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Esmolol and Left Ventricular Function in the Awake Dog

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Hypotension has been the most frequently reported adverse reaction associated with infusion of the β_1-adrenergic receptor antagonist esmolol. In some patients, this hypotension has apparently occurred independent of reduction in heart rate or systemic vascular resistance, suggesting decreased stroke volume. In the present study, the preload recuitable stroke work area (PRSWA) model was used to evaluate the negative inotropic effects of esmolol in nine chronically instrumented awake dogs. Left ventricular (LV) transmural pressure and minor axis diameter were measured by micromanometers and sonomicrometry, respectively. Vena caval occlusions were performed so that an analog of stroke work (area within LV transmural pressure-diameter loop) could be measured over a range of preloading conditions during esmolol infusions of 0, 100, 300, 1000, and 3000 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (n = 9), and at 15 and 30 min after termination of esmolol (n = 8). The linear relationship between stroke work and end-diastolic diameter was characterized for each caval occlusion by a slope and x-intercept. PRSWA was calculated for each caval occlusion as slope/two times the square of the difference between x-intercept and the largest end-diastolic diameter observed in the study of a particular dog. Heart rate was different from control (91 ± 4) only at the highest esmolol dose (127 ± 4). LV peak positive dP/dt, minor axis ejection shortening, stroke work, and PRSWA were depressed from control at esmolol doses ≥ 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$. All parameters except dP/dt recovered within 30 min following termination of esmolol. Decline in PRSWA with esmolol occurred largely through an increase in x-intercept, which may indicate diastolic dysfunction. In the awake dog, moderate to large doses of esmolol impair LV function; the lack of any negative chronotropic effect by esmolol suggests that the negative inotropic effect of esmolol in this canine preparation is not by β_1 blockade. (Key words: Antagonists: beta adrenergic receptor; esmolol. Heart: left ventricular function; preload recruitable stroke work. Pharmacology: esmolol. Receptors: beta adrenergic.)

ESMOLOL HYDROCHLORIDE (Brevibloc®, Dupont Critical Care, Waukegan, IL) is a water soluble β_1-adrenergic receptor antagonist administered by continuous intravenous infusion. Esmolol has a brief duration of action with a pharmacokinetic profile that permits rapid titration to any desired level of β-adrenergic blockade. Esmolol offers new flexibility in the acute treatment of supraventricular tachyarrhythmias,[1] acute myocardial ischemia,[2] perioperative tachycardia,[3–5] and postoperative hypertension.[6]

Hypotension has been the most frequently reported adverse effect in patients and volunteers receiving esmolol. Analysis[7] of data from 369 patients treated with esmolol suggested a decrease in the benefit-risk ratio (*i.e.*, benefit of achieving a therapeutic response *versus* risk of developing systolic hypotension [<90 mmHg] at each dose of esmolol) for esmolol dosages greater than 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$; in human studies, esmolol has been used[8] in dosages as high as 750 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Since esmolol does not reduce systemic vascular resistance,[3,6,9] esmolol-induced hypotension must be due to decreased cardiac output. If due to β_1 antagonistic activity, esmolol would be expected to reduce cardiac output by parallel decreases in heart rate and stroke volume, the magnitude of which should depend on the background level of sympathetic tone present. There is evidence that esmolol is capable of producing hypotension independent of changes in heart rate in humans,[2,8] thus suggesting a negative inotropic effect of esmolol or the ability of esmolol to produce venous pooling and, thus, decreased preload. To learn more about the possible contribution of these factors in esmolol-induced hypotension, the present investigation was designed to study the effects of esmolol on left ventricular (LV) function in the chronically instrumented awake dog. This preparation has little chronotropic sympathetic tone and is free from the pharmacological influences of anesthesia, thereby permitting isolated examination of the inotropic effects of esmolol.

