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Specific Bradycardic Agents, A New Therapeutic Modality for Anesthesiology: Hemodynamic Effects of UL-FS 49 and Propranolol in Conscious and Isoflurane-anesthetized Dogs

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A "specific bradycardic agent" has direct negative chronotropic actions without producing other systemic or coronary hemodynamic alterations. UL-FS 49, a recently synthesized structural analog of verapamil without classical slow channel calcium blocking activity, is proposed as such an agent. The purpose of this investigation was to characterize the hemodynamic and electrocardiographic actions of UL-FS 49 (0.25, 0.50, and 1.0 mg/kg) and compare its effects with those of propranolol (0.25, 0.50, and 1.0 mg/kg) in conscious or isoflurane-anesthetized (with and without neuromuscular blockade by pancuronium) chronically instrumented dogs. In six groups, comprising 52 experiments, UL-FS 49 was found to be more efficacious than propranolol in reducing heart rate, although this agent did not block the hemodynamic response to isoproterenol. UL-FS 49 produced 45–50% reductions in heart rate in dogs with isoflurane-induced tachycardia as compared to 15 and 30% reductions following propranolol. Furthermore, few other hemodynamic alterations were produced by UL-FS 49 indicating the remarkable specificity of this drug for reducing heart rate. A "specific bradycardic agent" such as UL-FS 49 may be useful clinically during the perioperative period. Such a drug may be especially advantageous for patients with documented or suspected ischemic heart disease, those who cannot tolerate the side effects of beta adrenergic blockade, as well as patients requiring a greater reduction in heart rate than can be obtained with beta adrenergic receptor antagonists. (Key words: Anesthetics, volatile: isoflurane. Antagonists, beta adrenergic receptors: propranolol. Heart: specific bradycardic agents. Neuromuscular relaxants: pancuronium. Pharmacology, specific bradycardic agent: UL-FS 49. Sympathetic nervous system: beta adrenergic receptors; isoproterenol.

UL-FS 49 (FIG. 1) is a new "specific bradycardic agent" with few additional hemodynamic effects compared to other drugs utilized to reduce heart rate. Although UL-FS 49 is a structural analog of verapamil, this drug does not possess classical calcium channel antagonist activity.[1–5] In isolated tissue preparations, this compound has been shown to produce marked negative chronotropic actions without any negative inotropic effects,[1–3] and, in conscious dogs, UL-FS 49 administration results in a decrease in heart rate with little change in arterial blood pressure.[1] An agent such as UL-FS 49 that selectively reduces heart rate without producing other hemodynamic alterations would be highly useful in the perioperative setting.

The volatile anesthetic, isoflurane, has been shown to produce tachycardia in dogs[6–8] and humans;[9–14] however, many of the previous studies[7,8] utilized a baseline anesthetic which may have complicated the findings of isoflurane on cardiac rate. An elevated heart rate has also been demonstrated following pancuronium, a vagolytic neuromuscular blocking agent, in anesthetized dogs[15] and humans.[16,17] Tachycardia may also result from perioperative anxiety, fever, or pain and intraoperative surgical stimulation. An elevation in heart rate increases myocardial oxygen demand, may be associated with hemodynamic instability, and is especially detrimental for myocardium with a limited coronary reserve. Inappropriate increases in rate may decrease perfusion to the left ventricular subendocardium.[18,19] While beta adrenergic antagonists are commonly used perioperatively to reduce heart rate, beta adrenoceptor blockade may be deleterious in certain conditions, such as broncho-spastic pulmonary disease or heart failure. A "specific bradycardic agent" would ideally reduce heart rate without producing bronchoconstriction, negative inotropic, or other hemodynamic effects. UL-FS 49, 1,3,4,5-tetrahydro-7,8-dimethoxy-3-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylimino] propyl]-2H-3-benzazepin-2-on hydrochloride, a newly synthesized structural analog of verapamil, has been reported to have relatively specific actions on the sinus node.[1,2]

The present study was designed to evaluate the hemodynamic effects of UL-FS 49 in chronically instrumented dogs in the conscious state and during anesthesia produced by isoflurane with and without neuromuscular blockade by pancuronium. Results were compared to those produced by the beta adrenergic antagonist, propranolol. The results indicate that UL-FS 49 is a remarkably specific bradycardic agent having little other systemic or coronary hemodynamic effects.

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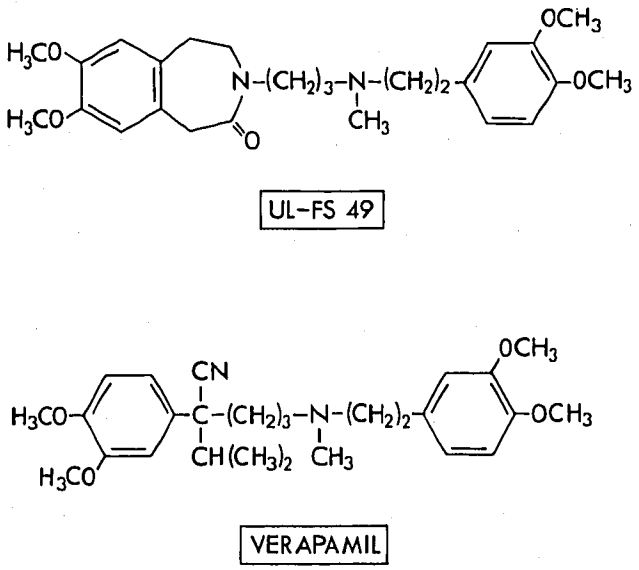

FIG. 1. Chemical structure of the "specific bradycardic agent," UL-FS 49 as compared to the slow channel calcium antagonist, verapamil.

