Managing Critically Ill Patients with Esmolol*
An Ultra Short-Acting β-Adrenergic Blocker

Richard J. Gray, M.D., F.C.C.P.

Esmolol is a new intravenous β-adrenergic blocker with an ultrashort (nine-minute) elimination half-life, which has been studied predominantly for control of supraventricular tachycardia and management of certain types of hypertension. Clinical studies indicate that the efficacy of esmolol is equivalent to that of propranolol and verapamil for control of supraventricular tachycardia and to sodium nitroprusside for control of postoperative hypertension. Esmolol also has been shown to control heart rate and blood pressure during episodes of acute myocardial ischemia. Cardioselectivity is similar to that of metoprolol, and the ability to titrate the effect of esmolol may provide additional assurance that β-adrenergic blockade will remain within the cardioselective range. The most commonly observed adverse effect seen in clinical trials was asymptomatic hypotension. Hypotension may be minimized by titrating to the minimum effective dose and is readily reversed within 10 to 30 minutes of discontinuing the infusion of esmolol. These unique features represent advantages of great potential merit in critical care medicine.

Intravenous β-adrenergic blockade has demonstrated ability to limit the size of an infarct, the extent of infarction, and the incidence of mortality in the acute phase of myocardial infarction. Unfortunately, all β-adrenergic blockers have the potential to exacerbate congestive heart failure, impair cardiac conduction, reduce blood pressure, and precipitate bronchospasm. These agents are therefore contraindicated, especially during the acute period of myocardial infarction, for 18 to 28 percent of otherwise eligible patients with ischemic heart disease and virtually all patients with obstructive disease of the airways. These excluded patients are often the patients in whom reduction of myocardial oxygen demand would be most useful, but the risk of developing effects from β-adrenergic blockade requires cautious use of conventional, long-acting intravenous β-adrenergic blockers.

The long action of traditional intravenous β-adrenergic blockers precludes rapid and aggressive titration of effects to match changing autonomic conditions. The need for a more flexible intravenous agent administered by constant infusion has given rise to the development of the ultra short-acting intravenous β-adrenergic blocker, esmolol. Important characteristics of esmolol are as follows:

<table>
<thead>
<tr>
<th>Primary route of metabolism</th>
<th>Red blood cell esterases</th>
</tr>
</thead>
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<tr>
<td>Excretion</td>
<td>Via liver</td>
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<tr>
<td>Lipophilicity</td>
<td>Weak</td>
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</table>

The plasma elimination half-life of esmolol is nine minutes, compared to two to five hours for conventional intravenous β-adrenergic blockers, a difference which would appear to offer theoretic benefits relative to safety and control, especially in patients at higher risk for side effects. Should typical side effects of β-adrenergic blockers develop, the infusion of esmolol can be discontinued or adjusted, with rapid diminution or reversal of its effects. The metabolism of esmolol is via rapid hydrolysis by red blood cells and is not dependent upon renal or hepatic function, which can be important in critically ill patients with multiorgan system failure.

In vitro studies have demonstrated that in equipotent doses, esmolol is equivalent to propranolol in producing β-adrenergic blockade and that cardioselectivity is similar to that of metoprolol. The hemodynamic effects have been studied in man and several species of animals.

This review will survey the clinical safety and efficacy of esmolol in the management of the critically ill patient. The unique pharmacokinetics of this agent make it potentially suitable for managing (1) supraventricular tachycardia, (2) postoperative hypertension and tachycardia, (3) intraoperative hypertension and tachycardia, and (4) acute myocardial ischemia.

SUPRAVENTRICAL TACHYCARDIA

Supraventricular tachycardia (principally atrial
fibrillation and atrial flutter) is a frequent and occasionally life-threatening complication of myocardial ischemia. Sinus tachycardia, atrial fibrillation, and atrial flutter are also common after open-heart surgery. In both settings, enhanced adrenergic tone is a suspected mechanism for these arrhythmias, thus providing a rationale for β-adrenergic blockade.

