An Enantiomerically Pure Formulation of Esmolol Attenuates Hypotension and Preserves Heart Rate Control in Dogs

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ABSTRACT

Background: Esmolol is marketed as a racemate (RS-esmolol) with hypotension being the most frequently reported adverse event. Previously, it has been shown that the S-enantiomer (S-esmolol) possesses all of the heart rate (HR) control. The authors studied whether S-esmolol alone mitigates hypotension at similar degrees of HR control compared with RS-esmolol.

Methods: The effects of RS- and S-esmolol on blood pressure (BP) were compared at multiple infusion rates producing similar HR control in dogs (N = 21). Differences in BP were further interrogated by monitoring global cardiovascular function and included the R-enantiomer (R-esmolol) (N = 3).

Results: S-esmolol at half the rate (μg kg^{-1} min^{-1}) of RS-esmolol provided the same degree of HR control over all infusion rates. RS-esmolol lowered BP by 3, 6, 11, 20, and 38 mmHg at 90, 300, 600, 1,000, and 2,000 μg kg^{-1} min^{-1}, compared with 2, 4, 5, 10, and 16 mmHg at 45, 150, 300, 500, and 1,000 μg kg^{-1} min^{-1} for S-esmolol. Decreased BP with RS-esmolol was attributed to decreases in left ventricular developed pressure (LVDP) (−34 mmHg), LVdP/dt+max (−702 mmHg/s), and cardiac output (−1 l/min). R-esmolol also decreased BP (−10 mmHg), LVDP (−10 mmHg), LVdP/dt+max (−241 mmHg/s), and cardiac output (to −0.2 l/min). S-esmolol reversed these trends toward pre-esmolol values by increasing BP (+13 mmHg), LVDP (+12 mmHg), LVdP/dt+max (+76 mmHg/s), and cardiac output (+0.4 l/min).

Conclusions: R-enantiomer provided no HR control, but contributed to the hypotension with RS-esmolol, which appears to be due to negative inotropy. Thus, an S-enantiomer formulation of esmolol may provide similar HR control with less hypotension. **(Anesthesiology 2014; 121:1184-93)**

ESMOLOL is effective in reducing tachycardia and hypertension due to perioperative stimulation. Although the blood pressure (BP)–lowering effect of esmolol is often desirable in clinical applications such as neuroanesthesia, excessive hypotension is not desirable, especially in high-risk surgery with low cardiac output (CO) secondary to ventricular dysfunction, and similar situations.[1–6] Concern over hypotension with β-blockade led to the American Heart Association Guideline strongly recommending titration to achieve effective heart rate (HR) control while avoiding frank hypotension.[7] Hypotension is the most frequently reported adverse event with esmolol. Although esmolol-induced hypotension is resolved rapidly upon cessation of administration, it would be better if the 30 min required for stabilization of an esmolol-treated hypotensive patient[8] could be minimized. Mitigating hypotension may reduce clinician reluctance permitting higher dosing to achieve HR control in recalcitrant patients.[9]

In the current work, we asked whether the S-enantiomer alone (S-esmolol) could decrease the severity of hypotension compared with racemic esmolol (RS-esmolol) at similar degrees of HR control—a question not previously addressed in the literature. Secondary questions included what was driving the hypotension (CO and/or systemic vascular resistance), and could hypotension be attributed, in part, to the R-enantiomer. Lastly, we asked whether cardiovascular differences between RS-, S-, and R-esmolol are attributable to differences in their pharmacokinetic profiles. Based on its well-characterized utility in *in vivo* studies evaluating β-agonists and β-blockers, the dog was selected as the model system to address these questions.[10–13]

What We Already Know about This Topic

- Esmolol is an ultrashort-acting selective β-1 adrenergic receptor blocker used to prevent or treat tachycardia resulting from perioperative stimulation
- The most frequently observed adverse event accompanying its administration is hypotension
- Esmolol is marketed as a racemic mixture (*i.e.*, it contains both R- and S-enantiomers)

What This Article Tells Us That Is New

- An esmolol formulation containing only the S-enantiomer achieved the same degree of heart rate control as the RS-esmolol formulation when infused at half the rate of RS-esmolol in a large animal model but with less-associated hypotension

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Materials and Methods

Model System

Dogs were obtained from Covance Research Products Inc. (Cumberland, VA). All animal care and use procedures were approved by the institution's animal care and use committee (Round Lake, IL) and were conducted in accordance with U.S. Department of Agriculture Regulations, 9 Code of Federal Regulations Parts 1, 2, and 3, and with the Guide for the Care and Use of Laboratory Animals at an Association for Assessment and Accreditation of Laboratory Animal Care International accredited facility.[14,15]

Esmolol Preparation

Samples of S-enantiomer (98.5% S-enantiomer, 1.5% R-enantiomer) and R-enantiomer (98.4% R-enantiomer, 1.6% S-enantiomer) were obtained from a commercial supplier to formulate batches of RS-, S-, and R-esmolol. Batches were filtered (0.2 μm), filled into the commercial container closure system, and steam sterilized. The batches were characterized before and after all *in vivo* testing to confirm stability (table 1). Personnel performing the dosing procedures were not blinded to the esmolol formulations administered.

First Cardiovascular Study

Surgery and Instrumentation. Twenty-one mongrel dogs were weighed, anesthetized with sodium pentobarbital, intubated, and mechanically ventilated. A sterile, saline-filled catheter was placed into a femoral artery for measuring the mean arterial pressure (MAP) and HR. Respiratory minute volume was adjusted to maintain the highest end-tidal carbon dioxide at which the animals did not breathe spontaneously. Circulating heating blankets maintained normal body temperature.