Materials and Methods

Conditioned mongrel dogs of either sex weighing between 20 and 30 kg were fasted overnight, and anesthesia was induced with sodium thiamylal (10 mg/kg, iv). After tracheal intubation with a cuffed endotracheal tube, anesthesia was maintained with halothane (1.0–1.5%) and 100% oxygen (1 l/min) *via* a respirator (Monaghan 300 D/M; 9–12 breaths/min; tidal volume of 15 ml/kg). Atelectasis was prevented by maintaining end-expiratory pressure at 5 cm of water. The left lateral chest wall was shaved, scrubbed, disinfected, and draped. Under sterile conditions, a thoracotomy was performed in the left fifth intercostal space and the lungs gently retracted. The left internal thoracic artery and vein were isolated, and heparin-filled catheters inserted and advanced to the aortic arch and superior vena cava for measurement of aortic blood pressure (Statham P50) and drug administration, respectively. Position of all catheters was confirmed during surgery by palpation and upon completion of the experiment after killing each animal.

The heart was suspended in a pericardial cradle and a 1.5–2.0-cm section of either the proximal left anterior descending (distal to the first diagonal branch) or left circumflex coronary artery (proximal to the first marginal branch) carefully isolated. A precalibrated Doppler ultrasonic flow transducer (20 MHz) was placed on the vessel for measurement of phasic and mean coronary blood flow velocity. A catheter was positioned in the left atrial appendage. A Konigsberg high-fidelity miniature micromanometer (P7) was inserted in the left ventricular chamber through a stab wound in the apex and tightly secured for recording of left ventricular pressure. The intraventricular transducer was cross calibrated *via* measurements of systolic arterial and diastolic left atrial pressures from fluid-filled catheters. The maximum rate of rise of left ventricular pressure (peak positive dP/dt), an index of global left ventricular contractility, was obtained by electronic differentiation of the ventricular pressure waveform. A triangular wave signal with known slope was used to calibrate the differentiator. Electrocardiographic leads (corresponding to limb lead II) were sutured to the internal thoracic wall. The chest was closed in layers and pneumothorax evacuated by a chest tube with suction drainage. Each dog was fitted with a jacket to prevent damage to the instruments and catheters which were housed in an aluminum box within the jacket pocket. After surgery, each dog was allowed to recover for 7 days prior to experimentation and was treated with 400,000 U procaine penicillin G and 560 mg dihydrostreptomycine, im. During the postoperative recovery period, the dogs were trained to stand quietly in a sling during monitoring of hemodynamics.

The electrocardiogram and all other hemodynamic parameters were recorded continuously on a polygraph (Hewlett-Packard®) and FM analog magnetic tape (Vetter). In addition, arterial blood samples were obtained at various intervals for measurement of blood gases (ABL 2). Hemodynamics were digitized by means of an ISAAC 91A analog-to-digital converter interfaced to an Apple® IIe computer.[20] The average values of eight consecutive cardiac cycles were utilized. Hemodynamic parameters were calculated for each cardiac cycle and reported as the average over the completed cycles in the collection. Because conscious dogs have a prominent sinus arrhythmia, data were collected during periods of expiration at a stable hemodynamic state.

The PR interval, QRS duration, and QT interval were determined directly from electrocardiographic strip chart recordings. The QT interval corrected for changes in heart rate (QT_c) was calculated by dividing the QT interval by the square root of the RR interval.

Six groups of experiments were performed during which hemodynamics were continuously recorded. All animals were fasted overnight, and, prior to experimentation, fluid deficits were corrected with crystalloid (0.9% normal saline) and maintenance continued with 3 $ml \cdot kg^{-1} \cdot h^{-1}$ for the duration of each experiment. In two groups, either UL-FS 49 (N = 8) or propranolol (N = 9) (0.25, 0.5, and 1.0 mg/kg administered sequentially) dissolved in drug vehicle (saline) was administered intravenously after a 30-min control period in awake, unsedated dogs. Doses of each agent were selected in preliminary experiments to provide a wide

range of hemodynamic effects. Furthermore, in additional experiments, the actions of these agents on the response to isoproterenol were tested. Hemodynamics were recorded for 30 min after each dose. Isoproterenol (0.05 μg/kg bolus, iv) was administered at the end of the control period and 30 min after each subsequent dose of drug to demonstrate efficacy of beta adrenergic blockade. In the third and fourth groups, the actions of UL-FS 49 (N = 9) and propranolol (N = 10) were studied in isoflurane-anesthetized dogs. Following a 30-min control period in the conscious state, anesthesia was induced with sodium thiamylal (10 mg/kg, iv), the trachea intubated with a cuffed endotracheal tube, and positive pressure ventilation initiated. Anesthesia was maintained for 60 min at an inspired concentration of 1.5% isoflurane in 100% oxygen. Isoflurane was delivered into the gas flow by means of an Ohio Fortec vaporizer. A gas mass spectrometer (Perkin-Elmer Corp., Model MGA-1100, Pamona, CA) was used to calibrate the vaporizer. During a stable hemodynamic state, UL-FS 49 or propranolol was administered as in conscious dogs. In the fifth and sixth groups (N = 8 each), the hemodynamic effects of UL-FS 49 and propranolol were investigated in isoflurane-anesthetized dogs with concomitant neuromuscular blockade. Dogs were anesthetized as described above; however, pancuronium (0.1 mg/kg) was administered during maintenance anesthesia with isoflurane. After a stable hemodynamic state was obtained, either UL-FS 49 or propranolol were administered as in conscious dogs. A total of 52 experiments were completed in which 18 instrumented conscious dogs were randomly assigned to various groups.