Materials and Methods

Nine adult mongrel dogs of either sex were surgically instrumented for chronic study. The dogs were anesthetized with intravenous thiamylal sodium and succinycholine, an endotracheal tube was inserted, and the animals were mechanically ventilated. Under sterile conditions, a thoracotomy was performed through the left fifth intercostal space. Silicone rubber pneumatic occluders were positioned around both venae cavae. A pericardiotomy was made from the apex of the heart to the great vessels, and a silicone rubber tube (2.6 mm i.d., 4.9 mm o.d.) was placed into the left atrium through a purse-string suture in the base of the left atrial appendage for subsequent passage of a micromanometer across the mitral valve into the LV. A similar tube with multiple side holes was sutured to the epicardial surface of the base of the heart to allow measurement of pleural pressure. One pair of pulse transit ultrasonic dimension transducers[10] oriented across the

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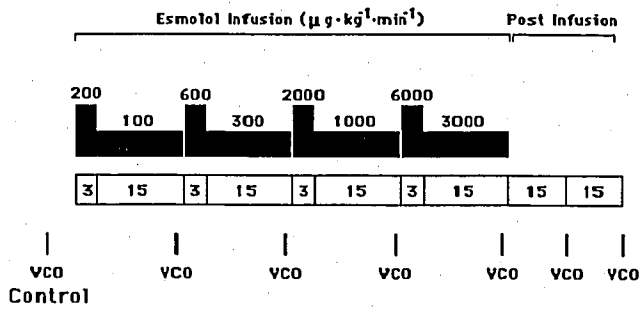

FIG. 1. Study protocol. VCO = vena caval occlusion.

LV minor axis diameter was sutured to the epicardial surface of the LV. The catheters, transducer leads, and caval occluder tubes exited through the chest wall into a subcutaneous pouch dorsal to the thoracotomy incision. The pericardium was left widely open, and the thoracotomy was repaired in layers. Each dog was allowed to recover for 7–10 days before the hardware was exteriorized through a small skin incision. One day after exteriorization, each dog was studied in a conscious, unmedicated state while lying quietly on its right side. The ultrasonic dimension transducers were coupled to a sonomicrometer constructed in this laboratory. With this device, the time required for transmission of a burst of ultrasound from one of the piezoelectric transducers to the opposite transducer was measured and converted into an analog voltage output, which was linearly proportional to the distance between the transducers and, therefore, measured the length of the LV minor axis diameter. The minimum resolution of this system was approximately 0.08 mm and the maximum electronic drift was 0.05 $mm \cdot h^{-1}$. High fidelity micromanometer-tipped catheters (Model PC-350, Millar Instruments, Houston, TX) were passed through the implanted tubes into the LV and pleural space. The micromanometers were prewarmed in a water bath at 38° C, and were balanced and calibrated against a water column immediately before each study. Resultant manometer drift was less than 0.5 $mmHg \cdot h^{-1}$.

Esmolol, infused through a cannula acutely inserted into a cephalic vein, was administered (fig. 1) in stepwise incremental dosages of 100, 300, 1000, and 3000 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Each dosage was preceded by a 3-min loading dose at twice the desired infusion rate. This infusion scheme was designed based on the pharmacokinetics of esmolol[11] to achieve steady-state plasma concentrations of drug at each data collection point. Vena caval occlusions of about 40 s duration were performed so that stroke work could be obtained over a range of preloading conditions prior to esmolol infusion (control), after at least 15 min at each esmolol dosage, and in eight of the dogs at 15 and 30 min following termination of the last dose. Beginning approximately 10 s prior to the start of each vena caval occlusion and continuing until the release of the occlusion, the analog voltages representing LV pressure, pleural pressure, and LV minor axis diameter were digitized in real time at a rate of 200 samples per second.

After data collection and storage on digital magnetic tape, data analysis was performed on a minicomputer using software developed in this laboratory. LV transmural pressure was calculated as LV pressure minus pleural pressure; for the remainder of this paper, all references to ventricular pressures are transmural pressures. The time derivative of LV pressure, dP/dt, was computed from the digital pressure waveform as a running five-point polyorthogonal transformation. Beginning- and end-ejection and beginning- and end-diastole of each cardiac cycle were defined by the computer.[12] These beatpoint definitions were checked visually on all data with a videographics display system, and were manually redefined when necessary.

