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Cardiovascular Properties of a New Cardiotonic Agent: MDL 17,043 (1,3-Dihydro-4-methyl-5-[4-(methylthio)-benzoyl]-2*H*-imidazol-2-one)

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Summary: The cardiovascular properties of a new noncatechol, nonglycoside cardiotonic agent, MDL 17,043, were investigated in anesthetized and conscious dogs and the dog heart–lung preparation. MDL 17,043 (0.1–1 mg/kg), administered to anesthetized dogs by intravenous injection, produced dose-related increases in cardiac contractile force lasting more than 1 h. It also produced relatively minor and shorter-lasting increases in heart rate, and brief decreases in blood pressure. These effects were not blocked by propranolol. Of these effects, the increase in cardiac contractile force was, by far, the most prominent. The cardiac effects were also observed in the dog heart–lung preparation. When administered to anesthetized dogs by constant intravenous infusion, MDL 17,043 (0.03 and 0.1 mg/kg/min) produced a marked and sustained increase in cardiac contractile force and a sustained decrease in blood pressure without altering heart rate, suggesting a wide separation between the inotropic and chronotropic effects of this drug. Given orally to conscious, chronically instrumented dogs, MDL 17,043 (3–30 mg/kg) produced a sustained increase in dP/dt without altering heart rate or blood pressure. It reversed the depressant effect of pentobarbital on the ventricular function curve in the dog heart–lung. When the hemodynamic characteristics of compensated heart failure were produced by propranolol in anesthetized dogs, MDL 17,043 reversed these effects. These studies suggest that MDL 17,043 may have a beneficial effect in the treatment of heart failure. **Key Words:** Cardiotonic—Heart failure—Propranolol—Pentobarbital—MDL 17,043.

The cardiac glycosides have been the mainstay of therapy for heart failure for nearly 200 years. This is in spite of their very narrow therapeutic index with life-threatening arrhythmias as the first manifestation of toxicity. Digitalis intoxication is one of the most common adverse drug reactions in the United States (1–4). Such toxicity has stimulated the search for new positive inotropic agents. Other agents with positive inotropic activity, such as glucagon, the methyl xanthines, and the ionophores have been studied but have not found general clinical use for the treatment of heart failure (5–9). The catecholamines, isoproterenol, epinephrine, dopamine, and dobutamine, exert useful positive inotropic activity; however, their usefulness is limited because of their concomitant positive chronotropic activity and the fact that they must be given by intravenous infusion (8–10). Thus, none of the presently available drugs approaches the ideal for the treatment of heart failure (9). This has led to the search for alternative approaches. Recently, the combination of a cardiac glycoside and afterload reduction with a vasodilator has proved of value (11,12).

The report, in 1973, of the positive inotropic activity of imidazole, *in vitro* and *in vivo* (13), stimulated our investigation of the cardiovascular properties of substituted imidazolones. A number of

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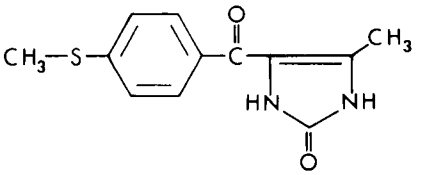

FIG. 1. Structure of MDL 17,043: 1,3-dihydro-4-methyl-5-[4-(methyl-thio)-benzoyl]-2*H*-imidazol-2-one.

compounds of this series were found to possess potent positive inotropic activity (Dage, Schnettler, and Grisar, unpublished data). This report describes the results of the initial investigation of one member of the series, MDL 17,043 (Fig. 1), which is currently undergoing clinical trials in congestive heart failure.

METHODS

Anesthetized dogs

Dogs of either sex, weighing 10–25 kg, were anesthetized with 35 mg/kg i.v. of sodium pentobarbital. The lungs were ventilated artificially with a Bird Mark 7 respirator following tracheal intubation. The left femoral vein was cannulated for the injection of drugs. The left femoral artery was cannulated and the cannula advanced into the thoracic aorta to measure blood pressure. The chest was opened at the left fifth intercostal space, and the pericardium was cut to expose the heart. A calibrated Walton–Brodie strain gauge arch was sutured to the left ventricle to record cardiac contractile force. Cardiac output was estimated by measurement of ascending aortic blood flow with an electromagnetic flow transducer placed around the root of the ascending aorta and connected to a flowmeter (Statham, SP2202). Left atrial pressure was measured with a pressure transducer (Statham, P23B) attached to a cannula placed in the left atrium. Heart rate was recorded from the EKG (lead II) using a tachograph (Grass, 7P4). Stroke volume was estimated as the quotient of cardiac output and heart rate. Two studies were performed. In one, single doses of 0.1, 0.3, or 1 mg/kg i.v. of MDL 17,043 were given to five dogs, and in the other, 0.03 or 0.1 mg/kg/min i.v. of MDL 17,043 was infused into six dogs at a constant rate with an infusion pump (Harvard 600) for 120 min. All variables were recorded continuously before, during, and after drug administration.