Data during control, and following drug intervention with and without the presence of anesthesia, were analyzed by means of analysis of variance[21] followed by Dunnett's modification of the *t* test. Changes between the conscious state and anesthesia or following administration of bradycardic drugs were considered significant when the probability (*P*) value was less than 0.05. All data are expressed as mean ± SEM.

Results

Hemodynamic Effects of Propranolol

In conscious dogs, propranolol (0.25–1.0 mg/kg) produced no significant change in heart rate (fig. 2), aortic pressure, left ventricular systolic pressure, coronary blood flow velocity, or electrocardiographic and blood gas data (table 1). In contrast, propranolol at 0.5 and 1.0 mg/kg produced a reduction in peak positive dP/dt, which was associated with a significant increase in left ventricular end-diastolic pressure at the highest dose (1 mg/kg) (table 1). All doses of propranolol significantly inhibited the increase in heart rate and dP/dt following a standard dose of isoproterenol (fig. 3).

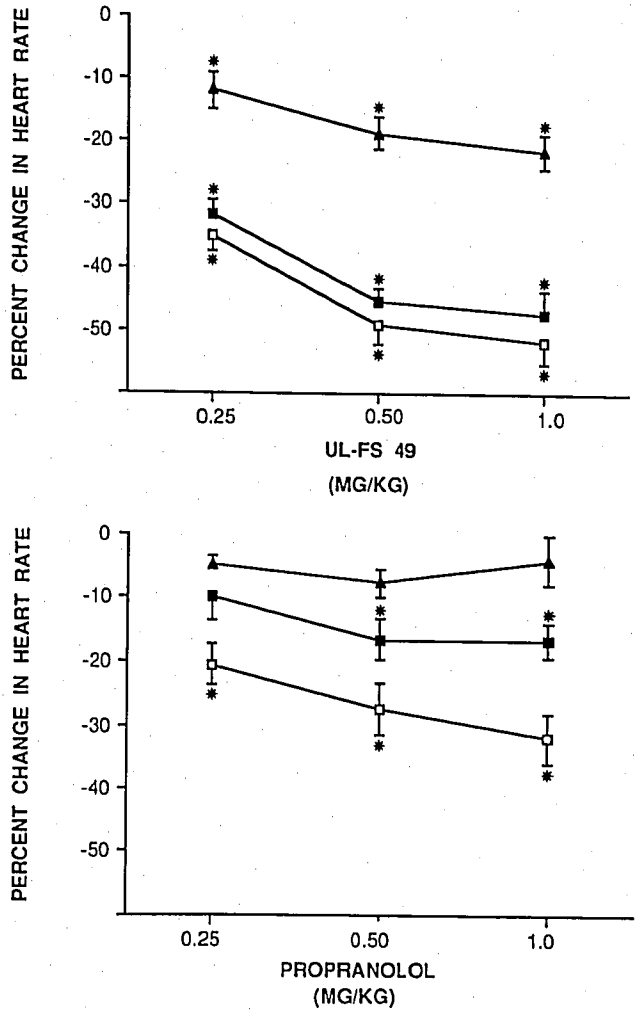

FIG. 2. Change in heart rate (expressed as percent change from control) produced by UL-FS 49 and propranolol in conscious (▲) and isoflurane anesthetized dogs with (□) and without (■) concomitant pancuronium-induced neuromuscular blockade. Mean ± SEM data. * Significantly ($P < 0.05$) different from control.

Isoflurane anesthesia with and without neuromuscular blockade by pancuronium produced significant ($P < 0.05$) increases in heart rate in all experiments (tables 2, 3). Isoflurane also caused a significant reduction in systolic arterial and left ventricular systolic pressures.

Isoflurane produced a decrease in peak positive dP/dt, in the absence or presence of pancuronium. No change in diastolic or mean coronary blood flow velocity was observed. Whereas isoflurane was not associated with any change in PR interval or QRS duration, prolongation of the QT interval was observed. Furthermore, when the QT interval was corrected for changes

TABLE 1. Propranolol in Conscious Dogs: Hemodynamic, Electrocardiographic, and Blood Gas Data

