

# Intravenous prenalterol in acute and chronic heart failure.

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## ABSTRACT

The new inotropic agent prenalterol was administered intravenously in a canine model of acute ischemic heart failure and in patients with severe chronic heart failure. Experimental heart failure in anesthetized dogs was induced by two vessel coronary artery constriction and intravenous prenalterol (0.005-15  $\mu\text{g}/\text{kg}/\text{min}$ ) was compared to dobutamine (0.001-30  $\mu\text{g}/\text{kg}/\text{min}$ ) and saline. Significant dose-dependent increases in left ventricular  $\text{dP}/\text{dt}_{\text{max}}$ , cardiac output and non-ischemic zone contractile force and significant reductions in systemic vascular resistance were present during infusions of both inotropic agents. High dose dobutamine caused greater increases in mean arterial pressure and pressure rate product with a trend toward greater increases in heart rate. However, neither inotropic agent significantly improved ischemic zone contractile force. Prenalterol possessed a markedly longer hemodynamic half-life than dobutamine (3.0 hours compared to 1.7 minutes).

Nine patients with severe chronic heart failure (left ventricular ejection fraction mean $\pm$ SD 17 $\pm$ 5%, cardiac index 1.7 $\pm$ 0.4 l/min/m<sup>2</sup>) responded to intravenous prenalterol (1, 4, and 8 mg) with significant increases in cardiac index, left ventricular ejection fraction and left ventricular stroke work index. Left ventricular filling pressure, mean right atrial pressure and pulmonary arteriolar resistance were significantly reduced. No significant differences were present among peak responses to the three doses employed. An inverse correlation between basal heart rate and increase in left ventricular ejection fraction following prenalterol was noted.

The mechanisms by which prenalterol causes hemodynamic improvement appear to include a direct inotropic effect, a reduction in left ventricular outflow resistance and a reduction in left and right ventricular filling pressure (venodilating effect). The net result is an upward and leftward shift of the depressed ventricular function curve.

Both prenalterol and dobutamine were associated with sustained ventricular tachyarrhythmias in the experimental acute low output state and two digitalized patients with ischemic cardiomyopathy developed transient ventricular tachycardia after prenalterol administration. These findings indicated that adrenergic stimulants should be administered in severe ischemic states with careful monitoring.

## INTRODUCTION

New advances in the pharmacological therapy of low cardiac output states have included the introduction of vasodilator agents and the introduction of catecholamine inotropic agents dopamine and dobutamine. These inotropic agents, however, are restricted to parenteral administration and cardiac glycosides remain the only available oral inotropic agents for long-term therapy of heart failure. Prenalterol is a new orally and parenterally effective catecholamine-like inotropic agent with a chemical structure (Figure 1) similar to isoproterenol. Prenalterol has been shown to

cause relatively selective increases in myocardial contractility in normal experimental animals [1] and human volunteers [2, 3] with lesser effects on heart rate and blood pressure. Limited information, however, is available regarding its effects in low cardiac output states. In order to assess the efficacy of acute intravenous prenalterol administration in experimental and clinical heart failure and to compare its effects in the acute ischemic low output state with those of dobutamine, the following studies were undertaken in a canine model of acute heart failure and in patients with chronic severe heart failure.

## METHODS

### I. Experimental acute ischemic heart failure

Nineteen male mongrels weighing (mean $\pm$ SEM) 18.9 $\pm$ 0.7 kg (range 11.6 to 25 kg) were anesthetized with 0.5-0.8 ml/kg intravenous Dial-Urethane and mechanically ventilated on room air via endotracheal tube by Harvard respirator with a tidal volume of 15-25 ml/kg and a rate of 10-20 cycles/min. Respiratory settings were adjusted to maintain arterial pH, PO<sub>2</sub> and PCO<sub>2</sub> within normal limits. Arterial pressure was monitored by carotid artery cannulation and a continuous infusion of 30 ml/h, physiological saline was administered via the external jugular vein. Following left fifth intercostal space thoracotomy and formation of a pericardial cradle, the heart was instrumented as shown in Figure 2: Brodie-Walton open arch strain gauges were sutured into the myocardium of the right ventricular (RV) free wall in an area remote from subsequent coronary artery constriction and in the anterior left ventricular (LV) free wall in the distribution of the left anterior descending (LAD) coronary artery, which was subsequently rendered ischemic. Measurements of non-ischemic zone contractile force were obtained from the RV strain gauge and measurements of ischemic zone contractile force from the LV strain gauge. Triplicate thermodilution cardiac outputs were determined by Columbus Cardiac Output Computer using 2.0 ml room temperature saline injections in the right atrium with a pulmonary artery thermister. Left ventricular end-diastolic pressure (LVEDP) and rate of LV pressure change (LV dP/dt) were obtained from a Miller