In a third study, 0.3 or 3 mg/kg i.v. of MDL 17,043 was injected during a constant propranolol infusion. A 4 mg/kg i.v. dose of propranolol was injected into 12 dogs followed immediately by the infusion of 0.18 mg/kg/min i.v. (0.2 ml/min) for 90 min. Vehicle for MDL 17,043 was injected intravenously in an equivalent amount 25 min after the injection of propranolol in each dog. Each dose of MDL 17,043 was injected into six dogs 5 min later. An additional group of six dogs received only propranolol. All variables were recorded as described above.

Conscious dogs

Dogs of either sex, weighing 6–12 kg, were instrumented to monitor arterial blood pressure, *dP/dt* (the rate of change of pressure in the left ventricle of the heart during systole), and lead II of the electrocardiogram. Under halothane–nitrous oxide anesthesia, a pressure transducer (Königsberg, P6.5) was implanted into the left ventricle of the heart through a stab incision at the apex. The dog was used in the experiment 4–9 days following this procedure. A differentiator (Grass 7P20) was used to measure *dP/dt*. Immediately prior to each experiment, an indwelling catheter was placed into the right femoral artery of each dog under local anesthesia to measure blood pressure. Local anesthesia was produced by subcutaneous injections of 1% procaine hydrochloride and the topical application of lidocaine jelly. The animals were then suspended in a sling. The lead II EKG was obtained by means of needle electrodes inserted subcutaneously. Variables were recorded continuously before and for 5 h after dosing. Gross behavioral observations of the animals were made continuously before and at various time points after dosing. Doses of 3, 10, or 30 mg/kg of MDL 17,043 were administered by gavage to dogs that had been fasted 18 h. There were seven dogs in each MDL 17,043 dose group and five dogs in the control group (vehicle). The volume administered was 2 ml/kg followed by a 5-ml vehicle wash.

Heart–lung preparation

The heart–lung preparation employed was similar to that described by Somani and Bachand (14). Mongrel dogs of either sex, weighing 11–19 kg, were used. They were anesthetized with pentobarbital sodium (35 mg/kg i.v.) and prepared for recording as described above. Mean systemic blood pressure was recorded from the aortic cannula. Aortic blood flow was measured extracorporeally with a flowmeter (Biotronex, model BL610). Cardiac output was taken as aortic blood flow, which does not include coronary arterial inflow. Stroke volume was calculated as described previously. Heparin sodium USP (700 U/kg) was given to retard blood coagulation.

The extracorporeal blood perfusion circuit consisted of latex tubing, a Windkessel chamber, a flow transducer (IVM, model FT-E SN2121), an adjustable screw clamp for controlling systemic resistance, a temperature-controlled double-jacketed glass blood reservoir (1L capacity), and more latex tubing. The temperature of the blood in the reservoir was maintained at 38°C. The brachiocephalic artery and the superior vena cava were cannulated, and blood allowed to flow through the extracorporeal circuit via these ports. All other extracardiopulmonary blood vessels were ligated. Additional blood was obtained from donor dogs anesthetized with sodium pentobarbital (35 mg/kg i.v.) and heparinized as described previously. Their blood was added to the reservoir to bring its volume to 800 cc at the beginning of each experiment. The blood volume of the entire heart–lung circuit was estimated for the purpose of expressing drug concentration. The blood volume of the heart and lungs was taken as 15.2 ml/kg of body weight based on a pulmonary blood volume of 11 ml/kg, ventricular ejection volumes totaling 1.44 ml/kg, residual ventricular volumes totaling 1.44 ml/kg, a coronary blood volume of 0.53 ml/kg, and a residual amount in the aorta and vena cava of 0.79 ml/kg, and this amount was added to the blood volume of the circuit to obtain the total blood volume (15–18). Systemic blood pressure was set between 85 and 95 mm Hg by adjusting systemic resistance at the beginning of each experiment; venous return was held constant by maintaining the reservoir height constant at 18–25 cm

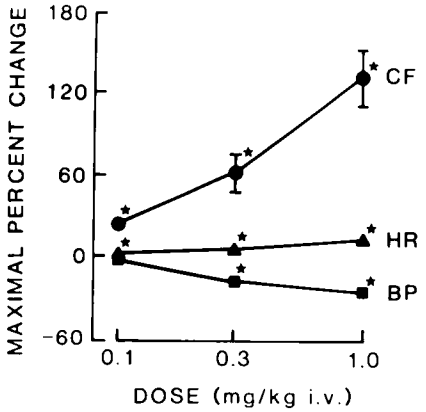

FIG. 2. Effects of MDL 17,043 on cardiac contractile force (CF), heart rate (HR), and mean systemic blood pressure (BP) in anesthetized dogs. Shown are means and standard errors of the maximum effect observed in 10 min. Each dose was given i.v. to five dogs. *Significant effect by *t* test ($p < 0.05$). Pretreatment CF, HR, and BP values for the 0.1, 0.3, and 1 mg/kg treatment groups were 134 ± 6 g, 130 ± 12 g, and 124 ± 8 g; 156 ± 4 beats/min, 140 ± 12 beats/min, and 130 ± 5 beats/min; and 110 ± 10 mm Hg, 106 ± 5 mm Hg, and 107 ± 6 mm Hg, respectively.

above the opening of the inferior vena cava; cardiac output was set by adjusting venous return so that it was about 2/3 of that expected based on the dog's weight (100 ml/kg). When cardiac function curves were determined, the reservoir height was increased in steps of 5, 10, and 15 cm above the primary value, and the resultant changes in left atrial pressure and cardiac output were measured.