	Conscious	Propranolol (mg/kg) 0.25	0.50	1.0
Heart rate (bpm)	83 ± 4	79 ± 3	76 ± 4	79 ± 3
Systolic aortic pressure (mmHg)	121 ± 5	124 ± 7	126 ± 7	129 ± 5
Mean aortic pressure (mmHg)	101 ± 5	105 ± 7	107 ± 7	110 ± 5
Diastolic aortic pressure (mmHg)	89 ± 6	91 ± 8	94 ± 8	97 ± 5
Left ventricular systolic pressure (mmHg)	122 ± 5	125 ± 1	127 ± 7	129 ± 5
Left ventricular end diastolic pressure (mmHg)	8 ± 1	13 ± 2	13 ± 1	14 ± 2*
+dP/dt (mmHg/s)	2820 ± 120	2610 ± 110	2450 ± 90*	2430 ± 70*
Diastolic coronary blood flow velocity (Hz × 10^2)	51 ± 5	55 ± 6	55 ± 6	56 ± 5
Mean coronary blood flow velocity (Hz × 10^2)	29 ± 3	32 ± 3	31 ± 3	33 ± 3
PR interval (s)	0.11 ± 0.04	0.11 ± 0.03	0.11 ± 0.04	0.11 ± 0.03
QRS duration (s)	0.07 ± 0.01	0.07 ± 0.02	0.07 ± 0.01	0.06 ± 0.03
QT interval (s)	0.24 ± 0.01	0.26 ± 0.01	0.25 ± 0.01	0.26 ± 0.01
QT_c (s)	0.29 ± 0.01	0.31 ± 0.01	0.29 ± 0.01	0.30 ± 0.01
*p*H (u)	7.43 ± 0.01	7.43 ± 0.01	7.43 ± 0.02	7.44 ± 0.02
P_{O_2} (mmHg)	89 ± 3	98 ± 4	89 ± 3	91 ± 2
P_{CO_2} (mmHg)	33 ± 2	28 ± 1	30 ± 1	29 ± 1

Mean ± SEM data (N = 7–9).

* Significantly ($P < 0.05$) different: propranolol *vs.* conscious.

in heart rate (the tachycardia associated with isoflurane), QT_c was also found to be significantly increased. Anesthesia in all groups was associated with a significant increase in arterial P_{O_2}, as all animals were ventilated with 100% oxygen. There were no significant changes in arterial P_{CO_2} or *p*H.

In contrast to conscious dogs, propranolol produced a reduction in heart rate during isoflurane anesthesia with and without concomitant neuromuscular blockade (fig. 2). In addition, a significant decrease in peak positive dP/dt was observed following propranolol (tables 2, 3). No changes in electrocardiographic or arterial blood gas data were observed following beta adrenergic blockade.

HEMODYNAMIC EFFECTS OF UL-FS 49

In conscious, chronically instrumented dogs, UL-FS 49 (0.25–1.0 mg/kg) produced a significant reduction in heart rate (from 76 ± 5 to 60 ± 3 bpm; fig. 2). The reduction of heart rate was not associated with any change in PR interval, QRS duration, or QT interval. The specific bradycardic action of this agent was remarkable in that there were no alterations in arterial or left ventricular pressures, peak positive dP/dt, coronary hemodynamics, or arterial blood gases (table 4). UL-FS 49 had little effect on the hemodynamic response to a standard dose of isoproterenol demonstrating that the action of this drug was not mediated through beta receptor blockade (fig. 3).

Administration of UL-FS 49 to isoflurane-anesthetized dogs in the absence (table 5) and presence (table 6) of neuromuscular blockade by pancuronium also resulted in a profound decrease in heart rate. Whereas propranolol at the highest dose (1.0 mg/kg) produced 15 and 30% reductions in heart rate in isoflurane-anesthetized dogs in the absence and presence of neuromuscular blockade, respectively, UL-FS 49 decreased heart rate by 45 and 50% (fig. 2). Similar to awake, unsedated dogs, there was no change in aortic pressure, left ventricular systolic pressure, or coronary blood flow velocity following UL-FS 49 during anesthesia. In isoflurane-anesthetized dogs, UL-FS 49 further increased the QT interval than that produced by isoflurane alone; however, when corrected for the reduction in heart rate, no significant change was observed (QT_c). Similarly, no changes in PR interval or QRS duration occurred.

Discussion

The purpose of this study was to evaluate the hemodynamic effects of UL-FS 49, a "specific bradycardic agent," and propranolol, a beta adrenergic antagonist, in both the conscious and isoflurane-anesthetized (with and without pancuronium neuromuscular blockade) chronically instrumented dog. In the latter experiments, some residual barbiturate effect (used for induction of anesthesia) may have also been present. The results demonstrate a greater efficacy of UL-FS 49 than propranolol to reduce heart rate in conscious, as well as