Experimental Design. This study determined whether esmolol containing only the S-enantiomer (S-esmolol) could attenuate hypotension compared with racemic esmolol (RS-esmolol) at similar degrees of HR control. RS-esmolol was infused at 90, 300, 600, 1,000, and 2,000 μg kg^{-1} min^{-1} and S-esmolol at 45, 150, 300, 500, and 1,000 μg kg^{-1} min^{-1}. Infusions were approximately 15 min to require MAP to achieve a steady state. Then a bolus dose of isoproterenol was given to assess RS- and S-esmolol effectiveness to block the increase in HR. Isoproterenol is also a β_2 agonist causing a net decrease in MAP. Therefore, hypotension with RS- and S-esmolol was evaluated at the end of the infusion and before isoproterenol. Dogs were exposed to two or more infusions in a single day with infusions separated by 30 min. For dogs receiving more than two infusions, RS- and S-esmolol were alternated and the infusion rates were evaluated from low to high. The HR peak and MAP nadir following isoproterenol were also compared before any and after all esmolol exposures to assess the potential for tachyphylaxis.

Second Cardiovascular Study

Surgery and Instrumentation. Three mongrel dogs were weighed, anesthetized with sodium pentobarbital, intubated, and mechanically ventilated. A sterile, saline-filled catheter was placed into a femoral artery for measuring MAP and HR. For assessment of ventricular function, dogs were instrumented with a high-fidelity pressure transducer (Millar, Houston, TX) inside the left ventricle. For assessment of CO, a 7.5-French Swan-Ganz® CCO/VIP catheter (Edwards Lifesciences Corporation, Irvine, CA) was passed into the pulmonary artery. Placement was facilitated with fluoroscopy and verified by pressure waveforms. Respiratory minute volume was adjusted to maintain the highest end-tidal carbon dioxide at which the animals did not breathe spontaneously. Circulating heating blankets maintained normal body temperature.

Experimental Design. This study determined the cause of hypotension associated with RS- and S-esmolol, and if differences could be attributed to the R-enantiomer. Clinically relevant and supraclinical infusion rates were evaluated. For the former, RS-esmolol was administered at 300 μg kg^{-1} min^{-1} and compared with S- and R-esmolol each infused at 150 μg kg^{-1} min^{-1}. For the latter, RS-esmolol was administered at 2,000 μg kg^{-1} min^{-1} and compared with S- and R-esmolol each infused at 1,000 μg kg^{-1} min^{-1}. Infusions were approximately 15 min to require MAP to achieve a steady state. Unlike the first study, there was no washout period between infusions. Instead, there was an immediate switchover from administering one formulation to another. This design was decided beforehand to accentuate cardiovascular differences between RS-, S-, and

Table 1. Analysis of the Experimental Batches of Esmolol

	Before *In Vivo* Testing Started			After *In Vivo* Testing Completed		
Parameter	RS-esmolol (Target 20 mg/ml)	S-esmolol (Target 25 mg/ml)	R-esmolol (Target 25 mg/ml)	RS-esmolol	S-esmolol	R-esmolol
Esmolol (mg/ml)	20.52 ± 0.06	21.86 ± 0.07	25.19 ± 0.04	20.16 ± 0.10	21.66 ± 0.03	24.85 ± 0.14
ASL-8123 (%)	2.05 ± 0.01	1.60 ± 0.01	4.22 ± 0.01	3.75 ± 0.02	2.81 ± 0.37	5.85 ± 0
pH	4.83 ± 0	4.81 ± 0.02	4.91 ± 0.01	4.79 ± 0.01	4.75 ± 0.03	4.85 ± 0.02
Osmolality (mOsm/Kg)	299 ± 0	322 ± 1	299 ± 1	301 ± 1	326 ± 2	303 ± 2

All values represent the mean ± SD of triplicate measurements. All parameters remained stable over the period of *in vivo* testing. As expected, ASL-8123, the primary degradant of esmolol, increased slightly in all batches.

R-esmolol. To control for the effects of a preceding infusion on subsequent infusions, the experiment was designed as a Latin-square[16] (table 2).

Cardiovascular Assessment. Mean arterial pressure and HR were measured continuously and tabulated at 15-s intervals. Left ventricular end-diastolic pressure (LVEDP), left ventricular $dP/dt+_{max}$ ($LVdP/dt+_{max}$), and left ventricular developed pressure [LVDP = (Systolic Pressure − LVEDP)] were measured continuously and tabulated at 15-s intervals. LVDP and $LVdP/dt+_{max}$ were surrogate markers for evaluating inotropy.[17] LVEDP was a surrogate marker for left ventricular end-diastolic volume and assumes ventricular compliance remained constant. CO was measured at the start and end of each infusion and used to calculate stroke volume and systemic vascular resistance.

Pharmacokinetic Study

Experimental Design. This study determined the pharmacokinetics of RS-, S-, and R-esmolol. Six, conscious Beagle dogs each received RS-, S-, and R-esmolol in a replicated Latin-square design with a washout period of 6 days between esmolol infusions (table 3). The 6-day washout period was conservative and based on the unknown persistence of esmolol's primary metabolite (4-(2-hydroxy-3-((1-methylethyl)amino)propoxy)phenylpropanoic acid; hereafter referred to as ASL-8123) of the two enantiomers. A percutaneous catheter was inserted into a jugular vein, and RS-esmolol was infused at 600 μg kg^{-1} min^{-1} and S- and R-esmolol were each infused at 300 μg kg^{-1} min^{-1} *via* a cephalic vein for 10 min using a calibrated pump. The infusion rates were selected to ensure the detection of esmolol in plasma for at least three half-lives, and represented the middle of the range of infusion rates evaluated in the first cardiovascular study. Following the last scheduled blood sample, the percutaneous catheter was removed, and the dogs returned to their pens.