Drugs

In these studies, MDL 17,043 was dissolved in 0.12 ml of 1.0 N sodium hydroxide for each 10 mg of drug and diluted to the appropriate volume with n-saline or Sorensen's phosphate buffer, pH 7.38. The final pH of the MDL 17,043 solutions and the vehicle ranged from 11.4 to 12.8. Propranolol was dissolved in n-saline. All drug solutions were made up daily and used within 60 min following preparation.

Statistical analysis

Data are expressed as means and standard errors. Statistical significance of the mean changes or percent changes with time was assessed in anesthetized dog studies using the *t* test and in conscious dog studies using the one-sided Dunnett's multiple comparison test (19). In the heart–lung experiments, the data were analyzed using an analysis of variance, Dunnett's test, and a multivariant analysis of variance (19,20). Statistical significance was taken as $p < 0.05$.

RESULTS

Single intravenous doses of 0.1, 0.3, and 1 mg/kg of MDL 17,043 produced significant and dose-related increases in cardiac contractile force and heart rate in anesthetized dogs (Fig. 2). In addition, the 0.3 and 1 mg/kg doses also produced a very brief (<2 min) but significant decrease in mean blood pressure. The relative magnitude and duration of the cardiovascular effects elicited by the 0.3 mg/kg dose of MDL 17,043 are illustrated in Fig. 3. The increase in cardiac contractile force was, by far, the most prominent and long-lasting effect of this drug. The times required for cardiac contractile force to recover 50% and 80% following the 0.3 mg/kg dose were 20.1 ± 8.2 min and 63.5 ± 26.6 min, respectively. By comparison, the recovery times for heart rate were 14.9 ± 6 and 24.1 ± 7.1 min, respectively.

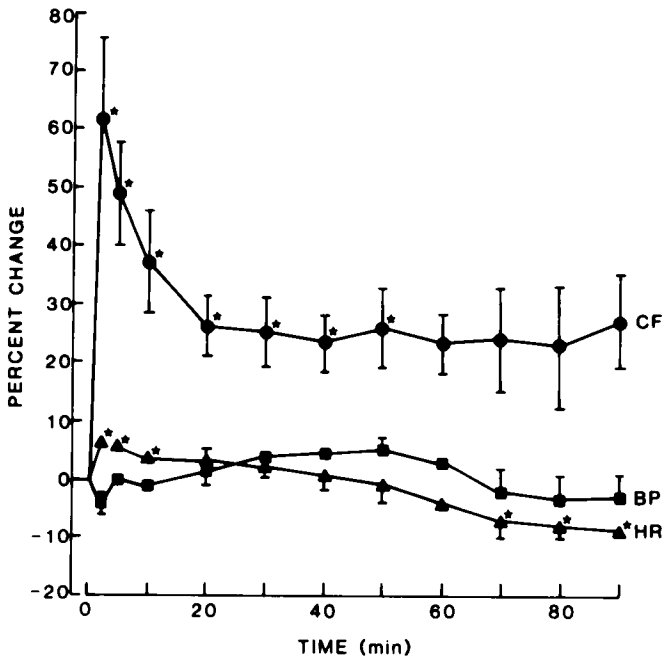

FIG. 3. Time course of the effects produced by a 0.3 mg/kg i.v. dose of MDL 17,043 on cardiac contractile force (CF), heart rate (HR), and mean systemic blood pressure (BP) in anesthetized dogs. Shown are periodic means and standard errors from five dogs. *Significant effect by *t* test ($p < 0.05$). Pretreatment values are shown in Fig. 2.