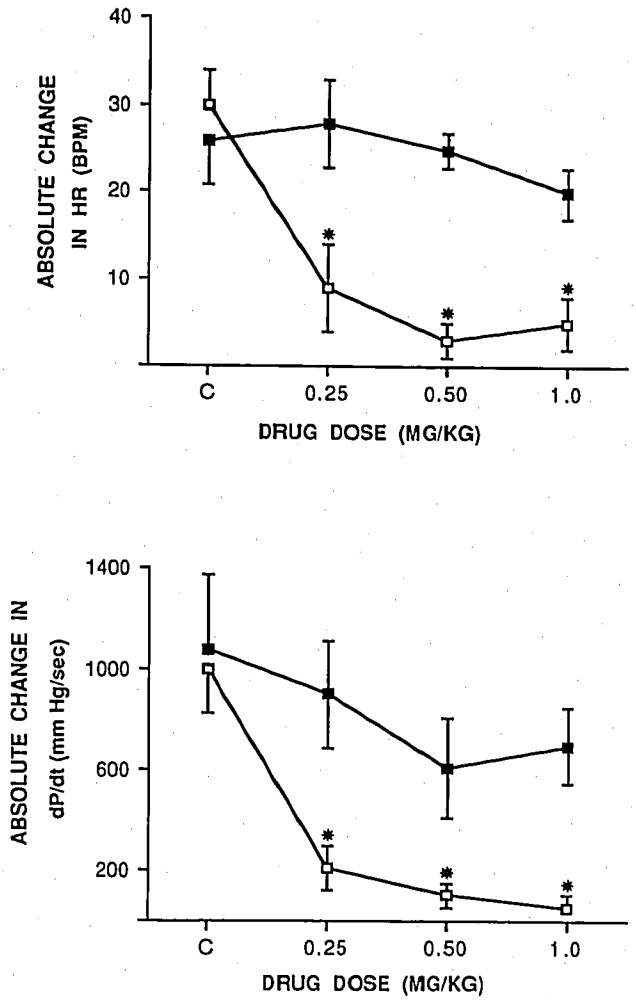

FIG. 3. Change in heart rate and peak positive dP/dt (expressed as absolute change from control) following a standard dose of isoproterenol (0.05 μg/kg) in conscious dogs before (C = control) and after pretreatment with propranolol (□) or UL-FS 49 (■). Mean ± standard SEM data. * Significantly ($P < 0.05$) different from control.

anesthetized, dogs in the doses utilized in this study. Differences in potency between UL-FS 49 and propranolol may be responsible as larger doses of the latter agent were not administered. In addition, UL-FS 49 was found to produce no other major hemodynamic changes. A potential limitation of the present study, however, was that cardiac output was not determined. Thus, despite maintenance of arterial pressure, cardiac output may have been reduced. Previous studies with a similar compound, AQA 39, in pentobarbital anesthetized dogs, however, have indicated cardiac output to be maintained by an increase in stroke volume.[4]

Adequacy of beta adrenergic blockade by propranolol was verified by ability to block the hemodynamic effects of isoproterenol. In contrast, isoproterenol produced the expected increase in heart rate and contractility in UL-FS 49-treated dogs. The mechanism of action of UL-FS 49 is presently unknown, but is probably not related to blockade of beta adrenergic receptors or antagonism of calcium channels. Apparently, the actions of this drug are uniquely specific to the sinus node. In conscious dogs, Kobinger and Lillie have shown UL-FS 49 (1.0 mg/kg) produces a significant decrease in heart rate with no change in blood pressure.[1] Similar decreases in heart rate without changes in intravascular pressure, contractility, or coronary blood flow velocity were found in the present investigation.

Isoflurane (and, possibly, residual barbiturate action from induction) produced an elevation in heart rate in the present study, as well as a decrease in mean aortic blood pressure and peak positive dP/dt. While tachycardia has previously been observed with isoflurane in both dogs[6-8] and humans,[9-14] the mechanism of the increase in cardiac rate is not well understood. Other investigators have noted no change, or a decrease in heart rate during isoflurane anesthesia in humans[22-25] or dogs.[26,27] In general, when acute preparations are utilized, isoflurane does not produce an increase in heart rate. In contrast, in conscious, trained dogs, inhalational anesthesia is associated with a significant increase in rate. The mechanism of isoflurane-induced tachycardia may involve a balance between direct effects on the cardiac conduction system and the autonomic baroreflex arc, and indirect baroreceptor reflex responses to accompanying arterial hypotension. Isoflurane has been shown to exert direct negative chronotropic effects in both isolated guinea pig sinoatrial node cells[28] and the intact dog that has the baroreceptor reflex arc blocked with atropine, hexamethonium, and propranolol (unpublished results from this laboratory). Seagard *et al.*[29] have shown that isoflurane attenuated the baroreflex arc and reduced renal sympathetic efferent nerve activity during arterial hypotension which would be expected to increase sympathetic tone.[30] Skovsted *et al.* have also observed a decrease in sympathetic efferent nerve activity, but an even greater decrease in parasympathetic efferent nerve activity following isoflurane anesthesia. Such preferential vagal depression might represent the mechanism of isoflurane-induced tachycardia.[31]

Isoflurane has been shown to directly depress both vascular smooth muscle tone and myocardial contractility *in vitro*.[32,33] In the present investigation, isoflurane-induced decreases in left ventricular systolic pressure and peak positive dP/dt are consistent with these findings. However, the use of peak positive dP/dt as an index of global contractility is only of limited value in

TABLE 2. Propranolol in Isoflurane Anesthetized Dogs: Hemodynamic, Electrocardiographic, and Blood Gas Data

	Conscious	Isoflurane	Propranolol (mg/kg) 0.25	0.50	1.0
Heart rate (bpm)	75 ± 5	101 ± 4*	90 ± 4	84 ± 3†	84 ± 3†
Systolic aortic pressure (mmHg)	115 ± 5	104 ± 3*	103 ± 3	103 ± 4	102 ± 3
Mean aortic pressure (mmHg)	96 ± 5	89 ± 3	89 ± 3	89 ± 5	90 ± 4
Diastolic aortic pressure (mmHg)	84 ± 4	82 ± 3	80 ± 3	80 ± 5	81 ± 4
Left ventricular systolic pressure (mmHg)	116 ± 4	101 ± 3*	102 ± 3	101 ± 4	102 ± 3
Left ventricular end diastolic pressure (mmHg)	9 ± 2	7 ± 1	9 ± 1	9 ± 1	10 ± 1
+dP/dt (mmHg/s)	2540 ± 130	1900 ± 100*	1650 ± 60	1500 ± 50†	1420 ± 60†
Diastolic coronary blood flow velocity (Hz × 10^2)	49 ± 7	54 ± 9	58 ± 10	56 ± 10	55 ± 10
Mean coronary blood flow velocity (Hz × 10^2)	28 ± 4	33 ± 5	36 ± 6	35 ± 10	34 ± 6
PR interval (s)	0.10 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.11 ± 0.01
QRS duration (s)	0.07 ± 0.01	0.06 ± 0.01	0.06 ± 0.01	0.06 ± 0.01	0.07 ± 0.01
QT interval (s)	0.26 ± 0.01	0.33 ± 0.02*	0.33 ± 0.01	0.33 ± 0.01	0.32 ± 0.01
QT_c (s)	0.30 ± 0.02	0.39 ± 0.02*	0.41 ± 0.01	0.40 ± 0.01	0.39 ± 0.01
*p*H (u)	7.41 ± 0.01	7.39 ± 0.02	7.39 ± 0.02	7.39 ± 0.01	7.38 ± 0.02
P_{O_2} (mmHg)	99 ± 6	442 ± 16*	430 ± 29	466 ± 17	476 ± 25
P_{CO_2} (mmHg)	29 ± 1	28 ± 2	27 ± 1	28 ± 1	27 ± 1