Blood Sample Collection and Analysis. Blood was collected before each infusion (baseline or 0 min), at the halfway point of each infusion (5 min), immediately after each infusion (10 min), and 5, 8, 12, 16, 20, 30, and 45 min and 1, 2, 3, 5, and 8 h after the end of each infusion. Blood (0.5 ml) was collected into tubes containing the esterase inhibitor sodium fluoride and potassium oxalate as an anticoagulant. Plasma was stored at approximately −70°C until analyzed. Freeze-thaw (three times) and 60-day frozen sample stability were confirmed. Enantiomers were separated on a chiral column (Astec® Chirobiotic® T, 10 cm × 2.1 mm, 5 μm, SKU 12018AST; Sigma-Aldrich, St. Louis, MO) using 5% 5 mM ammonium trifluoroacetate in methanol and 95% 0.1% formic acid in acetone mobile phase. Enantiomers were measured using liquid chromatography–tandem mass spectrometry (1100 series; Agilent Technologies, Santa Clara, CA) with an injection volume of 2 μl, flow rate of 0.8 ml/min, column temperature of 25°C, and a run time of 13 min. Assay validation demonstrated a lower limit of quantitation of 10 ng/ml for both enantiomers. Accuracy ranged from −6% to 3% and −12% to 2% of the theoretical values for the S- and R-enantiomer, respectively, from 10 to 500 ng/ml. Precision ranged from 2% to 9% and from 4% to 7% coefficient of variation for the S- and R-enantiomer, respectively, from 10 to 500 ng/ml.

Pharmacokinetic Analysis. Noncompartmental modeling (WinNonlin Pro®, version 5.2; Pharsight A Certara Company, St. Louis, MO) was used to determine pharmacokinetic parameters for the S- and R-enantiomers as a result of administering RS-esmolol, the S-enantiomer as a result of administering S-esmolol, and the R-enantiomer as a result of administering R-esmolol. Analysis included maximum observed concentration (C_{max}), apparent terminal elimination half-life ($T_{1/2}$), area under the plasma concentration–time curve from 0 to last measurable time point, area under the plasma concentration–time curve from 0 to infinity, and clearance. Based on the number of blood sampling time points with values above the assay's lower limit of quantitation, and that each of these time points represents the average of six dogs, a noncompartmental analysis was considered adequate to derive the pharmacokinetic parameters of interest and to detect biologically meaningful differences between RS-, S-, and R-esmolol.

Statistical Analysis

Data were analyzed using General Linear Model ANOVA (MINITAB® Release 14.20; Minitab Inc., State College,

Table 2. Second Cardiovascular Study Design

Infusion Rate	Dog	Sequence of Esmolol Administration		
Clinically relevant*	1	RS-esmolol	S-esmolol	R-esmolol
	2	S-esmolol	R-esmolol	RS-esmolol
	3	R-esmolol	RS-esmolol	R-esmolol
25-min washout				
Supraclinical†	1	RS-esmolol	S-esmolol	R-esmolol
	2	S-esmolol	R-esmolol	RS-esmolol
	3	R-esmolol	RS-esmolol	R-esmolol

* RS-esmolol administered at 300 μg·kg^{-1} min^{-1}, S-esmolol administered at 150 μg·kg^{-1}·min^{-1}, and R-esmolol administered at 150 μg·kg^{-1}·min^{-1} with no washout period between infusions. † RS-esmolol administered at 2,000 μg·kg^{-1}·min^{-1}, S-esmolol administered at 1,000 μg·kg^{-1}·min^{-1}, and R-esmolol administered at 1,000 μg·kg^{-1}·min^{-1} with no washout period between infusions.

Table 3. Pharmacokinetic Study Design

	Dog	Sequence of Esmolol Administration				
Latin square 1	1	RS-esmolol	6-day washout	S-esmolol	6-day washout	R-esmolol
	2	S-esmolol	6-day washout	R-esmolol	6-day washout	RS-esmolol
	3	R-esmolol	6-day washout	RS-esmolol	6-day washout	R-esmolol
Latin square 2	4	RS-esmolol	6-day washout	S-esmolol	6-day washout	R-esmolol
	5	S-esmolol	6-day washout	R-esmolol	6-day washout	RS-esmolol
	6	R-esmolol	6-day washout	RS-esmolol	6-day washout	R-esmolol

RS-esmolol administered at 600 μg kg^{-1} min^{-1}, S-esmolol administered at 300 μg kg^{-1} min^{-1}, and R-esmolol administered at 300 μg kg^{-1} min^{-1} with 6-day washout period between infusions.

PA). Statistical tests were performed at the α-level of 0.05. Individual data were checked for normality using the Individual Distribution Identification function in MINITAB® and, if necessary, nonnormal data were transformed using the Johnson Transformation function in MINITAB® before analysis. Sample size selection is consistent with best demonstrated pharmaceutical industry practice for nonclinical study designs using large animal species and was considered adequate to demonstrate or rule out the presence of biologically significant differences between RS-, R-, and S-esmolol.

For the first cardiovascular study, the effect of RS- and S-esmolol on MAP and HR were evaluated at the end of the infusion using the values immediately before the infusion as a covariate. The MAP nadir and HR peak following isoproterenol were evaluated using the values at the end of the esmolol infusion and immediately before isoproterenol as a covariate. The model included main effects of "Esmolol" and "Infusion Rate," and the "Esmolol × Infusion Rate" interaction. If the interaction was significant, pairwise comparisons between RS- and S-esmolol were performed at each infusion rate using Tukey *post hoc* test. If the interaction was not significant, then the data were averaged and analyzed across all infusion rates. To evaluate the potential for tachyphylaxis, the MAP nadir and HR peak following isoproterenol were compared before any and after all esmolol exposures using the MAP and HR values immediately before isoproterenol as a covariate. The model included a single factor of "Time."

For the second cardiovascular study, changes in cardiovascular parameters associated with RS-, S-, and R-esmolol were calculated by subtracting the value at the end of each infusion from the value at the beginning of each infusion, which were then used for statistical analysis. This analysis was performed only for the supraclinical infusion rate. The model included factors for "Dog," "Sequence of Esmolol Administration," and "Esmolol" (*i.e.*, RS-, S-, or R-esmolol). Pairwise comparisons were performed using Tukey *post hoc* test, if the "Esmolol" factor was significant.