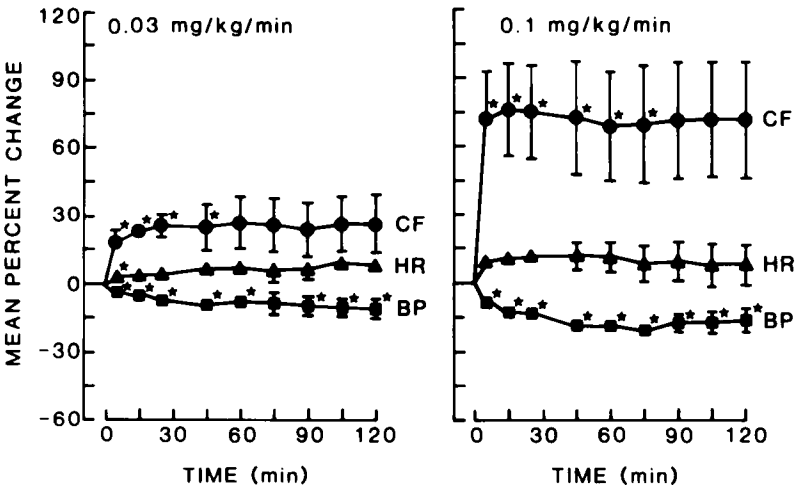

FIG. 4. Effects of intravenous infusions of MDL 17,043 on cardiac contractile force (CF), heart rate (HR), and mean systemic blood pressure (BP) in anesthetized dogs. Either 0.03 or 0.1 mg/kg/min of drug was constantly infused into six dogs for 120 min. Shown are means and standard errors. *Significant effect by *t* test ($p < 0.05$). Pretreatment CF, HR, and BP values for both treatment groups were 183 ± 8 g and 171 ± 6 g; 170 ± 6 beats/min and 167 ± 11 beats/min; and 106 ± 8 mm Hg and 113 ± 7 mm Hg, respectively.

When MDL 17,043 was infused intravenously at 0.03 or 0.1 mg/kg/min for 120 min, its most prominent effects were to increase cardiac contractile force and to decrease mean blood pressure (Fig. 4). Both effects appeared to be dose related. Heart rate was increased only very slightly during the infusion of 0.03 or 0.1 mg/kg/min of drug. In addition, cardiac output, stroke volume, or left atrial pressure were not significantly altered (data not shown). Variables returned to within 10% of control levels 60–90 min after cessation of the drug infusion.

The oral activity of MDL 17,043 was investigated in conscious, chronically instrumented dogs. The effects of 3, 10, and 30 mg/kg p.o. on *dP/dt*, heart rate, and mean blood pressure are illustrated in Fig. 5. MDL 17,043 produced a significant dose-related increase in *dP/dt* without significantly altering heart rate or mean blood pressure. Under these circumstances, the MDL 17,043-induced increases in *dP/dt* indicated increases in cardiac contractility. The onset, peak, and duration of the maximum *dP/dt* response elicited by MDL 17,043 are shown in Table 1. The onset did not appear dose related, but the time to peak effect and the duration of effect

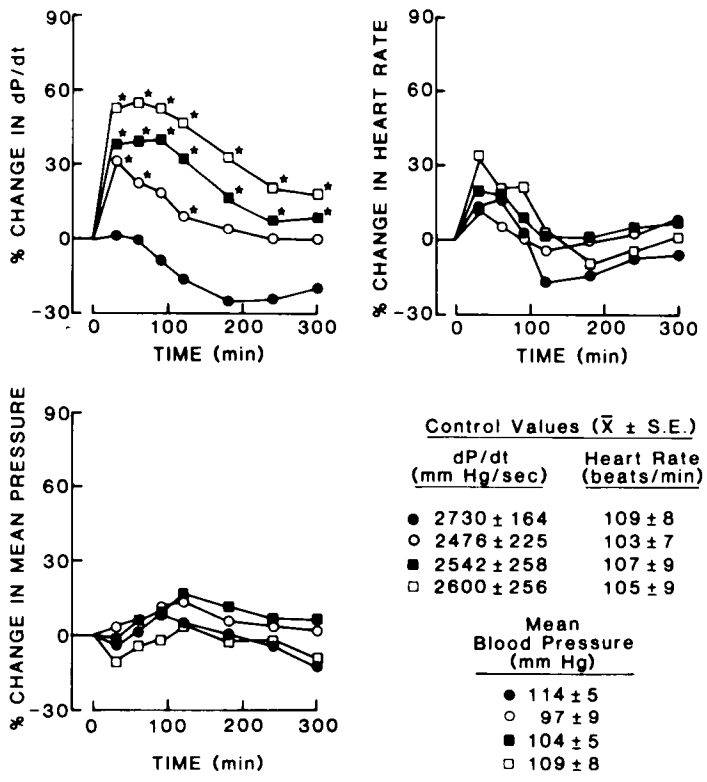

FIG. 5. Effect of oral doses of MDL 17,043 on the rate of change of pressure in the left ventricle of the heart during systole (*dP/dt*), heart rate (HR), and mean systemic blood pressure (BP) in conscious dogs. An oral dose of 3 mg/kg (open circles), 10 mg/kg (solid squares), or 30 mg/kg (open squares) was given to seven dogs. Vehicle (solid circles) in an amount equivalent to the 30 mg/kg dose of drug was given to five dogs. The changes from control are shown at 30, 60, 90, 120, 180, 240, and 300 min after treatment. The control values for each treatment group are shown at the lower right. *Significant effect compared to the control group by one-sided Dunnett's multiple comparison test ($p < 0.05$).