Heart rate, end-diastolic diameter, mean ejection pressure, LV minor axis ejection shortening and stroke work, and peak positive and negative dP/dt were calculated as mean values from the ten cardiac cycles prior to each vena caval occlusion. For each of the vena caval occlusions, stroke work and end-diastolic diameter were determined for each cardiac cycle. Stroke work was defined as the area within each LV pressure-diameter loop. Because LV volume was not measured or computed, this is not true stroke work, but it has been demonstrated that LV minor axis diameter is linearly related to ventricular volume under most conditions.[13] Therefore, the calculations of stroke work used in this study should be directly proportional to stroke work defined as the integral of LV pressure with respect to volume.

Linear regression analysis was performed on the data from individual vena caval occlusions to determine the slope and x-intercept of each stroke work *versus* end-diastolic diameter relation. Preload recruitable stroke work area[14] (PRSWA) was calculated as an index of LV function, and was computed for each vena caval occlusion by the formula:

$$PRSWA = (SLOPE/2)(EDDMAX - \text{x-intercept})^2$$

$$(\text{units} = N \cdot mm^{-2} \cdot mm^2 = N),$$

where EDDMAX was the largest end-diastolic diameter observed in the study of a particular dog (*i.e.*, PRSWA is the area within a triangle defined by the regression line, the x-axis, and EDDMAX). Variables were compared by Student's two-tailed paired *t* test, with significance assumed at $P < 0.05$. Comparisons were made *versus* control, and *versus* the previous data point during es-

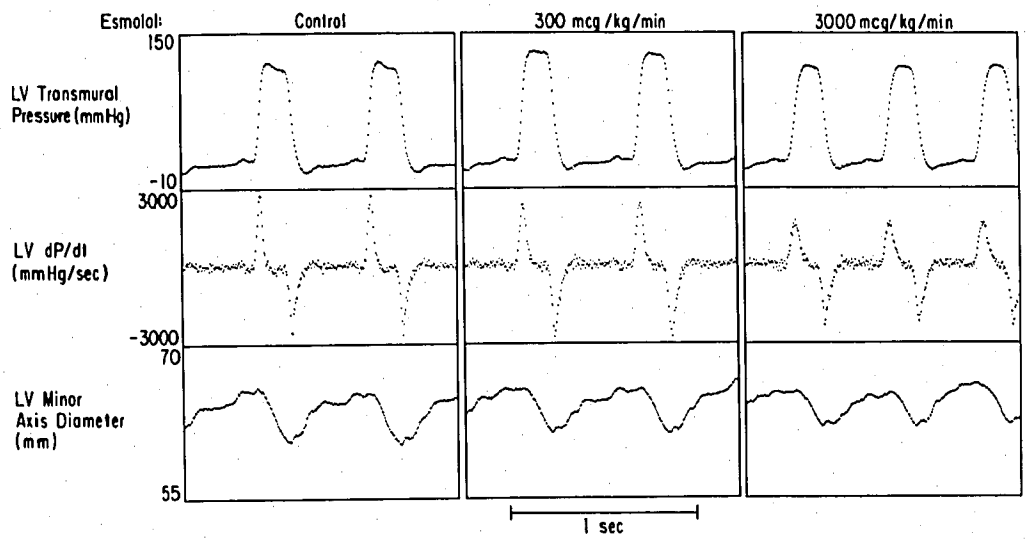

FIG. 2. Typical digital data demonstrating measurements of left ventricular transmural pressure and minor axis diameter and the derived pressure derivitive. Data are from control conditions and during steady-state infusion of esmolol at 300 and 3000 $\mu g \cdot kg^{-1} \cdot min^{-1}$. LV = left ventricular.

molol infusion. Unless otherwise stated, all values are mean ± SEM.