Mean ± SEM data (N = 7–10).
* Significantly ($P < 0.05$) different: isoflurane *vs.* conscious.
† Significantly ($P < 0.05$) different: propranolol *vs.* isoflurane.

TABLE 3. Propranolol in Isoflurane Anesthetized Dogs with Pancuronium Neuromuscular Blockade: Hemodynamic, Electrocardiographic, and Blood Gas Data

	Conscious	Isoflurane	Isoflurane & Pancuronium	Propranolol 0.25	0.50	1.0
Heart rate (bpm)	75 ± 3	95 ± 4*	109 ± 4*	86 ± 4†	78 ± 4†	74 ± 4†
Systolic aortic pressure (mmHg)	118 ± 5	102 ± 10*	103 ± 6*	105 ± 6	102 ± 6	100 ± 6
Mean aortic pressure (mmHg)	99 ± 4	79 ± 5*	90 ± 7	91 ± 5	89 ± 5	87 ± 5
Diastolic aortic pressure (mmHg)	86 ± 4	72 ± 6*	85 ± 7	84 ± 5	80 ± 5	77 ± 5
Left ventricular systolic pressure (mmHg)	116 ± 6	97 ± 5*	106 ± 7	106 ± 6	103 ± 7	100 ± 6
Left ventricular end diastolic pressure (mmHg)	9 ± 1	6 ± 2	9 ± 2	12 ± 2	12 ± 2	13 ± 2
+dP/dt (mmHg/s)	2575 ± 250	1700 ± 210*	1930 ± 230*	1710 ± 200	1590 ± 190	1420 ± 170†
Diastolic coronary blood flow velocity (Hz × 10^2)	45 ± 5	42 ± 5	48 ± 5	44 ± 5	44 ± 5	46 ± 6
Mean coronary blood flow velocity (Hz × 10^2)	26 ± 2	25 ± 2	30 ± 3	27 ± 3	28 ± 3	29 ± 3
PR interval (s)	0.11 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.12 ± 0.01	0.12 ± 0.01
QRS duration (s)	0.07 ± 0.01	0.07 ± 0.02	0.07 ± 0.01	0.07 ± 0.01	0.06 ± 0.01	0.06 ± 0.01
QT interval (s)	0.28 ± 0.02	0.35 ± 0.02*	0.32 ± 0.01*	0.35 ± 0.01	0.36 ± 0.02	0.36 ± 0.02
QT_c (s)	0.33 ± 0.02	0.42 ± 0.02*	0.43 ± 0.01*	0.43 ± 0.01	0.41 ± 0.01	0.40 ± 0.01
*p*H (u)	7.41 ± 0.01	7.41 ± 0.01	7.40 ± 0.02	7.40 ± 0.02	7.39 ± 0.01	7.39 ± 0.01
P_{O_2} (mmHg)	87 ± 5	433 ± 22*	458 ± 21*	463 ± 19	502 ± 27	487 ± 27
P_{CO_2} (mmHg)	31 ± 2	27 ± 2	28 ± 2	28 ± 2	29 ± 2	28 ± 2

Mean ± SEM data (N = 6–8).
* Significantly ($P < 0.05$) different: isoflurane or isoflurane and pancuronium *vs.* conscious.
† Significantly ($P < 0.05$) different: propranolol *vs.* isoflurane and pancuronium.

TABLE 4. UL-FS 49 in Conscious Dogs: Hemodynamic, Electrocardiographic, and Blood Gas Data

	Conscious	UL-FS 49 (mg/kg)		
		0.25	0.50	1.0
Heart rate (bpm)	76 ± 5	67 ± 4*	62 ± 3*	60 ± 3*
Systolic aortic pressure (mmHg)	123 ± 7	128 ± 6	131 ± 7	130 ± 6
Mean aortic pressure (mmHg)	107 ± 7	108 ± 6	109 ± 6	108 ± 6
Diastolic aortic pressure (mmHg)	96 ± 7	93 ± 5	93 ± 6	94 ± 6
Left ventricular systolic pressure (mmHg)	122 ± 7	126 ± 7	129 ± 7	126 ± 6
Left ventricular end diastolic pressure (mmHg)	11 ± 2	12 ± 1	16 ± 1	16 ± 1
+dP/dt (mmHg/s)	2660 ± 240	2710 ± 200	2660 ± 230	2760 ± 190
Diastolic coronary blood flow velocity (Hz × 10^2)	58 ± 7	58 ± 8	52 ± 9	61 ± 7
Mean coronary blood flow velocity (Hz × 10^2)	34 ± 4	31 ± 6	32 ± 5	30 ± 4
PR interval (s)	0.11 ± 0.03	0.11 ± 0.04	0.11 ± 0.02	0.11 ± 0.01
QRS duration (s)	0.06 ± 0.01	0.06 ± 0.01	0.06 ± 0.01	0.06 ± 0.02
QT interval (s)	0.27 ± 0.01	0.30 ± 0.01	0.31 ± 0.01	0.30 ± 0.01
QT_c (s)	0.32 ± 0.02	0.34 ± 0.02	0.32 ± 0.02	0.30 ± 0.02
*p*H (u)	7.41 ± 0.01	7.39 ± 0.01	7.39 ± 0.01	7.41 ± 0.03
P_{O_2} (mmHg)	99 ± 4	98 ± 2	99 ± 3	100 ± 5
P_{CO_2} (mmHg)	29 ± 1	32 ± 2	30 ± 2	29 ± 2