For the pharmacokinetic study, the comparisons of interest were as follows: (1) S-enantiomer *versus* R-enantiomer as a result of administering RS-esmolol (referred to as RS-S-enantiomer and RS-R-enantiomer, respectively), (2) S-enantiomer as a result of administering RS-esmolol *versus* S-enantiomer following S-esmolol, (3) R-enantiomer as a result of administering RS-esmolol *versus* R-enantiomer following R-esmolol, and (4) S-enantiomer following S-esmolol *versus* R-enantiomer following R-esmolol. For the first comparison, because the S-enantiomer and the R-enantiomer were both derived from the infusion of RS-esmolol, the model included factors for "Square," "Dog(Square)," and "Enantiomer." The model for the latter three comparisons included factors for "Square," "Dog(Square)," "Sequence of Esmolol Administration," and "Enantiomer" (*i.e.*, RS-S-enantiomer, RS-R-enantiomer, S-enantiomer, or R-enantiomer). For the latter three comparisons, pairwise comparisons were performed using Tukey *post hoc* test, if the "Enantiomer" factor was significant.

Results

Stability of Esmolol

Esmolol concentrations before and after all *in vivo* testing indicate that the batches of RS-, S-, and R-esmolol were stable, and that the targeted *versus* actual doses administered (μg kg^{-1} min^{-1}) were the same (table 1).

First Cardiovascular Study

An average, individual response to increasing infusion rates of RS- and S-esmolol on MAP, and their relative effectiveness to block HR following isoproterenol is depicted in figure 1, A–C. Data from all dogs are tabulated in table 4. Overall, baseline MAP was 100 ± 10 mmHg for S-esmolol *versus* 103 ± 16 mmHg for RS-esmolol. An esmolol × infusion rate interaction was detected for MAP ($P < 0.001$) where RS-esmolol at 2,000 μg kg^{-1} min^{-1} decreased MAP from 98 ± 11 mmHg at baseline to 60 ± 7 mmHg immediately after esmolol infusion and before isoproterenol, compared with S-esmolol at 1,000 μg kg^{-1} min^{-1} that decreased MAP from 98 ± 10 mmHg to only 82 ± 13 mmHg. Overall, baseline HR was 105 ± 13 beats/min for S-esmolol *versus* 112 ± 18 beats/min for RS-esmolol. Paradoxically, overall HR increased with both S- and RS-esmolol to 110 ± 15 and 118 ± 15 beats/min, respectively. The overall HR increase with RS-esmolol was greater than S-esmolol ($P < 0.048$). The HR increases with esmolol were modest and were only considered biologically significant at infusion rates well in excess of clinical practice. Overall, the MAP nadir following isoproterenol was similar at 45 ± 12 mmHg with S-esmolol compared with 42 ± 12 mmHg with RS-esmolol.

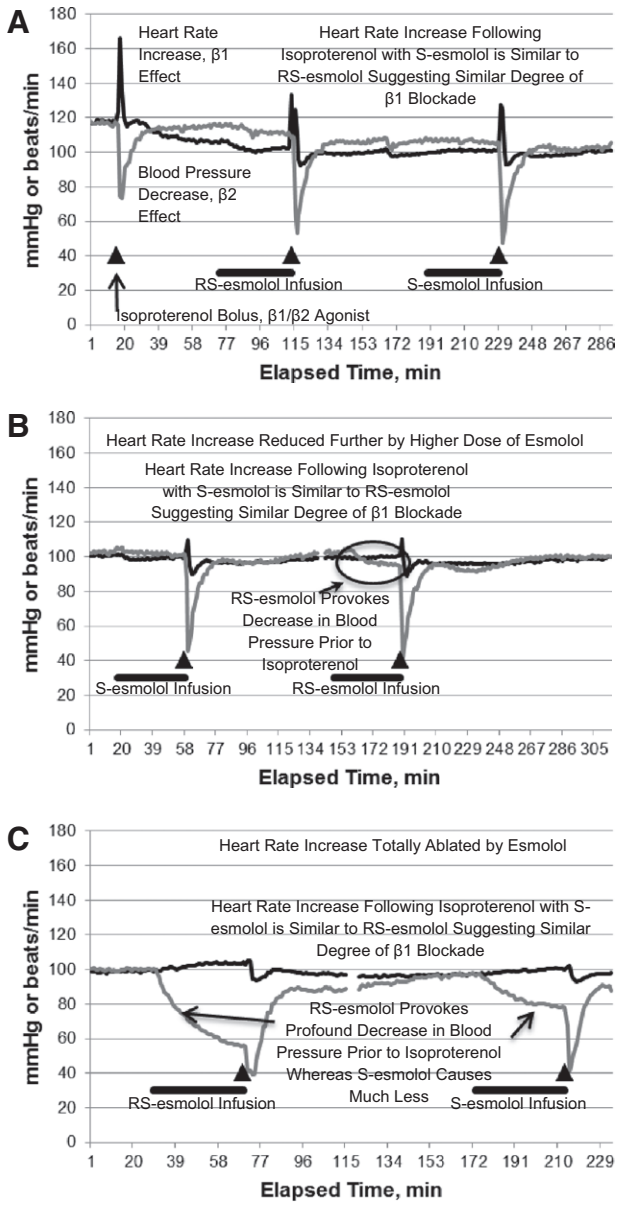

Fig. 1. (*A*) The effect of RS-esmolol (90 μg kg^{-1} min^{-1}) then S-esmolol (45 μg kg^{-1} min^{-1}) on blood pressure before isoproterenol challenge and on heart rate control following isoproterenol challenge in dog DG0023. (*B*) The effect of S-esmolol (150 μg kg^{-1} min^{-1}) then RS-esmolol (300 μg kg^{-1} min^{-1}) on blood pressure before isoproterenol challenge, and on heart rate control following isoproterenol challenge in dog DG0023. (*C*) The effect of RS-esmolol (2,000 μg kg^{-1} min^{-1}) then S-esmolol (1,000 μg kg^{-1} min^{-1}) on blood pressure before isoproterenol challenge and on heart rate control following isoproterenol challenge in dog DG0023.

More important, the HR peak following isoproterenol was similar at 137 ± 15 beats/min with S-esmolol compared with 136 ± 18 beats/min with RS-esmolol.