Results

Typical digitized data from one dog are shown in figure 2. When stroke work was plotted as a function of end-diastolic diameter during vena caval occlusions (*i.e.*, the Frank-Starling relation), linear relationships consistently resulted (fig. 3). For this study, regression analysis was performed on data from 67 vena caval occlusions; the mean r-value was 0.977 ± 0.003, and the average number of data points per regression was 33 ± 2. Measured and derived mean hemodynamic data are expressed graphically in figures 4 and 5.

ESMOLOL INFUSION

During the infusion of esmolol, heart rate did not change from its baseline value of 91 ± 4 bpm until the highest dosage, where it increased to 127 ± 4 bpm. Mean LV ejection pressure fell below baseline during the 1000 and 3000 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusions. All derived indexes of LV function, peak positive dP/dt, ejection shortening, stroke work, and PRSWA were depressed from their control values during esmolol infusion ≥ 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The fall in ejection shortening and stroke work were dose dependent. LV preload, assessed by end-diastolic diameter, did not change from its baseline value, but demonstrated a trend towards increasing at 1000 and 3000 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Peak negative dP/dt decreased in magnitude at the highest esmolol dosage. There were no statistically significant changes in the slope of the stroke work *versus* end-diastoic diameter relation, but the x-intercept was significantly increased at 300 and 3000 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

POST ESMOLOL INFUSION

All variables except positive dP/dt returned to their baseline values within 30 min following termination of esmolol at 3000 $\mu g \cdot kg^{-1} \cdot min^{-1}$, with most of the measured variables returning to control within 15 min.

Discussion

The present investigation demonstrates that esmolol produces a dose-related decrease in LV function independent of a decline in heart rate or LV preload in the chronically instrumented awake dog. The effects of esmolol were rapidly reversed upon discontinuation of the infusion, which was presumably due to rapid hydrolysis of the drug.[15] LV function was assessed by LV dP/dt, LV minor axis ejection shortening, and LV

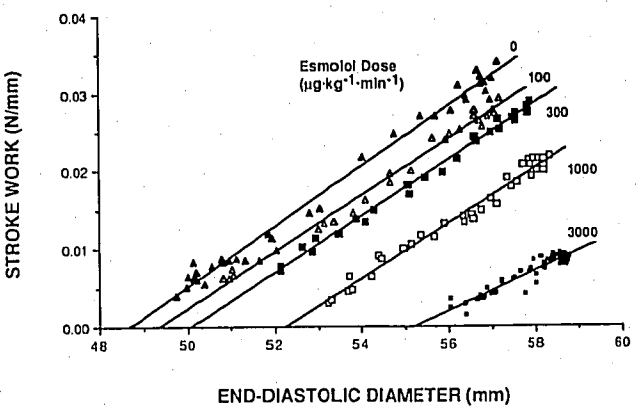

FIG. 3. Representative stroke work versus end-diastolic minor axis diameter relationships from 1 dog during vena caval occlusions during administration of esmolol.