In a multicenter, double-blind parallel study, Abrams et al. compared the safety and efficacy of esmolol (given as a constant infusion titrated in stepwise fashion) to intravenous bolus injections of propranolol (3 to 6 mg) in 127 patients (at 12 study centers) with supraventricular tachyarrhythmias. One-third of the patients had diseases commonly associated with increased risk of adverse response to β-adrenergic blockade. These diseases include diabetes, mild congestive heart failure, pulmonary disease, recent myocardial infarction, and renal insufficiency. Titration end points were defined as 20 percent or more reduction from average baseline heart rate, reduction in heart rate to 100 beats per minute or less, or conversion to sinus rhythm. The percentage of patients achieving a therapeutic response were similar for esmolol (72 percent) and propranolol (69 percent). Conversion to sinus rhythm occurred in seven patients receiving esmolol (14 percent) and in nine patients receiving propranolol (16 percent). The overall therapeutic response rate with either β-adrenergic blocker did not differ.

Esmolol was well tolerated in these patients at increased risk. Hypotension (blood pressure less than 90 mm Hg systolic or 50 mm Hg diastolic) was the principal adverse effect reported (esmolol, 46 percent; propranolol, 7 percent); however, the majority of cases (77 percent) were mild and asymptomatic and, when symptomatic (diaphoresis or dizziness), were resolved within 30 minutes after discontinuation of esmolol.

Esmolol proved to be as efficacious as propranolol for the control of the ventricular response during atrial fibrillation or flutter regardless of age, gender, or diagnostic category (Table 1); however, due to its short elimination half-life, esmolol had the advantage of also providing a margin of control and safety. Recovery from β-adrenergic blockade (as evidenced by changes in heart rate) was observed in patients receiving esmolol within ten minutes, compared to propranolol-treated patients, whose heart rates did not change for up to 4.3 hours after bolus administration of propranolol.

Michelson et al. compared infusion of esmolol to a bolus of verapamil for control of atrial fibrillation or flutter in a randomized open-label study. The mean percentage of reduction in ventricular response rate was similar for the two drugs (esmolol, 24 percent; verapamil, 31 percent); however, esmolol was more effective in reducing heart rate to 100 beats per minute or less (nine of 11 patients, compared to five of ten given verapamil). The incidence of hypotension (less than 90 mm Hg systolic) was somewhat less in the esmolol-treated patients (three of 11 patients vs six of ten verapamil-treated patients). It was concluded that esmolol is comparable to verapamil, but the advantage of titration of esmolol compared to bolus injection of verapamil was the ease with which any adverse effects could be controlled.

In postoperative cardiac surgical patients, esmolol was effective for the treatment of postoperative atrial fibrillation and flutter, especially in conjunction with digoxin. Hypotension (less than 90 mm Hg systolic or 50 mm Hg diastolic) was the most common side effect and occurred in 13 of 24 patients. In 11 of these 13 patients, hypotension was asymptomatic and transient and was rapidly reversible through adjustment of dosage alone. Such lowered blood pressure was tolerated by the patient at bed rest and was often self-terminating or controlled by intravenous fluid administration. In two patients, discontinuation of esmolol was necessary, and hypotension resolved within ten minutes in both cases.

Another multicenter open-label study of supraventricular tachyarrhythmia was conducted in 160 patients at 12 centers. A therapeutic response (defined as 15 percent or more reduction in baseline heart rate or conversion to sinus rhythm) was achieved in 79 percent of the patients at a dosage of 97.2 μg/kg/min ± 5.5 μg/kg/min (mean ± SE). Of this group, 60 patients had a sustained therapeutic response, in 82 percent (49) of whom esmolol was continued for up to 24 hours. When hypotension was observed, it was most often asymptomatic (70 percent of hypotensive patients) and resolved while receiving esmolol by infusion in 58 percent of the cases. When esmolol was discontinued due to symptomatic hypotension (19 of 160 patients; 12 percent), the hypotension resolved within 30 minutes after esmolol was discontinued. The authors noted that adverse effects were often due to doses of esmolol above those required to achieve a