Mean ± SEM data (N = 7–8).

* Significantly ($P < 0.05$) different: UL-FS 49 *vs.* conscious.

this study due to changes in heart rate and afterload produced by isoflurane. Previous studies have shown that when heart rate, preload, and afterload are held constant, peak positive dP/dt provides a reliable and sensitive measure of contractility.[34] Nevertheless, the balance of an increase in heart rate and a decrease in arterial pressure indicates the decrease in dP/dt in the present study to be consistent with a negative inotropic action of isoflurane.

In the presence of isoflurane, propranolol produced decreases in heart rate and peak positive dP/dt. UL-FS 49, however, decreased heart rate without any corre-

TABLE 5. UL-FS 49 in Isoflurane Anesthetized Dogs: Hemodynamic, Electrocardiographic, and Blood Gas Data

	Conscious	Isoflurane	UL-FS 49 (mg/kg)		
			0.25	0.50	1.0
Heart rate (bpm)	78 ± 4	103 ± 4*	71 ± 4†	57 ± 3†	54 ± 5†
Systolic aortic pressure (mmHg)	118 ± 5	101 ± 7*	102 ± 5	104 ± 5	104 ± 4
Mean aortic pressure (mmHg)	103 ± 5	89 ± 6*	89 ± 5	88 ± 4	88 ± 3
Diastolic aortic pressure (mmHg)	91 ± 5	83 ± 6	79 ± 4	76 ± 4	75 ± 3
Left ventricular systolic pressure (mmHg)	115 ± 5	101 ± 6*	104 ± 5	105 ± 5	104 ± 4
Left ventricular end diastolic pressure (mmHg)	8 ± 1	8 ± 2	9 ± 1	14 ± 2	12 ± 2
+dP/dt (mmHg/s)	2630 ± 200	1720 ± 200*	1900 ± 180	1960 ± 190	2200 ± 160
Diastolic coronary blood flow velocity (Hz × 10^2)	52 ± 5	53 ± 5	54 ± 8	50 ± 5	50 ± 6
Mean coronary blood flow velocity (Hz × 10^2)	30 ± 4	33 ± 4	36 ± 6	31 ± 3	31 ± 6
PR interval (s)	0.10 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.11 ± 0.01
QRS duration (s)	0.07 ± 0.01	0.06 ± 0.02	0.07 ± 0.01	0.07 ± 0.01	0.07 ± 0.01
QT interval (s)	0.30 ± 0.01	0.37 ± 0.02*	0.41 ± 0.04	0.50 ± 0.04	0.56 ± 0.08†
QT_c (s)	0.34 ± 0.01	0.44 ± 0.02*	0.44 ± 0.03	0.47 ± 0.02	0.51 ± 0.04
*p*H (u)	7.42 ± 0.01	7.41 ± 0.02	7.41 ± 0.02	7.42 ± 0.02	7.41 ± 0.01
P_{O_2} (mmHg)	94 ± 11	490 ± 16*	490 ± 22	523 ± 11	511 ± 25
P_{CO_2} (mmHg)	33 ± 1	29 ± 1*	29 ± 2	28 ± 2	27 ± 2

Mean ± SEM data (N = 7–9).

* Significantly ($P < 0.05$) different: isoflurane *vs.* conscious.

† Significantly ($P < 0.05$) different: UL-FS 49 *vs.* isoflurane.

TABLE 6. UL-FS 49 in Isoflurane Anesthetized Dogs with Pancuronium Neuromuscular Blockade: Hemodynamic, Electrocardiographic, and Blood Gas Data