There was no evidence of tachyphylaxis. The MAP nadir following isoproterenol was 53 ± 17 mmHg (mean ± SD) before any esmolol infusions compared with 48 ± 13 mmHg after all esmolol infusions (P = 0.326). Similarly, the HR peak following isoproterenol was 209 ± 26 beats/min (mean ± SD) before any esmolol infusions compared with 197 ± 19 beats/min after all esmolol infusions (P = 0.308).

Second Cardiovascular Study

At the clinically relevant infusion rate, MAP declined slightly with R-esmolol and was associated with a slight increase in HR (data not shown). The slight decrease in MAP was accompanied by a similar, time-matched decrease in LVdP/dt+$_{max}$ and LVDP. These changes became slightly more pronounced upon transitioning from R-esmolol to RS-esmolol, whereas these changes stabilized (MAP, HR, LVDP) or reversed toward preinfusion values (LVdP/dt+$_{max}$) after transitioning from RS-esmolol to S-esmolol.

Much more profound changes in cardiovascular parameters between RS-, S-, and R-esmolol became evident at the supraclinical infusion rate (table 5). RS-esmolol had the greatest effect on MAP (−28 ± 5 mmHg), LVdP/dt+$_{max}$ (−702 ± 317 mmHg/s), LVDP (−34 ± 5 mmHg), LVEDP (+5 ± 1 mmHg), CO (−1.0 ± 0 l/min), and stroke volume (−14 ± 3 ml/beat). These results indicate that whether RS-esmolol was administered first (before S- and R-esmolol), second (after S-esmolol or after R-esmolol), or last (after S- and R-esmolol), cardiovascular function declined. R-esmolol had similar effects on cardiovascular function but to a lesser extent. Specifically, R-esmolol affected MAP (−10 ± 3 mmHg), LVdP/dt+$_{max}$ (−241 ± 154 mmHg/s), LVDP (−10 ± 4 mmHg), LVEDP (+1 ± 1 mmHg), CO (−0.2 ± 0.1 l/min), and stroke volume (−4 ± 3 ml/beat). In contrast, S-esmolol, whether administered first (before RS- and R-esmolol), second (after RS-esmolol or after R-esmolol), or last (after RS- and R-esmolol), reversed these trends toward pre-esmolol infusion values. Specifically, S-esmolol increased MAP (+13 ± 10 mmHg), LVdP/dt+$_{max}$ (+76 ± 258 mmHg/s), LVDP (+12 ± 14 mmHg), LVEDP (to −2 ± 2 mmHg), and CO (+0.4 ± 0.2 l/min). Although the differences between RS-esmolol and S-esmolol in MAP, LVdP/dt+$_{max}$, CO, LVEDP, LVDP, and stroke volume were all considered biologically significant, only MAP, LVdP/dt+$_{max}$, and CO achieved statistical significance. Also of interest is that HR increased with all esmolol formulations similar to the first cardiovascular study.

Pharmacokinetic Study

Figure 2 depicts the mean plasma concentration–time profiles of the S-enantiomer and the R-enantiomer as a result of administering RS-esmolol (referred to as RS-S-enantiomer and RS-R-enantiomer, respectively), the S-enantiomer as a result of administering S-esmolol, and the R-enantiomer as a result of administering R-esmolol. For all blood samples beyond 26 min (16 min from the end of infusion), both enantiomers were below the assay's lower limit of quantitation for all esmolol formulations. The derived pharmacokinetic parameters are summarized in table 6. No statistical differences were detected for the S-enantiomer as a result of

Table 4. First Cardiovascular Study: Comparison of S-esmolol to RS-esmolol on MAP and Their Ability to Block the Increase in HR after Isoproterenol

Treatment	Infusion Rate, μg kg^{-1} min^{-1}	MAP and HR Immediately before Esmolol Infusion (Baseline)*		MAP and HR Immediately after Esmolol Infusion and before Isoproterenol Bolus		MAP Nadir and HR Peak after Isoproterenol Bolus*	
		MAP, mmHg	HR, beats/min	MAP, mmHg	HR, beats/min	MAP, mmHg	HR, beats/min
RS-esmolol	90 (N = 5)	98 ± 16	101 ± 10	95 ± 15	100 ± 10	53 ± 17	147 ± 18
	300 (N = 6)	111 ± 26	107 ± 26	105 ± 24	111 ± 18	41 ± 0	110 ± 0
	600 (N = 7)	105 ± 14	121 ± 17	94 ± 11	125 ± 9	38 ± 3	138 ± 18
	1,000 (N = 4)	101 ± 12	117 ± 5	81 ± 10	130 ± 6	38 ± 6	140 ± 11
	2,000 (N = 7)	98 ± 11	114 ± 17	60 ± 7	123 ± 10	34 ± 4	119 ± 12
	All rates	103 ± 16	112 ± 18	86 ± 21	118 ± 15‡	42 ± 12	136 ± 18
S-esmolol	45 (N = 5)	97 ± 11	101 ± 12	95 ± 11	99 ± 9	54 ± 16	147 ± 13
	150 (N = 4)	105 ± 7	97 ± 17	101 ± 6	97 ± 19	46 ± 0	110 ± 0
	300 (N = 5)	100 ± 14	108 ± 11	95 ± 14	113 ± 13	41 ± 8	130 ± 9
	500 (N = 4)	101 ± 10	115 ± 3	91 ± 12	123 ± 2	41 ± 4	145 ± 10
	1,000 (N = 6)	98 ± 10	104 ± 16	82 ± 13†	118 ± 12	34 ± 1	127 ± 6
	All Rates	100 ± 10	105 ± 13	92 ± 13	110 ± 15	45 ± 12	137 ± 15

Data are presented as the means ± SD.

* No significant esmolol × infusion rate interactions or main effects of esmolol. † Significant esmolol × infusion rate interaction where the blood pressure decrease associated with S-esmolol at 1,000 μg kg^{-1} min^{-1} was less ($P < 0.001$) than RS-esmolol at 2,000 μg kg^{-1} min^{-1}. ‡ Significant main effect of esmolol where HR at the end of RS-esmolol was greater ($P < 0.048$) than S-esmolol.

