Prompt control of heart rate is important for successful treatment of supraventricular tachyarrhythmias early after open heart surgery when sympathetic tone is high and ventricular response rates may be rapid. Esmolol, a new ultrashort-acting (9 minute half-life) beta-receptor blocking agent, was given by continuous intravenous infusion for up to 24 hours in 24 patients (21 with isolated coronary bypass surgery and 3 with valve replacement) 1 to 7 days after surgery. Atrial fibrillation was present in 9 patients, atrial flutter in 2 and sinus tachycardia in 13. Eleven patients had received intravenous digoxin (average dose 0.6 mg, average serum level 1.19 mg/100 ml) before esmolol infusion without adequate control of the supraventricular tachyarrhythmia. After a 1 minute loading infusion of esmolol (500 Ilg/kg per min), maintenance dose, titrated to heart rate and blood pressure response, varied from 25 to 300 Ilg/kg per min. After esmolol administration, at an average dose of 139 ± 83 Ilg/kg per min, mean heart rate decreased from 130 ± 15 to 99 ± 15 beats/min. Within 5 to 18 minutes after initiation of therapy, all patients had achieved a 15% reduction in heart rate at a maintenance dose of 150 Ilg/kg per min or less. A 20% reduction in heart rate was attained in 19 of the 24 patients, and conversion to sinus rhythm occurred during esmolol infusion in 5 of the 11 patients with atrial flutter or fibrillation. Transient asymptomatic hypotension (<90/50 mm Hg) was seen in 13 patients, requiring cessation of esmolol therapy in 2. Mild induration at the intravenous site (eight patients) and nausea (two patients) did not require interruption of therapy. Thus, in postoperative supraventricular tachyarrhythmias, esmolol 1) is effective in rapidly controlling heart rate for up to 24 hours; 2) may result in conversion to sinus rhythm; and 3) is well tolerated but may produce treatment-limiting hypotension in a small number of patients.

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or greater in the early postoperative period after cardiac surgery using cardiopulmonary bypass. A criterion for exclusion was a blood pressure level less than 90/60 mm Hg. Patients with significant pulmonary or renal insufficiency (creatinine >2.0 mg/100 ml), preoperative congestive heart failure (New York Heart Association functional class III or IV), a history of bronchospasm severe enough to preclude use of a beta-adrenergic blocking agent, life-threatening noncardiac disease or known malignancy were also excluded. None of the patients received other beta-adrenergic blocking or calcium channel blocking agents before or during the study for a period equal to two half-lives of the agent in question. No other antiarrhythmic agents were added during infusion of esmolol; however, such drugs were not discontinued if patients were receiving them before the start of the study and blood levels had stabilized. Eleven patients had received intravenous digitalizing doses before esmolol infusion without adequate clinical effect. Mean serum digoxin level in these 11 patients was 1.19 ± 0.71 mg/100 ml at the start of esmolol infusion.

Twenty-four patients ranging in age from 42 to 78 years (mean 61 ± 11) met these criteria and were studied 1 to 7 days after coronary bypass surgery or valve replacement surgery, or both. Although patients were eligible for treatment at any time after surgery, none received esmolol until 24 hours after surgery. No patient had rapid atrial fibrillation or flutter within 24 hours of surgery. Treatment with esmolol was begun as early as 1 to 2 hours after arrhythmia onset, but in many patients was delayed for up to 48 hours while attempts were made to control heart rate with conventional therapy using digoxin and verapamil. Sinus tachycardia was often present from the time of rewarming, but a delay in drug treatment was warranted to allow for spontaneous resolution and rule out a possible specific cardiac cause.

Twenty-one patients underwent isolated coronary bypass surgery, and three patients had one or more valves replaced (mitral in two, aortic in three), including two patients who had concomitant bypass surgery. On average, 3.5 grafts per patient were inserted. The surgical technique employed a bubble oxygenator with single cannulation for the patients undergoing coronary bypass grafting. A double venous cannula technique for mitral valve replacement was utilized. Moderate to profound systemic hypothermia and hyperkalemia, cold, multidose cardioplegia were used. The average cardiopulmonary bypass duration was 130 ± 51 minutes; the average cross-clamp time was 79 ± 33 minutes.

Tachyarrhythmias. Atrial fibrillation occurred in nine patients, and atrial flutter occurred in two; these arrhythmias appeared an average of 4 days after surgery. Three patients had a preoperative history of intermittent atrial fibrillation. Unexplained (primary) sinus tachycardia was present from the time of surgery in 13 patients. Long-term oral beta-adrenergic blocking therapy had been used in 6 of these 13 patients and 3 of the 11 patients with atrial fibrillation or flutter.

After a patient was found suitable for study, informed consent was obtained and a 30 minute period of continuous electrocardiographic observation was begun to evaluate the persistence of arrhythmia. During this time, a physical examination and 12 lead electrocardiogram were performed.