<table>
<thead>
<tr>
<th>Condition</th>
<th>Esmolol (N = 50)</th>
<th>Propranolol (N = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>28/38 (74)</td>
<td>34/46 (74)</td>
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<tr>
<td>Atrial flutter</td>
<td>6/8 (75)</td>
<td>3/8 (38)</td>
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<tr>
<td>Conversion to sinus rhythm</td>
<td>8/46 (17)</td>
<td>11/54 (20)</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>1/1 (100)</td>
<td>1/1 (100)</td>
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<tr>
<td>Automatic atrial tachycardia</td>
<td>1/3 (33)</td>
<td>0</td>
</tr>
</tbody>
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*Response was defined as 20 percent or more reduction in heart rate, heart rate less than 100 beats per minute, or conversion to sinus rhythm.
†Numbers within parentheses are percentages.
therapeutic effect and may have been avoided with careful titration to the minimum effective dose.

This dose-related effect on blood pressure was reinforced by the results of a double-blind, placebo-controlled crossover study of 71 patients with supraventricular tachycardia, showing that two-thirds achieved a therapeutic response and that 90 percent of those who responded did so at doses of 150 μg/kg/min or less. In contrast, adverse effects (18 percent overall) were seen primarily in patients receiving 200 μg/kg/min or more. During treatment with esmolol, predominantly for supraventricular tachycardias, Sung et al analyzed the adverse occurrence of systolic hypotension and demonstrated the risk to be greatest during the first 30 minutes (15 percent) of infusion. By the end of 60 minutes, the cumulative risk was 20 percent, and it remained at 5 percent in each of the next three hours. Although no statistical significance was seen, an increasing risk of developing hypotension was observed with increasing dosage of esmolol. There was a clear decrease in the benefit-risk ratio for dosages of esmolol greater than 100 μg/kg/min, whereas the incremental change in patients achieving a therapeutic response tends to decrease with increasing dosage of esmolol. The incremental change in the estimated percentage of patients developing hypotension remained constant; however, caution should be exercised in titrating dosage, in order to avoid hypotension; increments in dosage should be gradual, and blood pressure should be monitored constantly. It also appears that esmolol-induced hypotension is related to dose and pretreatment systolic blood pressure and may be avoided by careful titration to the minimum effective dose of esmolol.

**POSTOPERATIVE HYPERTENSION**

Systolic hypertension is common especially after cardiac surgery. It is particularly bothersome because it endangers fresh anastomoses and increases cardiac work. These effects are particularly undesirable at a time when the metabolic demand of normal convalescence is high. Catecholamines play a major role in the etiology of postoperative hypertension. In a recent group of 20 patients with postoperative hypertension, the serum norepinephrine level was greater than two standard deviations above normal values in all patients, with an elevation of serum levels of epinephrine and renin in six of 20 and in nine of 20 patients, respectively. Therapy for postoperative hypertension is usually intravenous and includes vasodilators and β-adrenergic blockers. Vasodilators lower blood pressure but can increase ventricular rate, and in the case of sodium nitroferricyanide, may diminish arterial oxygen saturation and lower diastolic blood pressure excessively. The onset of the antihypertensive effect of traditional intravenous β-adrenergic blockers is slow, and adverse effects are difficult to reverse. In contrast, the onset of action of esmolol is rapid, and the brief duration of esmolol's effects in postoperative hypertension is reflected in the fact that at 20 minutes after cessation of infusion, the heart rate (expressed as percentage of baseline) recovered to 100 percent, systolic blood pressure to 98 percent, and cardiac index to 99 percent of baseline values.