HR = heart rate; MAP = mean arterial pressure.

administering RS-esmolol *versus* S-esmolol, the R-enantiomer as a result of administering RS-esmolol *versus* R-esmolol, or the S-enantiomer *versus* the R-enantiomer as a result of administering S-esmolol and R-esmolol, respectively. For RS-esmolol, the elimination half-life ($T_{1/2}$) was statistically significantly longer for the R-enantiomer at 4.2 min compared with 3.8 min for S-enantiomer. In addition, plasma concentrations and area under the plasma concentration–time curve from 0 to last measurable time point and area under the plasma concentration–time curve from 0 to infinity values for the R-enantiomer as a result of administering either RS-esmolol or R-esmolol were numerically higher than those for the S-enantiomer as a result of administering either RS-esmolol or S-esmolol. These differences suggest slight, enantiomer-selective metabolism of esmolol favoring the S-enantiomer over the R-enantiomer, but are not considered biologically significant.

Discussion

The purpose of the current work was to determine whether the S-enantiomer of esmolol (S-esmolol), compared with the racemate (RS-esmolol), would mitigate hypotension at similar degrees of HR control using an anesthetized dog model. Multiple infusion rates of esmolol were utilized ranging from clinically relevant to supraclinical infusion rates in an attempt to discern potential cardiovascular and pharmacokinetic differences between RS-, S-, and R-esmolol.

The first cardiovascular study clearly demonstrates that over all infusion rates evaluated, S-esmolol infused at half the rate of RS-esmolol on a μg kg^{-1} min^{-1} basis achieved the same degree of HR control as demonstrated by its equivalent potency in preventing the tachycardia following isoproterenol. An esmolol formulation containing only the R-enantiomer was not investigated because the S-enantiomer has been shown previously to be two times more efficacious in lowering HR following isoproterenol when compared with racemic esmolol on an equal weight basis (μg kg^{-1} min^{-1}),* suggesting that the R-enantiomer does not control HR and, therefore, was not relevant to the goal of the current study. The more salient observation is that S-esmolol resulted in significant attenuation in hypotension compared with RS-esmolol, which became more pronounced as infusion rate increased. The differentiation between RS- and S-esmolol on BP in the current study was attributed to pharmacodynamics as opposed to pharmacokinetics. This conclusion is based on the pharmacokinetic study, which showed no differences in plasma concentrations and pharmacokinetic parameters of the S-enantiomer as a result of administering RS-esmolol *versus* S-esmolol. These data suggest that the R-enantiomer does possess pharmacologic activity despite previous reports suggesting otherwise.

Based on the calculated elimination half-life of esmolol in mongrel dogs of 4.5 min,* a 30-min washout period allowed for approximately seven half-lives to lapse between infusions. Although the half-life of esmolol's primary metabolite (ASL-8123) is longer, it is not believed to have impacted the study results as ASL-8123 has been found to be approximately 1,600 to 1,900 times less potent than esmolol as a β1-receptor antagonist.[18] Similar to esmolol, isoproterenol

* U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Esmolol HCl NDA 19–386 Pharmacology Review(s) approval date December 31, 1986. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/19-386_%20Brevibloc.cfm. Accessed May 28, 2014.

Table 5. Second Cardiovascular Study: Comparison of RS-esmolol, S-esmolol, and R-esmolol on Global Cardiovascular Function Regardless of Their Sequence of Administration

Treatment	Infusion Rate, μg kg^{-1} min^{-1}		Mean Arterial Pressure, mmHg	Heart Rate, beats/min	LVEDP, mmHg	LVDP, mmHg	LVdP/dt+$_{max}$, mmHg/s	Cardiac Output, l/min	Stroke Volume, ml/beats	Systemic Vascular Resistance, mmHg·min·l^{-1}
RS-esmolol	2,000 (N = 3)	Start infusion	90±12	115±26	6±4	98±14	1,359±616	3±0	31±4	31±1
		End infusion	62±13	125±5	11±4	63±14	657±109	2±0	17±1	30±3
		Change	−28±5	11±12	5±1	−34±5	−702±317	−1.0±0	−14±3	−1±3
R-esmolol	1,000 (N = 3)	Start infusion	90±15	111±8	6±2	97±14	1,227±238	3±0	26±5	31±5
		End infusion	80±16	124±14	7±3	87±14	986±72	3±1	22±6	30±6
		Change	−10±3	14±12	1±1	−10±4	−241±154	−0.2±0.1	−4±3	−1±1
S-esmolol	1,000 (N = 3)	Start infusion	73±31	109±28	9±4	78±38	943±549	3±1	30±18	30±3
		End infusion	86±14	120±12	7±3	91±14	1,019±117	3±0	27±6	29±2
		Change	13±10*	11±10	−2±2	12±14	76±258*	0.4±0.2*	−3±7	−2±1

Data are presented as the means ± SD (N = 3 dogs). Negative values indicate a decrease and positive values indicate an increase.

* Significant difference between S-esmolol and RS-esmolol ($P < 0.05$).

Dev. P = left ventricular developed pressure; LVdP/dt+$_{max}$ = change in left ventricular pressure as a function of time; LVDP = left ventricular developed pressure; LVEDP = left ventricular end-diastolic pressure.