Treatment end points and drug administration. This study was of the open label type, the end points of which were: 1) a 15% reduction in heart rate, or 2) conversion to sinus rhythm. Esmolol for infusion was prepared by diluting 10 g of esmolol hydrochloride (supplied by American Critical Care as 10 ml ampules containing 1 g of drug each) in 900 ml of 5% dextrose in water. This resulted in a final concentration of 10 mg/ml, which was infused using an accurate volumetric infusion pump.

Titration period. The drug administration period consisted of initial titration followed by maintenance infusion and was terminated by a follow-up period. The titration sequence began with a 1 minute loading infusion of 500 μg/kg per min followed by the initial titration infusion of 50 μg/kg per min for 4 minutes. At the end of 4 minutes, the patient’s vital signs were recorded, and if he or she had not met the study end points, a repeat 500 μg/kg per min loading infusion was given, followed by a 4 minute infusion at a dose level of 100 μg/kg per min. Progressively higher dose levels were used in sequence if needed, including 150, 200 and 250, up to a maximum of 300 μg/kg per min. Each increase in dose level was preceded by a 500 μg/kg per min loading infusion. If the patient had achieved a 15% reduction in heart rate, but a more optimal clinical response was desired, a still higher dose level (up to 300 μg/kg per min) could be chosen. After the first 20 patients had been studied, the protocol was altered to allow for an initial titration infusion of 25 μg/kg per min. This altered protocol was used in the last four patients, only one of whom remained at this dose level because the study end points had been achieved.

Maintenance period. After selection of the proper dose level by titration, the patient entered a maintenance period of 24 hours or less. If there was loss of control of heart rate during this period, the esmolol dose could be increased up to a maximum of 300 μg/kg per min provided that a loading infusion preceded the change. The maintenance dose could also be adjusted downward if needed. This adjustment was most often made because of mild hypotension or excessive reduction in heart rate, both of which commonly responded to a lowering of the dose. During maintenance and follow-up study, electrocardiograms and vital signs were monitored and the patient was closely watched for signs of an adverse reaction.

Follow-up period. After 24 hours (or sooner if an adverse reaction occurred), administration of esmolol was discontinued and the patient entered the follow-up period. At this time electrocardiographic monitoring was continued, a repeat 12 lead electrocardiogram was obtained and repeat physical examination was performed.

Atrial flutter or fibrillation versus sinus tachycardia. The
study group included 11 patients with either atrial fibrillation (9) or atrial flutter (2) as well as 13 patients with sinus tachycardia. Special care was taken within the latter group to rule out both cardiac and noncardiac causes of sinus tachycardia that might result in a rapid heart rate as a compensatory mechanism. It was believed that the augmented heart rate was part of an overall hyperdynamic postoperative cardiovascular state. Because of the inherent differences between atrial arrhythmias and sinus tachycardia, their differing effects on cardiac pump function and possible differences in etiology, patients with these two types of arrhythmias were compared.

Statistics. All data are reported as mean ± SD. Statistical analysis comparing patients with sinus tachycardia and atrial fibrillation utilized the Mann-Whitney U test (9).

Results

Heart rate response. The heart rate decreased from an average of 130 ± 15 to 99 ± 15 beats/min during esmolol infusion. Within 5 to 18 minutes all 24 patients had achieved a 15% reduction in heart rate at a maintenance dose of 150 μg/kg per min or less. This occurred regardless of type of rhythm (atrial fibrillation versus sinus tachycardia) or digoxin pretreatment. A 20% reduction in heart rate was attained in 19 patients. In 5 of 11 patients with atrial fibrillation or flutter the arrhythmia was converted to sinus rhythm during the infusion of esmolol. Heart rate decreased to a level of 100 beats/min or less in 15 patients.

Dose response. Although the maintenance doses ranged from 25 to 300 μg/kg per min, all patients achieved a 15% reduction in heart rate at a dose of 150 μg/kg per min or less. Eight patients were given a larger dose of esmolol in an attempt to further control their heart rate response. Two patients received the maximal dose of 300 μg/kg per min. Figure 1 shows the distribution of maximal doses in the 24 patients. The most common dose administered was 50 μg/kg per min and the mean dose administered was 139 ± 83 μg/kg per min. The dose-response information in Figure 2 shows that the greatest proportional heart rate reduction occurred at a low maintenance dose (50 μg/kg per min). However, certain patients were able to achieve a 15% reduction in heart rate only at 100 μg/kg per min (four patients) or 150 μg/kg per min (three patients). Doses of 200 μg/kg per min or greater resulted in no additional decrease in mean heart rate, conversion to sinus rhythm or clinically important individual end points.