TABLE 1. *Onset, peak, and duration of the maximum* dP/dt *response elicited by oral doses of RMI 17,043 in conscious dogs*[a]

Dose (mg/kg p.o.)	n	Onset (min)	Peak change (%)	Peak time (min)	Duration (min)	Area under curve
3	7	10.0 ± 0.0	38.6 ± 10.6	34.3 ± 6.5	125.6 ± 42.7	3,890 ± 1,542
10	7	12.9 ± 1.8	49.3 ± 7.2	50.0 ± 8.2	182.4 ± 24.0	6,878 ± 1,897
30	7	10.0 ± 0.0	65.1 ± 8.8	54.3 ± 19.1	261.3 ± 22.2	11,259 ± 1,787

[a] Shown are $X \pm$ SE for the following: onset (min)—the minimum time at which a 10% or greater increase was observed; peak % change—the maximal percent change from base line; peak time (min)—the time at which the peak percent change occurred; duration (min)—time from onset to return to plus 10% of base line; and area under the curve—the area under the percent change from base-line curve.

were dose related. MDL 17,043 did not produce any changes in gross behavior or the lead II EKG in this study.

To determine whether MDL 17,043 would improve the depressed hemodynamic state of heart failure, it was examined in anesthetized dogs given a 4 mg/kg i.v. injection followed by a constant infusion of 0.18 mg/kg/min of propranolol. Propranolol administered in this way produced significant decreases in cardiac contractile force, heart rate, mean blood pressure, and cardiac output and a significant increase in left atrial pressure for the 120-min experimental period (Table 2). Stroke volume was not significantly changed by propranolol. The effects produced by MDL 17,043 on the propranolol-induced depressed hemodynamic state in 12 other dogs is illustrated in Fig. 6. Either 0.3 or 3 mg/kg i.v. of MDL 17,043 was injected 30 min following the onset of the propranolol infusion. The injection of the vehicle for MDL 17,043 5 min before the injection of drug was without any effect. Both doses of MDL 17,043 produced significant increases in cardiac contractile force, decreases in left atrial pressure, and increases in heart rate. Cardiac output was significantly increased and mean blood pressure significantly decreased by the 3 mg/kg dose of MDL 17,043 only. Stroke volume was not significantly altered by either dose of MDL 17,043. The effect of propranolol on cardiac contractile force, left atrial pressure, heart rate, and cardiac output were reversed partially by the 0.3 mg/kg dose and completely by the 3 mg/kg dose of MDL 17,043. Both doses of MDL 17,043 produced an additional decrease in blood pressure beyond that produced by propranolol. It is noteworthy that the maximum increases in cardiac contractile force (84.8 ± 19.2% from 46 ± 13 g) and heart rate (6.1 ± 0.8% from 145 ± 4 beats/min) elicited by the 0.3 mg/kg i.v. dose of MDL 17,043 in the propranolol-treated dogs were not significantly different by *t* test from the responses observed in the nonpropranolol-treated animals of Fig. 2 (62.8 ± 14.0% from 129.6 ± 12 g and 6.6 ± 0.9% from 140 ± 12 beats/min, respectively).

Effects in the dog heart–lung preparation

The cardiac effects of MDL 17,043 when heart rate, systemic blood pressure, and venous return were kept constant are illustrated in Fig. 7. Cumulative blood concentrations of MDL 17,043, ranging from 2.3×10^{-6} *M* to 2.1×10^{-4} *M*, progressively increased cardiac contractile force from 90 ± 7 g to 240 ± 14 g in a concentration-related fashion. These concentrations of MDL 17,043 also increased heart rate from 133 ± 6 beats/min to 159 ± 9 beats/min and decreased left atrial pressure from 7.9 ± 0.7 mm Hg to 4.0 ± 0.8 mm Hg (not shown). A blood concentration of 1×10^{-6} *M* of MDL 17,043 did not

TABLE 2. *Effect of propranolol on the hemodynamic state of anesthetized dogs*[a]

Variable	Control	Change after propranolol (min)				
		5	10	30	60	120
Cardiac contractile force (g)	157.5 ± 18.1	−91.8 ± 16.8[b]	−86.8 ± 17.2[b]	−86.7 ± 14.8[b]	−92.5 ± 10.2[b]	−104.8 ± 13.2[b]
Heart rate (beats/min)	137 ± 8	−24 ± 3[b]	−24 ± 3[b]	−24 ± 3[b]	−26 ± 4[b]	−32 ± 5[b]
Mean blood pressure (mm Hg)	101 ± 7	−17 ± 3[b]	−14 ± 2[b]	−15 ± 3[b]	−14 ± 4[b]	−22 ± 8[b]
Cardiac output (ml/min)	1,505 ± 378	−347 ± 57[b]	−332 ± 56[b]	−358 ± 82[b]	−379 ± 108[b]	−585 ± 176[b]
Stroke volume (ml)	11.2 ± 2.8	−1.0 ± 0.5	−0.8 ± 0.5	−0.9 ± 0.5	−0.8 ± 0.6	−2.1 ± 0.9
Left atrial pressure (mm Hg)	5.1 ± 0.6	6.9 ± 1.2[b]	7.5 ± 1.5[b]	7.8 ± 2.2[b]	8.3 ± 2.8[b]	8.4 ± 2.6[b]

[a] Shown are control values and periodic changes from controls following the onset of a 0.18 mg/kg/min i.v. propranolol infusion. All dogs received a 4 mg/kg i.v. injection immediately prior to starting the infusion. Shown are means ± SE from six dogs.