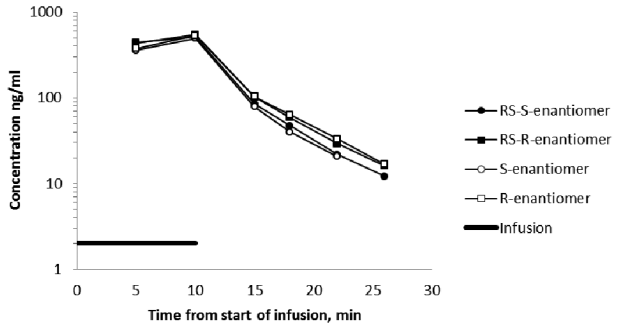

Fig. 2. Comparison of mean concentration–time profiles of the S-enantiomer and the R-enantiomer of esmolol as a result of administering RS-esmolol (RS-S-enantiomer and RS-R-enantiomer, respectively), the S-enantiomer as a result of administering S-esmolol (S-enantiomer), or the R-enantiomer as a result of administering R-esmolol (R-enantiomer).

has a very short-elimination half-life in dogs of 3.1 to 4 min following intravenous bolus doses of 0.4 to 1.6 μg/kg.[19] Furthermore, the primary metabolite of isoproterenol is inactive as a β-receptor agonist. In total, these data suggest that a 30-min washout period between infusions was sufficient.

The second cardiovascular study clearly demonstrates that R-esmolol produces a BP-lowering effect, which appears to be secondary to its similar effects on LVDP and LVdP/dt+$_{max}$. Given that LVDP and LVdP/dt+$_{max}$ decreased despite an elevated LVEDP suggests that the changes in these surrogate markers of ventricular contractility reflect a negative inotropic effect. The mechanism by which R-esmolol mediates the apparent negative inotropic effect is not known, but does not appear to be mediated by β1 receptors as evident by the similar potency of RS- and S-esmolol in blocking isoproterenol-induced tachycardia observed in the first study. This observation is consistent with the *in vitro* work of Fallouh *et al.*[20] demonstrating that racemic esmolol produced a direct negative inotropic effect not mediated by β1 receptors.

The increase in HR following a supraclinical infusion rate of R-esmolol was not unexpected as the R-enantiomer does not appear to block HR as evident by the same degree of HR control between RS- and S-esmolol following isoproterenol in the first cardiovascular study. The increase in HR with R-esmolol was attributed to the baroreceptor reflex in response to its BP-lowering effect. In contrast, the increase in HR with supraclinical infusion rates of RS- and S-esmolol is paradoxical as both possess β1-blocking activity. HR is dictated by the net effect of both parasympathetic and sympathetic nervous systems. Dogs were anesthetized suggesting that regulation of their HR was predominantly under parasympathetic regulation during esmolol administration. Under these conditions, the administration of esmolol would be expected to have little to no effect on HR and is the reason isoproterenol administration following esmolol infusion was necessary in the first cardiovascular study to evaluate the relative effectiveness of RS- and S-esmolol on HR control. The paradoxical increase in HR with RS- and S-esmolol was attributed to baroreceptor-mediated reflex withdrawal of parasympathetic regulation in response to their BP-lowering effects. We surmise that the reduction in parasympathetic tone dominated the β1-blocking effects of RS-esmolol and S-esmolol resulting in a net increase in HR. This supposition was substantiated by subsequently demonstrating in one dog that the same infusion rate of RS-esmolol caused profound bradycardia and was associated with more severe hypotension following pretreatment with the vagolytic agent atropine (fig. 3). More important, similar increases in HR have been reported in humans secondary to hypotension due to esmolol infusion rates of 500 μg kg^{-1} min^{-1} and higher.[21] The esmolol-induced increase in HR in both dogs and humans is not surprising as both species have similar low-frequency (marker of both sympathetic and parasympathetic activity) and high-frequency (marker of parasympathetic activity) HR variability.[22]

Table 6. Pharmacokinetic Study: Pharmacokinetic Parameters of the Individual Enantiomers after RS-esmolol, S-esmolol, or R-esmolol

Treatment	Enantiomer	$T_{1/2}$ (min)	C_{max} (ng/ml)	AUC_{0-t} (min·ng·ml^{-1})	$AUC_{0-\infty}$ (min·ng·ml^{-1})	CL (ml/min)
RS-esmolol	RS-S	3.8 ± 0.2*	545 ± 135	1,997 ± 354	2,071 ± 348	1,485 ± 272
	RS-R	4.2 ± 0.25	563 ± 138	2,203 ± 372	2,305 ± 374	1,333 ± 248
S-esmolol	S	4.0 ± 0.94	513 ± 101	1,834 ± 379	1,927 ± 384	1,606 ± 311
R-esmolol	R	4.2 ± 0.35	567 ± 45	2,291 ± 220	2,372 ± 212	1,273 ± 119

Data are presented as the means ± SD (N = 6 dogs). RS-S represents the S-enantiomer resulting from exposure to RS-esmolol; RS-R represents the R-enantiomer resulting from exposure to RS-esmolol; S represents the S-enantiomer resulting from exposure to S-esmolol; R represents the R-enantiomer resulting from exposure to R-esmolol.

* RS-S different from RS-R (P = 0.004).

AUC_{0-t} = area under the plasma concentration–time curve from 0 to last measurable time point; $AUC_{0-\infty}$ = area under the plasma concentration–time curve from 0 to infinity; CL = clearance; C_{max} = maximum observed concentration; $T_{1/2}$ = apparent terminal elimination half-life.

As MAP is a function of CO and systemic vascular resistance, the lower MAP observed with RS- and R-esmolol was due to a reduction in CO secondary to similar reductions in LVdP/dt+max and LVDP, as opposed to a reduction in systemic vascular resistance. Similarly, data from patients indicate that the hypotension associated with racemic esmolol could not be attributed to a change in peripheral vascular resistance.[23]

The differentiation between RS-, R-, and S-esmolol on cardiovascular function was attributed to differences in pharmacodynamics as opposed to pharmacokinetics. This conclusion is based on the pharmacokinetic study, which showed no differences in plasma concentrations and pharmacokinetic parameters of the individual enantiomers following RS-, R-, or S-esmolol.