Effect of pretreatment with intravenous digoxin. Intravenous digoxin (average dose 0.6 mg) had been given to 11 patients (6 with atrial fibrillation, 2 with atrial flutter and 3 with sinus tachycardia). The effects of this pretreatment on the dose-response relation noted with esmolol were compared. Figure 3 illustrates the proportion of patients achieving a 15% heart rate reduction at various esmolol doses with and without pretreatment with digoxin. Although no statistically significant differences are present, the trend suggests that pretreatment with digoxin allows a higher proportion of patients to achieve a 15% heart rate reduction end point at the same or smaller dose of esmolol. For example, after pretreatment with digoxin, 9 (82%) of the 11 patients responded to 50 μg/kg per min compared with 8 (62%) of 13 patients without digoxin. Digoxin pretreatment had been
given to four of the five patients with atrial fibrillation whose arrhythmia was converted to sinus rhythm.

**Comparison of esmolol response in atrial fibrillation or flutter versus sinus tachycardia (Table 1).** The mean baseline heart rate was faster in patients with atrial fibrillation (143 ± 15 beats/min) than in patients with sinus tachycardia (121 ± 7, p < 0.001). Systolic blood pressure was lower in those with atrial fibrillation (111 ± 10 mm Hg) than in those with sinus tachycardia (136 ± 26 mm Hg, p < 0.006), whereas the diastolic pressure was similar in both groups (66 ± 6 versus 65 ± 8 mm Hg). The percent heart rate reduction with esmolol tended to be greater in patients with atrial fibrillation (−29 ± 11%) than in those with sinus tachycardia (−22 ± 5%, p = 0.05). This occurred even though more patients with atrial fibrillation (5 of 11) than with sinus tachycardia (3 of 13) achieved their maximal heart rate reduction with the small maintenance dose of 50 μg/kg per min. The average maintenance dose in patients with atrial fibrillation was 134 ± 92 μg/kg per min compared with 142 ± 79 μg/kg per min in those with sinus tachycardia. The percent reduction in systolic blood pressure was similar (16 versus 17%), as was the reduction in diastolic blood pressure (9 versus 6%).

**Adverse effects.** The most common side effect was hypotension (≤90/50 mm Hg), which occurred in 13 patients (7 of the 11 with atrial fibrillation and 6 of the 13 with sinus tachycardia). This occurrence was related more to pretreatment blood pressure levels than to specific dose level of esmolol. In 11 patients, the hypotension was asymptomatic and transient, correcting without changes in regimen (7 patients) or with intravenous fluid administration or a reduction in the maintenance dose of esmolol, or both (4 patients). In two patients, hypotension did not resolve even at the smallest dose of esmolol (although both continued to have adequate heart rate control at this dose), necessitating discontinuation of therapy after 3.5 and 5.0 hours, respectively. In these two patients, blood pressure normalized within 4 to 10 minutes.

In eight patients, a painless localized induration developed at the intravenous infusion site (usually located on the inner aspect of the mid forearm), beginning approximately 12 hours after the initiation of therapy. The area was slightly red and swollen and disappeared within 24 hours after the cessation of therapy. These changes were noted despite a freshly inserted, well functioning plastic intravenous cannula.

**Mild nausea without vomiting** developed in two patients being treated on the first and fifth postoperative day, respectively. Headaches were noted during therapy in two patients, both of whom had headaches before initiation of esmolol therapy. A diffuse, nonpruritic, erythematous, maculopapular rash noted before the titration period in one patient worsened somewhat during the first few hours of esmolol administration, subsiding within 2 days after discontinuation of the drug.

One patient who experienced a particularly marked decrease in heart rate at a maintenance dose of 50 μg/kg per

**Table 1. Effects of Esmolol in Patients With Atrial Fibrillation or Flutter and Sinus Tachycardia**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Esmolol</th>
<th>Baseline</th>
<th>Esmolol</th>
<th>Baseline</th>
<th>Esmolol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (beats/min)</td>
<td>SAP (mm Hg)</td>
<td>Δ (%)</td>
<td>SAP (mm Hg)</td>
<td>Δ (%)</td>
<td>SAP (mm Hg)</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter</td>
<td>143</td>
<td>111</td>
<td>−30</td>
<td>16</td>
<td>66</td>
<td>−9</td>
</tr>
<tr>
<td>Mean</td>
<td>15</td>
<td>10</td>
<td>11</td>
<td>8</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>SD</td>
<td>123 to 170</td>
<td>103 to 138</td>
<td>−18 to −52</td>
<td>−5 to −27</td>
<td>57 to 78</td>
<td>5 to −26</td>
</tr>
<tr>
<td>Range</td>
<td>0.001</td>
<td>0.006</td>
<td>0.044</td>
<td>0.762</td>
<td>0.796</td>
<td>0.357</td>
</tr>
<tr>
<td>p value</td>
<td>0.001</td>
<td>0.006</td>
<td>0.044</td>
<td>0.762</td>
<td>0.796</td>
<td>0.357</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>121</td>
<td>136</td>
<td>−22</td>
<td>−17</td>
<td>65</td>
<td>−6</td>
</tr>
<tr>
<td>Mean</td>
<td>7</td>
<td>26</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>SD</td>
<td>112 to 136</td>
<td>106 to 193</td>
<td>−15 to −30</td>
<td>−7 to −24</td>
<td>51 to 84</td>
<td>7 to −18</td>
</tr>
</tbody>
</table>
| Range | p values refer to differences between atrial fibrillation or flutter versus sinus tachycardia. DAP = diastolic arterial pressure; HR = heart rate; SAP = systolic arterial pressure.
min developed frequent single ventricular extrasystoles that disappeared after 5 minutes with continuation of esmolol. These were asymptomatic and required no therapy.