[b] Significant change from control, $p < 0.05$.

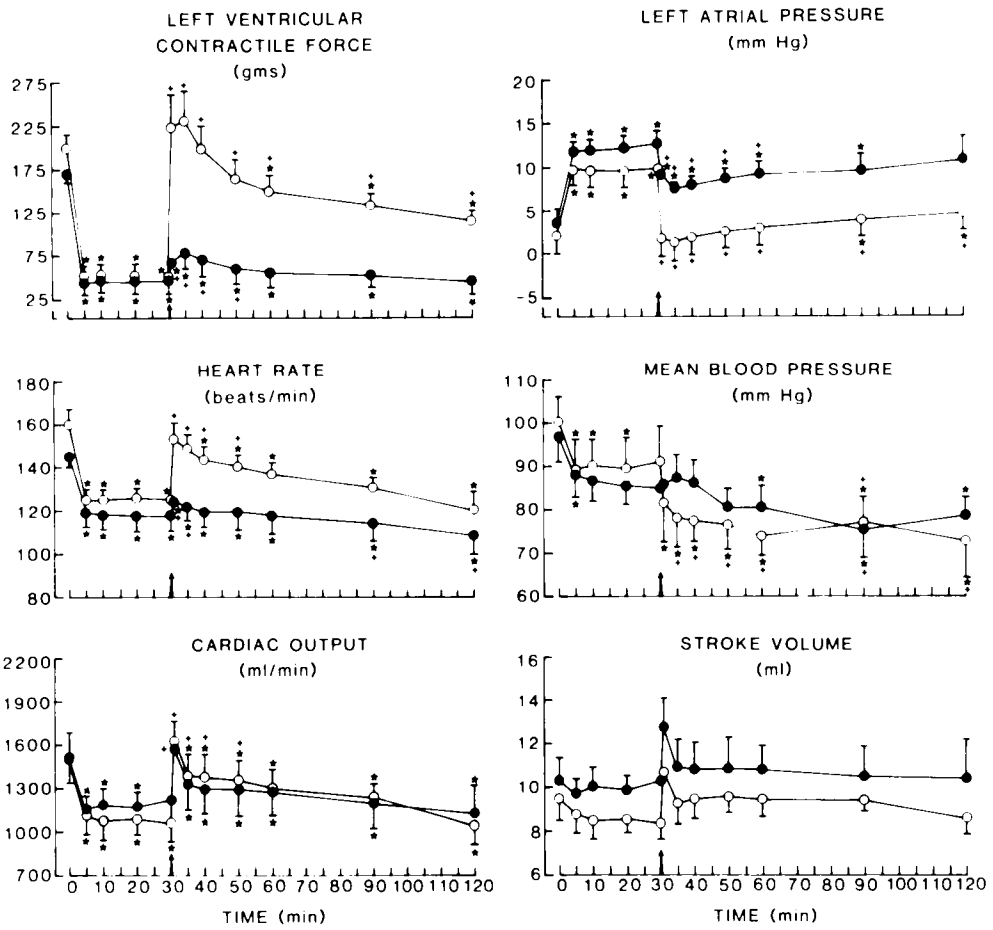

FIG. 6. Effects of MDL 17,043 in anesthetized dogs infused with a myocardial depressant dose of propranolol. A 4 mg/kg i.v. injection of propranolol was given at zero time, and it was followed immediately by a constant 0.18 mg/kg/min i.v. infusion for 120 min. Given in this way, propranolol produced many of the hemodynamic characteristics of heart failure. MDL 17,043, in a dose of either 0.3 mg/kg i.v. (solid circles) or 3 mg/kg i.v. (open circles) was given at 30 min (arrow). Shown are means and standard errors of six dogs. *Significant effect compared to zero time value and 30 min value (pre-MDL 17,043), respectively, by *t* test ($p < 0.05$).

produce a significant change in any of these variables. Cardiac output and mean systemic blood pressure, respectively, were 1,105 ± 71 ml/min and 92.3 ± 0.7 mm Hg before, and 1,110 ± 67 ml/min and 91.8 ± 0.8 mm Hg after all additions of MDL 17,043, to make a final concentration of 2.1×10^{-4} *M*, indicating that they were maintained practically constant throughout. The decrease in left atrial pressure elicited by MDL 17,043 without a change in cardiac output indicates an improvement in the pump function of the heart, i.e., the heart was capable of maintaining its output at a lower filling pressure.