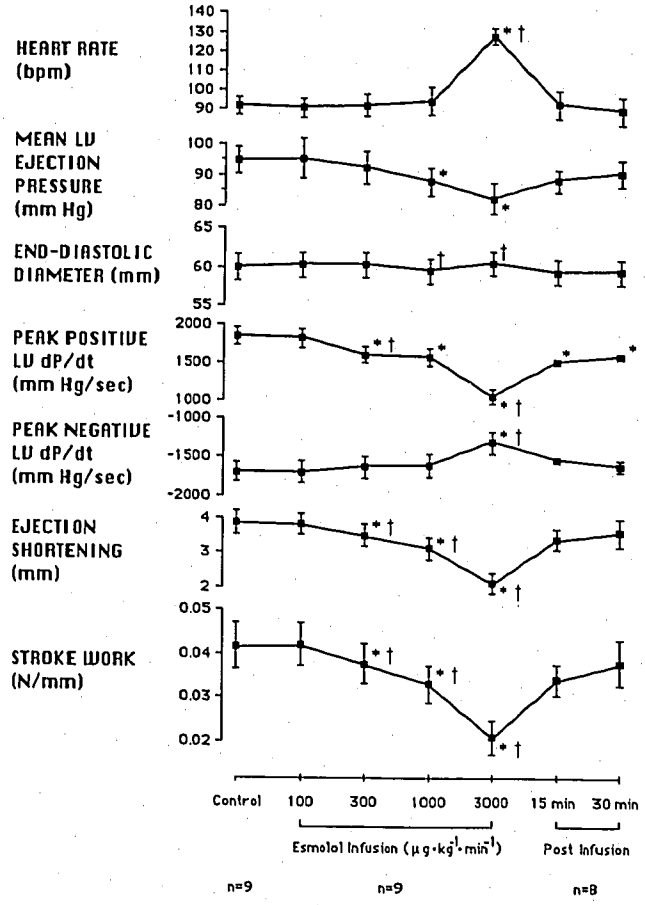

FIG. 4. Measured and derived hemodynamic data. $*P < 0.05$ *versus* control. $\dagger P < 0.05$ *versus* previous data point during esmolol infusion.

minor axis stroke work, and by a new index called PRSWA.

The increase in heart rate seen at the highest esmolol dose was probably the result of vagal withdrawal as a baroreflex response to the effects of declining ventricular function. However, there is also increasing evidence for the existence of stimulatory cardiac β_2 receptors;[16] the increase in heart rate at 3000 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and the plateau seen in peak positive dP/dt, x-intercept, and PRSWA between 300 and 1000 $\mu g \cdot kg^{-1} \cdot min^{-1}$ might, in part, reflect the influence of β_2 stimulation as endogenous catecholamines were reflexively liberated during the fall in function due to esmolol, a β_1 antagonist.

The relationship between stroke work and end-diastolic regional or global dimensions in the conscious dog has been found to be independent of preload, insensitive to physiologic changes in afterload, and responsive to alteration in inotropic state induced by calcium infusion, which resulted in an increase in the slope of the stroke work-end-diastolic dimension relation.[12] It was expected that, in the present study, the negative inotropic effect of β_1 blockade with esmolol, if any, would result simply in a decrease in slope, this effect being opposite to that of calcium infusion. However, there were no significant changes in slope in the present study. The significant rightward shift in x-intercept seen with esmolol necessitated that a more complex function be used to quantify its effect on the myocardium. Glower *et al.*[14] used the area (PRSWA) under the stroke work-end-diastolic dimension curve (Frank-Starling relation) to quantify regional myocardial function after acute ischemic injury, and found this to be a sensitive measure of intrinsic myocardial function. Since it incorporates both slope and x-intercept, and since, in the conscious dog, the stroke work-end-diastolic dimension relation is relatively afterload insensitive, PRSWA may prove to be a useful index of ventricular function. To account for changes in both slope and x-intercept, we have used PRSWA to describe the effects of esmolol on LV function, and have found it to be in qualitative agreement with the other indices of function. Additionally, the rightward shift in the x-intercept component of this index may signify diastolic dysfunction as a significant contributor to the decline in ventricular performance seen with esmolol infusion. The rightward shift may represent a subcellular analog of myocardial creep, such as malalignment of contractile proteins.[17] The reduction in magnitude of peak negative dP/dt at 3000 $\mu g \cdot kg^{-1} \cdot min^{-1}$ is suggestive of impaired ventricular relaxation.[18]

The negative inotropic activity of esmolol has been observed in several other canine models, including dogs