Discussion

Prevention and treatment of postoperative atrial arrhythmias. Although the mechanism of supraventricular tachyarrhythmias early after open heart surgery is not well understood, the frequent occurrence of such arrhythmias is well documented (1–3,10–12). Recognition of the value of beta-adrenergic blockade to control ventricular response rates and protect against paroxysmal supraventricular tachyarrhythmias dates from the mid 1960s (13–15). The value of beta-adrenergic blocking therapy in the management of these arrhythmias after cardiac surgery was also recognized early (16). Because of difficulties in management, various prophylactic regimens using either digoxin or beta-adrenergic blockade (or both) have been studied. Digitalization, either preoperative (1) or postoperative (17), has been shown to be superior to no treatment in preventing postoperative supraventricular tachyarrhythmias. The combination of digoxin and propranolol has also been advocated (2,18), as well as propranolol alone (12,19,20). Patients receiving long-term beta-adrenergic blocking therapy before surgery deserve special attention in this regard. Mounting clinical data support the nonwithdrawal or early postoperative reinstitution of beta-adrenergic blocking therapy to prevent the effects of excessive postoperative adrenergic stimulation on cardiac rhythm (3,4,12).

Potential value of esmolol. With the possible exception of patients on long-term preoperative beta-adrenergic blocking therapy, we, like others (21,22), have not observed significant benefits of these various preventive measures and instead have had to focus on acute “after the fact” management of postoperative supraventricular tachyarrhythmias. Our findings suggest that esmolol may fulfill the requirements of this unique setting. That is, it was rapidly effective in controlling ventricular response rates due either to atrial fibrillation or flutter or to sinus tachycardia and had few adverse effects. Although hypotension was common, it was well tolerated, particularly with the patient at bed rest, and was frequently self-terminating or controlled with intravenous fluid administration. In the two patients with treatment-limiting hypotension, this side effect reversed extremely rapidly when administration of the drug was discontinued.

The standard therapies have one or more drawbacks not seen with esmolol. Digoxin is not useful for control of sinus tachycardia and, in contrast to serum drug levels, the onset of its clinical effects is slow and sometimes, unpredictable. Intravenous verapamil is useful, but its effects are short-lived because it is not traditionally given by continuous infusion; it also has no role in the treatment of sinus tachycardia. Intravenous propranolol, also not usually given as a continuous infusion, has limited safety because it lacks cardioselectivity and its effects continue long after treatment has stopped.

Combination drug therapy. Some patients may require more prolonged oral beta-adrenergic blocking therapy for sinus tachycardia. Although conversion to sinus rhythm was not an expected outcome of our study, it did occur with encouraging frequency (in 5 of the 11 patients not in sinus rhythm). In other patients with atrial fibrillation whose arrhythmia is not converted to sinus rhythm, intravenous digoxin or type I antiarrhythmic medications may have to be added during or shortly after the cessation of esmolol therapy. Thus, the safety and efficacy of various combination regimens is now under investigation.

Precautions. Potential drawbacks to the use of esmolol should be pointed out. Because of its potency and rapidity of onset of effect, selection of a small initial dose is recommended, and the infusion rate should be carefully controlled, preferably with a volumetric intravenous pump. The rapidity of drug clearance adds a safety factor should an error of drug dose or concentration occur. In some patients with sinus tachycardia, esmolol is likely to have only a temporary effect because this arrhythmia may resume after discontinuation of esmolol.

Conclusions. In reviewing the overall results with esmolol for treatment of early postoperative supraventricular tachyarrhythmias, several conclusions are warranted. One can expect rapid and clinically important control of ventricular response rates in this inherently unstable clinical situation. These effects on heart rate should be seen at a dose level of 200 μg/kg per min or less, with little further benefit above this level. Because of dose-dependent hypotension, the optimal selection of patients would include those whose blood pressure associated with their arrhythmia is normal or only minimally depressed. Esmolol provides a useful addition to, but not a replacement for, traditional therapy.

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References
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