The effect of MDL 17,043 on cardiac pump function in hearts depressed with pentobarbital is illustrated in Fig. 8. The cardiac function was significantly depressed and significantly shifted to the right after the addition of sodium pentobarbital to a concentration of 0.15 mg/ml. The subsequent addition of MDL 17,043 to a concentration of 0.0125 mg/ml (5×10^{-5} *M*) significantly shifted the cardiac function curve to the left, thereby completely reversing the depressant effect of sodium pentobarbital on the heart. In these experiments, sodium pentobarbital increased left atrial pressure 9.7 ± 3.5 mm Hg from 6.2 ± 0.6 mm Hg, and decreased cardiac contractile force 45.8 ± 6.2 g from 101.0 ± 6.9 g, but did not significantly alter heart rate or cardiac output. When MDL 17,043 was given to the pentobarbital-depressed heart, it decreased left atrial pressure 9.5 ± 3.0 mm Hg from 16.0 ± 3.3 mm Hg; increased cardiac contractile force 118.2 ± 12.6 g from 49.8 ± 5.4 g; and increased heart rate 20.7 ± 1.9 beats/min from 131.3 ± 4.0 beats/min, but did not significantly change cardiac output.

MDL 17,043 did not produce arrhythmias in these heart–lung studies in either normal or depressed hearts. Interestingly, MDL 17,043 produced an improvement in one heart–lung preparation that had developed a ventricular tachycardia 10 min prior to the addition of any drug. When MDL 17,043 was added to a concentration of 0.025 mg/ml, the ar-

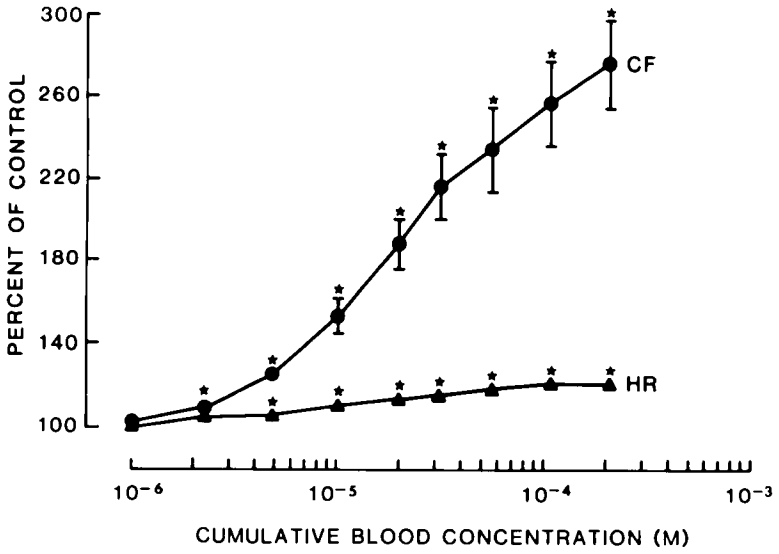

FIG. 7. Effect of cumulative blood concentrations of MDL 17,043 on cardiac contractile force (CF) and heart rate (HR) in the dog heart–lung preparation. MDL 17,043 was added sequentially to the systemic blood reservoir to make cumulative blood concentrations shown. Aortic blood pressure and venous return were regulated and did not significantly change throughout. Shown are maximum effects expressed as means and standard errors from six preparations. When standard error bars are not shown, they are enclosed within the symbol. *Significant effect compared to control by *t* test ($p < 0.05$). Control CF and HR were 90 ± 7 g and 133 ± 6 beats/min, respectively.

rhythmia reverted to a normal sinus rhythm within 1 min.

DISCUSSION

The results of these studies indicate that MDL 17,043 is a potent positive inotropic drug in anesthetized and conscious dogs and was effective by both the intravenous and the oral routes of administration. Besides its marked positive inotropic activity in anesthetized dogs, the intravenous injection of inotropic doses of MDL 17,043 produced relatively minor positive chronotropic effects and brief hypotensive effects that were unimpressive. The positive inotropic effect elicited by MDL 17,043 in anesthetized dogs did not involve β-adrenergic receptor stimulation, since its effect was evident even in dogs that had received propranolol in a dose sufficient to depress, markedly, cardiac function. Additionally, the MDL 17,043-induced increase in cardiac contractile force was demonstrated in the dog heart–lung preparation. Taken together, these data indicate that MDL 17,043 exerts a positive inotropic effect by a direct action on the heart.

The positive chronotropic activity of MDL 17,043 was too weak to produce a significant increase in heart rate in anesthetized dogs given inotropically effective doses by constant intravenous infusion. Additionally, no positive chronotropic responses were produced in conscious dogs by the oral administration of MDL 17,043 in doses adequate to produce a marked positive inotropic response. These differences indicate a wide separation between the inotropic and chronotropic activities of MDL 17,043 *in vivo*.