The key finding from the current work is that an esmolol formulation consisting of only the S-enantiomer appears to possess the same HR control and less-associated hypotension when compared with racemic esmolol. The ultimate question is how these findings translate to patients. To provide insight, the results of the current study are superimposed upon human meta-analysis results, showing a decrease in BP as a function of esmolol infusion rate in anesthetized patients (fig. 4).[24] In anesthetized dogs, the slope of the decrease in BP with the S-enantiomer (S-esmolol) is half that for the racemate (RS-esmolol). The human meta-analysis line has a slope approximately twice as steep as that for the dog RS-esmolol data, and may simply reflect the fact that dogs metabolize esmolol twice as fast as humans, 4 min *versus* 9 min,[25] respectively. The comparability of slopes for human and dog suggests that the halving of the BP decrease observed in the dog with the S-enantiomer, might be expected as well in man, possibly lowering the probability of excessive hypotension. Lowering BP is often a desirable outcome of esmolol and could be used to argue against the clinical value of an S-enantiomer only formulation of esmolol. The present work indicates that the difference in the BP-lowering effect between S- and RS-esmolol is due to a similar difference on LVdP/dt+max, LVDP, and ultimately CO. Therefore, a formulation of esmolol containing only the S-enantiomer may be of benefit to patients with ventricular dysfunction where similar HR control is needed.[1]

Potential limitations of the current work include (1) not formally randomizing dogs to experimental conditions, (2)

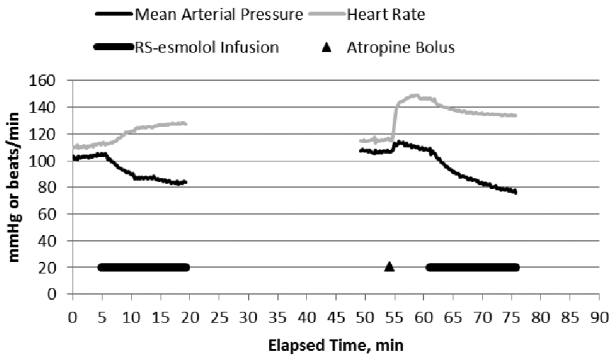

Fig. 3. The effect of RS-esmolol (1,000 μg kg^{-1} min^{-1}) on mean arterial pressure and heart rate before and after administration of atropine (0.4 mg/kg) from dog DG1010.

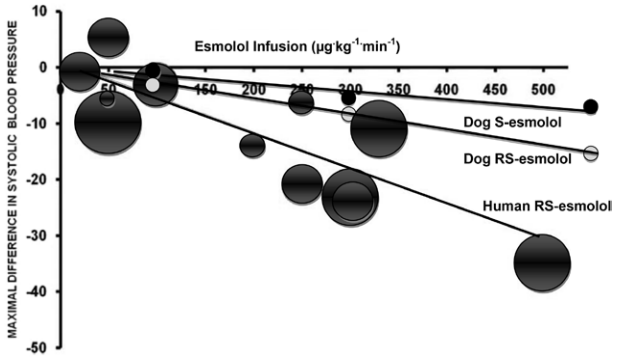

Fig. 4. Dog data superimposed on data from human patients receiving multiple infusion rates of the racemic mixture of esmolol (RS-esmolol). Human data were adapted from reference 24. Each *circle* represents data from a separate study. The size of each *circle* represents the weighting of each study and is a reflection of both the magnitude of the difference in mmHg and the number of patients in the study. For both dogs and humans, blood pressure was normal at baseline and subjects were anesthetized. Difference between human RS-esmolol and dog RS-esmolol is attributed to the difference in elimination half-life of esmolol of 9 min in humans and 4 min in dogs.

using mongrel dogs for the cardiovascular studies and Beagle dogs for the pharmacokinetic study, and (3) the potential effects of sodium pentobarbital on the cardiovascular studies. Not formally randomizing dogs to experimental conditions is not expected to have altered the results and conclusions based on (1) purpose-bred dogs for research are relatively homogenous phenotypically compared with humans; (2) purpose-bred dogs for research are certified healthy compared with patients, thus eliminating the introduction of potential bias due to cohort differences in underlying pathophysiology and demographics, which are of concern in the clinical setting; and (3) in each of the three studies, individual dogs received all experimental conditions. Formally randomizing dogs to experimental conditions would have been imperative if some dogs were assigned to receive only one experimental condition and the remaining dogs the other experimental condition(s). Mongrel dogs were used in the cardiovascular studies because the second study required the placement of a 7.5-French Swan-Ganz thermodilution catheter for measuring CO, which is too large for Beagle dogs. The pharmacokinetic parameters derived from Beagle dogs in the current study are virtually identical to that previously reported for mongrel dogs.* Sodium pentobarbital was used because it was used in the initial work describing the pharmacology of esmolol in dogs.*[18,26] Sodium pentobarbital at comparable doses to the current work elicits relatively minor effects on CO and regional blood flow distribution, has negligible effects on baroreceptor reflex to nitroglycerin and methoxamine challenges, and exerts a moderate myocardial depressant effect in mongrel dogs.[27]

In conclusion, the current work suggests that an S-enantiomer only formulation of esmolol is associated with less hypotension compared with racemic esmolol at similar HR control. The difference in hypotension was attributed to a direct effect of the R-enantiomer, which caused hypotension by reducing CO secondary to a negative inotropic effect mediated by an unknown mechanism of action. The cardiovascular differences between RS-, S-, and R-esmolol were not attributable to differences in their pharmacokinetics. An S-enantiomer only formulation of esmolol, therefore, may provide similar HR control with a lower probability of excessive hypotension.

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Competing Interests

The authors declare no competing interests.

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The Bullet Oscilloscope: The ORM-1 of "E for M"

Early efforts to display an anesthetic patient's electrocardiogram (ECG or EKG) on cathode screens were hazardous. Because of the risk of igniting flammable anesthetic vapors, the Operating Room Monitor (ORM-1, *above*) shielded the monitoring device electrically, thereby minimizing risks of fires or explosions. Due to its elongated shape, the ORM-1 was fondly known in the 1960s by many anesthesiologists as a "bullet" oscilloscope. The original Westchester, New York, manufacturer of the ORM-1, Electronics for Medicine ("E for M"), was eventually absorbed by Honeywell, and then acquired by PPG Industries, before disappearing entirely from the corporate landscape.

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