Representative hemodynamic effects of esmolol in postoperative hypertension are contrasted with those of nitroferricyanide in Table 2. Heart rate was decreased with esmolol, compared to an increase with sodium nitroferricyanide. Both drugs significantly lowered systolic and diastolic blood pressure, as well as the left ventricular stroke work index. While the cardiac index was decreased by esmolol and increased by nitroferricyanide, the stroke volume index was modestly decreased (not significant) by esmolol and

<table>
<thead>
<tr>
<th>Table 2—Hemodynamic Effects of Esmolol in Postoperative Hypertension</th>
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<tbody>
<tr>
<td><strong>Data</strong></td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
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<tr>
<td>Systolic</td>
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<tr>
<td>Diastolic</td>
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<tr>
<td>Right atrial pressure, mm Hg</td>
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<td>Pulmonary arterial wedge pressure, mm Hg</td>
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<tr>
<td>Cardiac index, L/min/m²</td>
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<tr>
<td>Stroke volume index, ml/beat/m²</td>
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<tr>
<td>Systemic vascular resistance, dynes·cm⁻⁵</td>
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<tr>
<td>Arterial oxygen pressure, mm Hg</td>
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<td>Therapeutic mean dose, μg/kg/min</td>
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*p<0.05 from baseline to after titration.
was unchanged by nitroferricyanide. Infusion of esmolol rapidly controls postoperative hypertension with less unwanted decrease in diastolic blood pressure and oxygen desaturation than was seen with sodium nitroferricyanide. Over half of the patients receiving sodium nitroferricyanide (58 percent), compared to 8 percent receiving esmolol, developed diastolic pressures below 50 mm Hg, considered by many clinicians to be an adverse effect. More stable control of blood pressure was noted during treatment with esmolol. Esmolol may be an excellent sole agent for hypertension in patients with adequate cardiac output. In severe postoperative hypertension or when cardiac output is mildly reduced, a combination of sodium nitroferricyanide and esmolol may provide a more safe approach than either agent alone by minimizing the potentially adverse effects of each; for example, nitroferricyanide-associated reflex tachycardia and reduction of diastolic blood pressure could be lessened and the depression of cardiac output by esmolol could be minimized by combined therapy.

**INTRAOPERATIVE HYPERTENSION AND TACHYCARDIA**

The effect of tachycardia in response to surgical stimuli is particularly significant because of the potential link between intraoperative tachycardia and the development of intraoperative ischemia and perioperative myocardial infarction. Intravenous β-adrenergic blockers are often used in this setting, but their long-acting effects can complicate postoperative recovery.

A placebo-controlled randomized study of infusion of esmolol begun prior to intubation for noncardiac surgery in ASA class 1 patients and a nonrandomized study in ASA class 2 and 3 patients indicated successful attenuation of postintubation increases in heart rate, systolic blood pressure, and the rate-pressure product. The dosages employed included a loading infusion of 500 μg/kg/min for four minutes, followed by a maintenance infusion of 100 μg/kg/min to 300 μg/kg/min.

Control of heart rate and blood pressure during anesthesia for myocardial revascularization using a similar preinduction protocol and infusion dosages has been reported by several investigators. Menkhaus et al found that at infusion rates of more than 100 μg/kg/min, the one-minute postintubation heart rate, blood pressures, and rate-pressure product were lower than in a placebo-treated group, but the cardiac index, pulmonary capillary wedge pressure, systemic vascular resistance index, and left ventricular stroke work index were not significantly affected. Compared to placebo, statistically significant but transient increases in pulmonary capillary wedge pressure were noted after infusion of esmolol (8.3 ± 1.7 to 13.2 ± 2.0 mm Hg; mean ± SE) or after infusion of esmolol followed by intubation (11.2 ± 0.6 to 15.5 ± 1.7 mm Hg). Similar blunting of the responses of heart rate and systolic blood pressure during anesthesia for carotid endarterectomy has also been demonstrated.

Compatibility of infusion of esmolol with techniques including thiopental, ketamine, pancuronium, fentanyl, diazepam, and nitrous oxide have been demonstrated.

