesthetic technique used in this study of fentanyl-O₂ characteristically produces a slow heart rate at induction. Therefore, despite the transient increase in heart rate seen at induction and intubation, the HRs during the study remained in a range considered favorable for patients with ischemic heart disease. This may explain the observation that the periods of recorded ischemia in our patients were not related to periods of hemodynamic instability seen at induction and intubation, but rather to a period when surgical stimulation or complications (e.g., bleeding during atrial cannulation) may contribute significantly to the incidence of bypass ischemia. In Slogoff's study, 40% of the patients who developed tachycardia (defined as a HR > 100 bpm) had associated ischemia. The maximum increase in HR in our study was seen during intubation, 25% from baseline value in the esmolol group, and 27% in the control group (fig. 1). However, the absolute values, a rise from 50 bpm to 64 bpm, makes this change of little clinical significance. As has been reported previously, we also noted a rise in heart rate starting at induction of anesthesia in both groups. This was attributed to the use of pancuronium, but there was no period of ischemia seen on the Holter tapes at this time. Thomson et al. postulated that, by delaying the administration of the pancuronium from the administration of the fentanyl, one might separate the potential synergistic effect of these two drugs on the sympathetic nervous system. We attempted to reduce this possible cause of tachycardia by administering the pancuronium in small increments over the 4–5 min induction period.

It is likely that the degree of beta blockade present in our patients during the bypass period was a major contributing factor for both the lower incidence of ischemia and the minor differences between the two groups. Sill et al. concluded that the plasma concentration of propranolol was a major factor influencing hemodynamic responsiveness in patients undergoing coronary artery surgery. Twenty-nine of the 30 patients studied were receiving beta adrenergic blocking drugs up to 2 h prior to the start of surgery. The one patient in our study not on chronic beta blocker therapy preoperatively was randomized to receive esmolol, and had a smooth bypass period. Our findings are in agreement with the results found by Menkhau et al. Although they claimed that esmolol attenuated the HR response to induction and intubation, there was a 23% increase in HR from baseline values in all three of their esmolol treatment groups, which is similar to our finding of a 25% increase in the esmolol group.

The average bypass time in our study was 90.3 min. It might be postulated that, by this time, there is a reduction in the therapeutic effect of the preoperative beta blockers given preoperatively in the control group, compared to the maintenance of an effective therapeutic plasma level in the esmolol group. This dissipation in beta blockade activity may account for the difference seen in the occurrence of "complex ventricular arrhythmias," with a marked reduction in the esmolol group. A further explanation for this reduction may be due to the antiarrhythmic properties that have been demonstrated by esmolol. It might be speculated that the addition of an infusion of a beta blocker during the bypass period attenuated the ventricular response to catecholamines, and so significantly reduced the incidence of arrhythmias observed in the control group.

Narcotic requirement in patients on chronic preoperative beta adrenergic blocking drugs has been shown to be reduced, as manifested by the reduction in the incidence of hypertension associated with noxious stimuli in the bypass period. Eleven patients in each group required additional volatile anesthetic, but the average total amount was significantly less in the patients receiving the esmolol infusion. Three patients in each group required additional volatile anesthetic, only to reduce their SBP below a mean of 100 mmHg at the time of aortic cannulation at the request of the surgeons. When these patients are removed from each group, the requirement for additional volatile agents remains virtually unchanged in the control group, in marked contrast to the esmolol group, where there is a further reduction of almost 50% (table 5). The mechanism of action here, whether potentiation or blunting of responses, is unclear. It has been suggested that possible mechanisms may include changes in CNS opiate receptor activity, decreases in drug distribution, plasma volume or metabolism, or changes that influence the opiate transfer across the blood-brain barrier.

Girard et al. studied 20 patients undergoing CABG anesthetized with comparable doses of fentanyl and given esmolol in a manner similar to the patients in our study. However, they withheld the morning dose of beta adrenergic and calcium channel blocking drugs, while our pa-
patients were maintained on these drugs to the time of surgery. In contrast to our results, patients receiving esmolol had significantly less tachycardia at intubation than did the control patients. The mean HR in their esmolol group was 67 bpm, similar to the HR of the esmolol group in this study. The greater increase in HR in their placebo group compared to ours probably reflects differences in preoperative drug regimens for heart rate control. In addition, our study describes the incidence of ischemia obtained by Holter monitoring, and suggests that patients given esmolol have significantly fewer ventricular arrhythmias and decreased requirements for additional volatile anesthetic drugs.

In conclusion, we found esmolol to be a safe drug for use in patients undergoing myocardial revascularization. Esmolol may prove to be of benefit in the treatment of tachycardia and hypertension, thereby preventing myocardial ischemia in the prebypass period. The greater incidence of arrhythmias in the control group seen at aortic dissection may be due to a wearing off of preoperative beta blockade effect at this time. The amount of isoflurane needed to supplement the fentanyl anesthesia was significantly lower in the esmolol group.

REFERENCES

2. Thomson IR, Mutch WAC, Culligan JD. Failure of intravenous nitroglycerin to prevent intraprocedure myocardial ischemia during fentanyl–pancuronium anesthesia. Anesthesiology 61:385–393, 1984