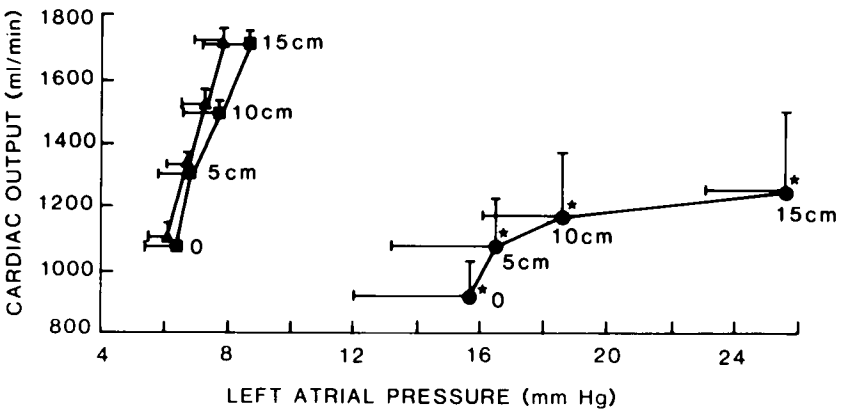

FIG. 8. Effects of pentobarbital and MDL 17,043 on left ventricular function in the dog heart–lung preparation. Left ventricular function curves were produced by raising the venous reservoir 5, 10, and 15 cm above the primary value (0) and measuring the resultant changes in the left atrial pressure and cardiac output. Mean aortic blood pressure was kept practically constant at 89.9 ± 0.6 mm Hg throughout. Shown are the left ventricular function curves from six preparations determined before (solid squares) and approximately 5–10 min after the sequential additions of 15 mg/ml pentobarbital (solid circles) and 0.0125 mg/ml (5×10^{-5} *M* of MDL 17,043, solid triangles). *Significant difference from control values; a multivariate analysis of variance ($p < 0.05$).

The MDL 17,043-induced hypotensive response apparently resulted from a vasodilator action not involving β-adrenergic receptor stimulation, since it was observed in the intravenous infusion experiments without an increase in heart rate or cardiac output and was unaltered by propranolol. The lack of even a reflex increase in heart rate in response to the MDL 17,043-induced hypotension in the intravenous infusion experiments, suggests that the baroreceptor reflexes were rendered inoperative by pentobarbital, since MDL 17,043 itself does not alter the baroreceptor reflex (21–23, and unpublished data).

In the dog heart–lung preparation, MDL 17,043 increased the pump function of the heart by a direct cardiac effect. In addition, it completely reversed the depressant effect of pentobarbital on cardiac pump function. In this respect, MDL 17,043 is similar to the cardiac glycosides and would be expected to exert a beneficial effect in the treatment of heart failure (24). The apparent vasodilator activity of MDL 17,043, although less prominent, would be expected to supplement its cardiotonic activity on cardiac pump function in heart failure. Vasodilator drugs alone have been reported to improve cardiac pump function in clinical heart failure and to produce an additive enhancement of pump function when used in combination with a positive inotropic drug (11,12).

Clinical congestive heart failure occurs when cardiac output is insufficient to meet the system's metabolic needs; hence, venous pressure rises leading to an abnormally enhanced preload (25). Depending on the degree of heart failure, the cardiac output may be normal or depressed. The hemodynamic characteristics of compensated heart failure were produced in our studies in anesthetized dogs by infusing a large dose of propranolol. When given to dogs with propranolol-induced heart failure, MDL 17,043 reversed the effects of propranolol on left atrial pressure without altering stroke volume, indicating an enhancement of cardiac pump function and, at the high dose, a reversal of the heart failure state. The inability of MDL 17,043 to increase stroke volume suggests that venous return was inadequate to support a detectable increase in stroke volume due, at least partly, to the reduced diastolic filling time brought about by the increase in heart rate (26). Additionally, MDL 17,043 may exert an effect to increase venous capacitance, thereby decreasing the venous return to the heart, but this remains to be assessed. The combined inotropic, chronotropic, and vasodilator effects of MDL 17,043 led to an increased cardiac output in dogs with propranolol-induced heart failure but not in those with a normal hemodynamic state. The ineffectiveness of MDL 17,043 under these circumstances is not surprising since other positive inotropic drugs, such as the cardiac glycosides, have been reported to be ineffective in increasing cardiac output in the nonfailing heart (27,28).

The mechanism by which MDL 17,043 exerts its positive inotropic action is not presently known. Studies *in vitro* suggest it does not directly alter the uptake, binding, or release of calcium from the sarcoplasmic reticulum vesicle preparation isolated from dog heart (29). Additionally, it did not inhibit the sodium–potassium ATPase isolated from dog kidney at reasonable concentrations. It did, however, specifically inhibit dog heart cAMP-phosphodiesterase, suggesting that an increase in intracellular cAMP may be responsible for the MDL 17,043-induced increase in cardiac contractility.

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