**ACUTE MYOCARDIAL ISCHEMIA**

The physiologic basis of acute myocardial ischemia and infarction would suggest the value of β-adrenergic receptor blocking drugs that possess antiischemic, antihypertensive, and antiarrhythmic properties; however, the fear of precipitating cardiac failure, atrioventricular conduction delay, or bronchospasm has limited the use of intravenous β-adrenergic blockers such as propranolol and metoprolol.

Kirshenbaum et al observed the effects of esmolol on 19 patients with acute myocardial infarction or unstable angina in whom there was concern that long-acting intravenous β-adrenergic blockers might not be tolerated. Esmolol was effective in slowing the ventricular rate (from a mean of 92 to 77 beats per minute) and in reducing systolic blood pressure (from a mean of 120 to 97 mm Hg) for up to seven hours in these patients. The effect of esmolol on the ventricular rate was reversed within 30 minutes from when the infusion was withdrawn. Adverse effects, principally hypotension, occurred in seven patients. In five of these patients, esmolol could be continued but at a lower dose. In two patients with acute myocardial infarction, esmolol had to be discontinued, but in both cases the hypotension resolved in 20 to 30 minutes.

The cardiac index fell from 2.8 to 2.2 L/min/m² (p < 0.01) during titration but returned to normal within 30 minutes of termination of the infusion. There was no significant change in pulmonary capillary wedge pressure (13 vs 14 mm Hg). The authors suggest that in the absence of congestive heart failure or shock, esmolol is effective in slowing the heart rate and reducing blood pressure in patients with acute myocardial ischemia in whom rapid titration of β-adrenergic blockade is clinically desirable. The effects of the drug on heart rate and blood pressure were rapidly eliminated on termination of the infusion.

Preliminary results from another study comparing esmolol to propranolol in unstable angina indicate similar rates for cardiac events and equal reduction in the rate-pressure product, but with esmolol doing so in less time than propranolol (22 vs 49 minutes).

The hemodynamic effects of esmolol in patients with stable coronary atherosclerosis has been reported by Iskandrian et al using first-pass radionuclide angiography. Esmolol (200 μg/kg/min) and propranolol (4 mg intravenously) produced similar reductions in heart
rate, systolic blood pressure, left ventricular ejection fraction, systolic blood pressure to end-systolic volume ratio, and cardiac index, both at rest and during exercise. The only difference between the agents was systolic blood pressure with exercise, which was lower with esmolol.

**Other Potential Indications for Esmolol**

Although officially approved only for management of supraventricular tachycardia, there are potential benefits of a short-acting β-adrenergic blocking agent in a number of clinical situations. Unstable angina, acute myocardial infarction, dissecting aortic aneurysm, idiopathic hypertrophic subaortic stenosis, and achieving a decrease in myocardial oxygen supply during PTCA are some other potential uses.

This agent is especially attractive for intraoperative use because of the rapid titration-like onset and short duration of action. Useful circumstances would include control of sinus tachycardia or hypertension due to the sympathetic stimulation of intubation and surgical manipulation, especially important in patients with coronary atherosclerosis having cardiac or noncardiac surgery. Other potential uses could include controlled hypotension for neurosurgery, vascular surgery, and pheochromocytoma and thyroidectomy.

**CABDIOSELECTIVITY**

In a placebo-controlled, double-blind, randomized crossover study by Sheppard et al of ten patients with mild bronchial asthma, it was suggested that esmolol could be given to these patients when control of ventricular rate is indicated. Esmolol was tolerated better than propranolol, as demonstrated by less effect on specific airway resistance during dry-air provocation testing and following inhalation of isoproterenol. The authors found that despite receiving the maximum dosage of esmolol (300 μg/kg/min), there was no significant increase in specific airway resistance, while in the same patients, clinically effective intravenous boluses of propranolol produced symptomatic bronchoconstriction in three of six patients. In a study by Byrd et al, six of 16 patients had a history of mild chronic pulmonary disease but no history of bronchial asthma, three of whom were being treated with aminophylline at the time of study. None of the patients in this study reported any change in symptoms, nor was there any appearance of wheezing while receiving esmolol by infusion for supraventricular tachycardia. The ultra-short elimination half-life of esmolol offers the further advantage that its activity may be titrated to retain β-adrenergic blockade consistently within the cardioselective (β₁) range.