	Conscious	Isoflurane	Isoflurane & Pancuronium	UL-FS 49 (mg/kg) 0.25	0.50	1.0
Heart rate (bpm)	68 ± 4	95 ± 10*	106 ± 8*	68 ± 4†	54 ± 5†	50 ± 4†
Systolic aortic pressure (mmHg)	116 ± 5	92 ± 6*	99 ± 7*	98 ± 7	97 ± 7	99 ± 6
Mean aortic pressure (mmHg)	94 ± 5	76 ± 6*	89 ± 7	83 ± 6	80 ± 6	82 ± 6
Diastolic aortic pressure (mmHg)	81 ± 5	68 ± 6*	83 ± 7	73 ± 5	67 ± 5	69 ± 5
Left ventricular systolic pressure (mmHg)	112 ± 5	90 ± 6*	98 ± 6*	98 ± 5	98 ± 6	99 ± 6
Left ventricular end diastolic pressure (mmHg)	8 ± 1	8 ± 2	7 ± 1	9 ± 1	11 ± 1	11 ± 1
+dP/dt (mmHg/s)	2350 ± 170	1590 ± 170*	1660 ± 140*	1780 ± 230	1990 ± 250	2080 ± 260
Diastolic coronary blood flow velocity (Hz × 10^2)	45 ± 7	50 ± 10	59 ± 10	44 ± 6	46 ± 7	47 ± 8
Mean coronary blood flow velocity (Hz × 10^2)	24 ± 4	27 ± 6	33 ± 6	24 ± 4	24 ± 4	26 ± 4
PR interval (s)	0.11 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.12 ± 0.01	0.12 ± 0.01
QRS duration (s)	0.07 ± 0.01	0.07 ± 0.01	0.07 ± 0.02	0.07 ± 0.01	0.07 ± 0.01	0.07 ± 0.01
QT interval (s)	0.27 ± 0.02	0.37 ± 0.02*	0.38 ± 0.02*	0.41 ± 0.02	0.51 ± 0.03†	0.54 ± 0.04†
QT_c (s)	0.31 ± 0.02	0.41 ± 0.01*	0.45 ± 0.02	0.43 ± 0.02	0.46 ± 0.02	0.50 ± 0.03
*p*H (u)	7.39 ± 0.01	7.43 ± 0.01	7.42 ± 0.01	7.42 ± 0.01	7.42 ± 0.02	7.43 ± 0.02
P_{O_2} (mmHg)	96 ± 6	458 ± 20*	470 ± 19*	480 ± 20	485 ± 25	507 ± 19
P_{CO_2} (mmHg)	33 ± 2	28 ± 1	26 ± 2*	26 ± 2	27 ± 2	26 ± 1

Mean ± SEM data (N = 7–8).
* Significantly ($P < 0.05$) different: isoflurane or isoflurane and pancuronium *vs.* conscious.
† Significantly ($P < 0.05$) different: UL-FS 49 *vs.* isoflurane and pancuronium.

sponding negative inotropic effect. In contrast, Horan *et al.* have shown propranolol (0.3 mg/kg) to produce no change in heart rate, left ventricular end diastolic pressure, or peak positive dP/dt, in isoflurane-anesthetized dogs.[7]

The vagolytic action of pancuronium produced only small (non-significant) elevations in heart rate above that caused by isoflurane in the present study. Studies in humans have shown that propranolol decreases pancuronium-induced increases in heart rate.[35,36] Propranolol provided similar results in dogs, while UL-FS 49 was able to decrease the combined isoflurane- and pancuronium-induced tachycardia to a greater extent.

The present results also indicate that, whereas propranolol produced a dose-dependent reduction in the hemodynamic response to isoproterenol, UL-FS 49 had only a small effect. Thus beta receptor function is not interfered with by UL-FS 49 providing an important advantage over beta adrenergic blockade. Whereas isoproterenol produced the expected hemodynamic response in the presence of UL-FS 49, the initial baseline was simply reduced to a lower level in the case of heart rate and unchanged for contractility.

UL-FS 49 has been shown to prolong repolarization of the ventricles, or increase the QT interval, in anesthetized cats.[1] The present results indicate no QT prolongation in conscious dogs. Any lengthening of the QT interval was related to a decrease in heart rate and was minimal when the reduction in heart rate was accounted for (QT_c). Interestingly, isoflurane alone significantly prolonged the QT interval, despite increasing heart rate.

The use of isoflurane in patients with ischemic heart disease remains controversial. Isoflurane may increase heart rate and decrease aortic blood pressure, both of which unfavorably influence the balance between myocardial oxygen supply and demand. By spending less time in diastole and reducing coronary perfusion pressure, oxygen supply to jeopardized myocardium may be diminished during periods of increased oxygen consumption (secondary to increased heart rate). In addition, isoflurane may produce a "steal" of blood flow away from an ischemic zone at the expense of enhanced perfusion in normal regions.[37] In contrast, experimental studies of UL-FS 49 in the dog indicate that this agent may enhance perfusion of ischemic myocardium.[38] The use of a "specific bradycardic agent" such as UL-FS 49 may provide beneficial effects for ischemic myocardium by rapidly and effectively decreasing heart rate and myocardial oxygen demand. Furthermore, by

increasing diastolic perfusion time, an increase in oxygen supply to a compromised area may be promoted.[39] In contrast, beta blocking agents such as propranolol may have significant negative inotropic actions. This reduction in contractility may increase the extravascular component of coronary resistance (by increasing left ventricular end diastolic pressure) and decrease overall cardiac performance.[39] A reduction in contractility may also decrease myocardial oxygen consumption and, thus, be beneficial under certain conditions.

In conclusion, the present investigation has shown that UL-FS 49, a new "specific bradycardic agent," decreases the heart rate of conscious and isoflurane-anesthetized (with and without pancuronium) dogs. In contrast to propranolol, no negative inotropic effects were found. "Specific bradycardic agents" such as UL-FS 49 may be useful clinically during the perioperative period, *e.g.*, during induction of anesthesia, maintenance of anesthesia with isoflurane, or during periods of surgical stimulation. These agents may be especially advantageous for patients with documented or suspected ischemic heart disease and those non-tolerant of a beta blocker, as well as patients requiring a greater reduction in heart rate. Additional future experiments are required to assess the clinical efficacy of UL-FS 49.

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