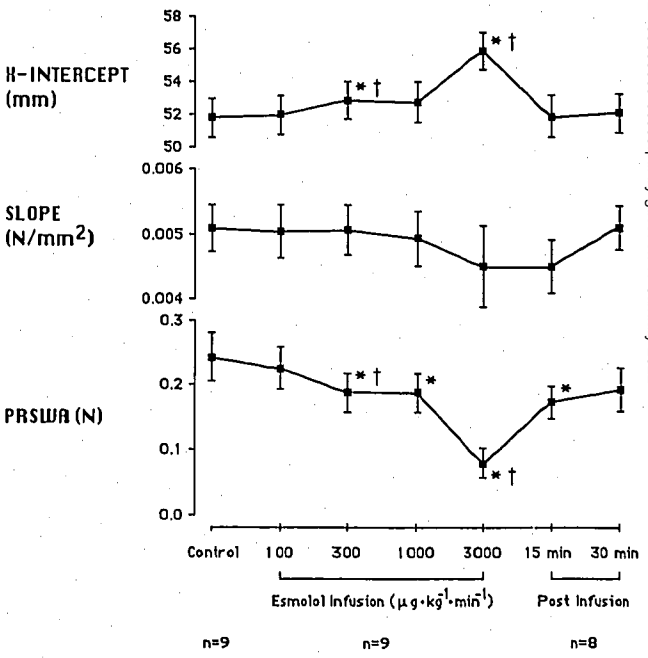

FIG. 5. Derived hemodynamic data. $*P < 0.05$ *versus* control. $\dagger P < 0.05$ *versus* previous data point during esmolol infusion.

anesthetized with enflurane,[19] pentobarbital-anesthetized dogs,[20] catecholamine-depleted vagotomized dogs,[21] and conscious dogs[21] in which peak positive dP/dt fell at esmolol doses as low as 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In these studies, a roughly parallel decrease in heart rate accompanied the decline in function, but the mean baseline heart rates in these studies ranged from about 107 to 174 bpm, suggesting substantial adrenergic activity. In assessing the effects of adrenergic receptor antagonists, it is critical that the level of background sympathetic tone be taken into consideration, and, in this regard, it would seem that the awake unmedicated canine preparation offers some advantages in investigations of the direct cardiac effects of pharmacological agents.

Increases in pulmonary capillary wedge pressure, presumed to be due to myocardial dysfunction, have been reported when esmolol has been administered to patients undergoing myocardial revascularization[4,22] and when administered to patients with LV dysfunction.[23] As mentioned previously, there have also been several reports[1,2,7,8] of striking hypotension associated with esmolol infusion, including a fall in systolic blood pressure of 20 mmHg without significant change in heart rate during esmolol infusion at 750 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in healthy males.[8] There is one report[2] of a patient requiring a brief infusion of dopamine to restore hemodynamic stability following esmolol infusion of 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Thus, there are clinical data corroborating in humans the myocardial depressant activity of esmolol noted in the present and other studies in dogs.

Cardiac β_1-adrenergic receptors have classically been implicated in the mediation of both positive chronotropic and positive inotropic effects.[24] That esmolol, a β_1-adrenergic receptor antagonist, produces dose-related negative inotropic effects is not surprising. However, myocardial depression occurred in the present study independent of a concomitant reduction in heart rate. This suggests that, in our canine preparation, with virtually no resting sympathetic tone, the negative inotropic effects of esmolol occurred largely through a mechanism other than classical β_1-adrenergic blockade.

Direct (β-blockade-independent) depression of myocardial contractile force, also known as "membrane stabilizing" activity or "quinidine-like" activity, has been described for some β antagonists, but this ill-defined effect is believed to be clinically significant only at plasma levels of the β blocking drugs far above their therapeutic range. In a previous study[21] in open-chest, vagotomized, reserpinized, anesthetized dogs, direct cardiodepressant activity of esmolol was reported to occur at doses greater than 500 $\mu g \cdot kg^{-1} \cdot min^{-1}$, but our investigation in a pharmacologically pure preparation shows this phenomenon to occur at doses as low as 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Data defining membrane stabilization are vague, and, certainly, esmolol's direct cardiodepressant activity is by some specific physiological mechanism, such as antagonism of an inotropic receptor[25] or interference with one or more specific biochemical pathways. A satisfactory explanation for the means by which esmolol and other β-blockers exert non-β-adrenergic depression of myocardial function remains to be elucidated. Further, in the presence of sympathetic tone, do the direct and indirect cardiodepressant actions of a β antagonist like esmolol occur concurrently and additively, or do the direct effects predominate until β blockade has been achieved? Also to be explored is to what extent reduction in inotropism by the non-adrenergic component of esmolol's cardiodepressant effect contributes to a reduction in myocardial oxygen consumption.

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