**Details of Administration**

Esmolol is available in 10-ml glass ampules containing 2.5 g. Two ampules are diluted in 500 ml of diluent (D₅W, dextrose saline, physiologic saline, or Ringer’s lactate), which produces a concentration of 10 mg/ml. The dosage of esmolol must be individualized by titration, in which each step is preceded by a loading infusion of 500 μg/kg/min for one minute. This is followed by a progressively increasing rate of infusion at four-minute intervals, beginning at 25 μg/kg/min and increasing to 50 μg/kg/min, and subsequently by increments of 50 μg/kg/min until the desired response is seen. This maintenance dose can be adjusted downward if necessary. Dosages over 200 μg/kg/min are rarely needed, but dosages up to 300 μg/kg/min have been given safely. The average effective dose for the treatment of supraventricular tachycardia is 100 μg/kg/min, for instance. Esmolol has been given via peripheral and central lines up to 24 hours. There are limited data indicating its safety and efficacy out to 48 hours.

**Adverse Effects**

Esmolol has now been given to over 400 patients in clinical trials for supraventricular tachycardia. In addition, 600 patients have been entered into other clinical studies for conditions other than supraventricular tachycardia.

Of the patients treated for supraventricular tachyarrhythmias, the most common adverse effect, hypotension, has been reported in 13 to 39 percent of the patients. Symptomatic hypotension was reported in 12 percent of the total patients. Asymptomatic hypotension was reported in about 25 percent of the patients. Most hypotension is asymptomatic and resolved during continued infusion in 63 percent of the patients and resolved within 30 minutes after discontinuation of infusion in 80 percent of the remaining patients. Abrams et al reported that the average dose at which a therapeutic response was achieved was 115 μg/kg/min, but the average maximum dose was 200 μg/kg/min. Several patients achieved therapeutic response at 50 μg/kg/min but were advanced to higher doses which resulted in hypotension. Therefore, hypotension can be avoided by careful titration to the minimum effective dose, and by monitoring closely, especially those patients with borderline blood pressure before treatment. Other side effects have been noted, as shown in the following tabulation listing adverse effects:

| Cardiovascular | Diaphoresis | 10% |
|               | Lower limb ischemia | 10% |
|               | Bradycardia; chest pain; syncope; pulmonary edema; heart block | 1% |
| Central nervous system | Dizziness | 3% |
|                     | Somnolence | 3% |
|                     | Confusion; agitation; headache | 2% |
| Respiratory | | |

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Bronchospasm; wheezing; dyspnea;
nasal congestion; rhonchi; rales 1%
Gastrointestinal
Nausea 7%
Vomiting 1%
Skin
Impression site reaction:
inflammation and induration 8%

CONCLUSION
Esmolol is indicated for the treatment of atrial fibrillation or flutter in perioperative, postoperative, or any other emergent situation. It is also approved for noncompensatory sinus tachycardia where clinical judgment deems it necessary to control rapid heart rate with a short-acting β-adrenergic blocker. When esmolol is given by continuous infusion, the effect is characterized by rapid onset, predictable titratability, rapid elimination when infusion is discontinued, and relative cardioselectivity. These characteristics make it especially suitable for critical care situations, where the need for β-adrenergic blockade varies widely and where continued effects of conventional intravenous β-adrenergic blockade might complicate management of the hemodynamically unstable patient. Such patients include the elderly and those with coronary artery disease, first-degree atrioventricular block, borderline congestive heart failure, and chronic obstructive pulmonary disease. Based on this profile, esmolol is unique among intravenous β-adrenergic blockers in the perioperative and acute care setting.

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