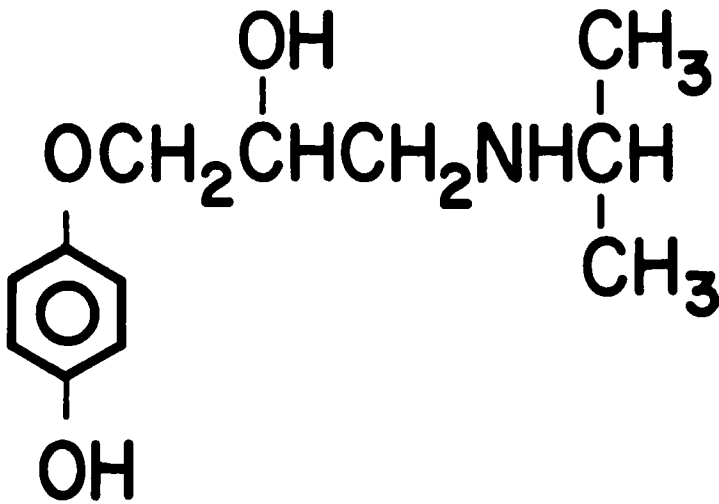


Figure 1. Chemical structure of prenalterol.

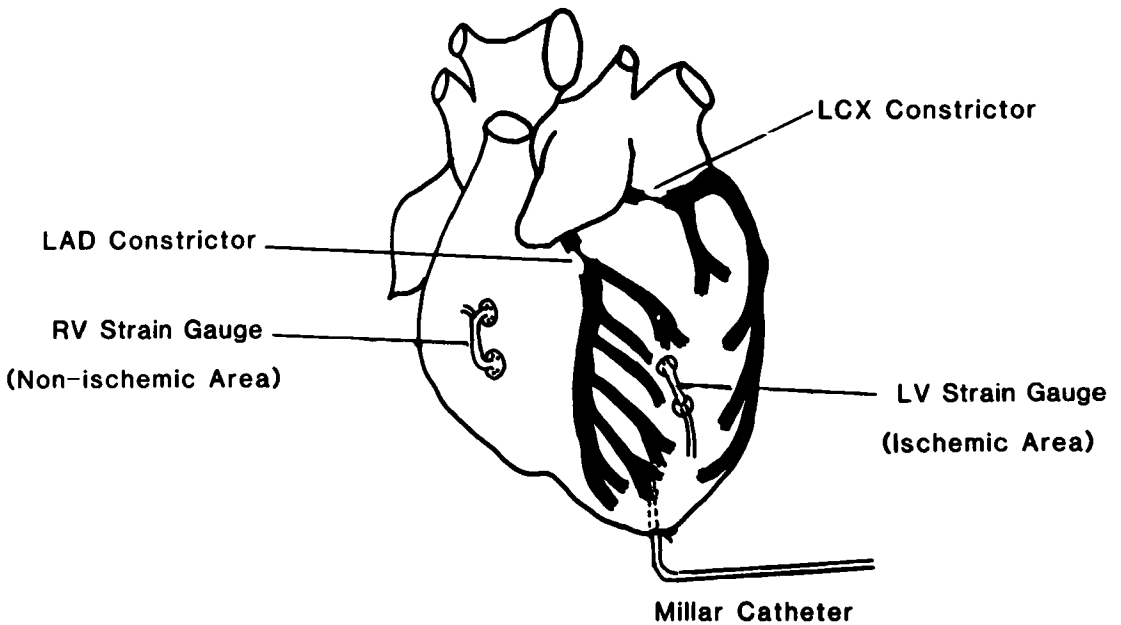


Figure 2. Schematic diagram of instrumentation for experimental ischemic low output state. Right atrial catheter and pulmonary artery thermistor for cardiac output determination are not illustrated.

Mikro-tip catheter in the LV apex. Lead II ECG was monitored throughout each experiment. Screw-type constrictors were placed around the left circumflex (LCX) and LAD coronary arteries for subsequent constriction. A Gross model 7 polygraph was used to record measurements.

An acute ischemic low output state was induced by progressive constriction of the LAD and LCX coronary arteries with the mechanical constrictors until cardiac output and maximum LV dP/dt (LV dP/dt<sub>max</sub>) diminished and LVEDP increased. Following baseline measurements in the ischemic low output state, intravenous prenalterol (dose range 0.005-15 µg/kg/min, n=7) or intravenous dobutamine (dose range 0.01-30 µg/kg/min, n=6) or comparable volumes of saline (n=6) were infused for 10-30 min without re-equilibration between doses.

Dose effect curves (Figures 3-10) are shown for the three groups. Values are expressed as mean±SEM. Statistical analysis for dose-response curve comparisons was performed by profile analysis for parallelism and analysis of changes within or between groups by paired or unpaired t-test. Analysis was performed by a computerized statistical program (MIDAS, University of Michigan Statistical Research Laboratory). A p-value of <0.05 was considered significant.

Arrhythmia analysis was performed by manual count of ectopic beats for the last five minutes of each infusion. Five animals successfully defibrillated after coronary artery constriction prior to drug administration are included.

## II. Chronic heart failure in patients

Nine patients with chronic, severe low output heart failure were studied. Age ranged from 48-70 years with mean±SD 59±7 years. Five patients were male and four were female. The cause of heart failure was ischemic in six patients, idiopathic in two patients and alcoholic in one patient. Each patient had symptoms of heart failure for at least three months prior to study; all patients except one were in New York Heart Association Functional Class III

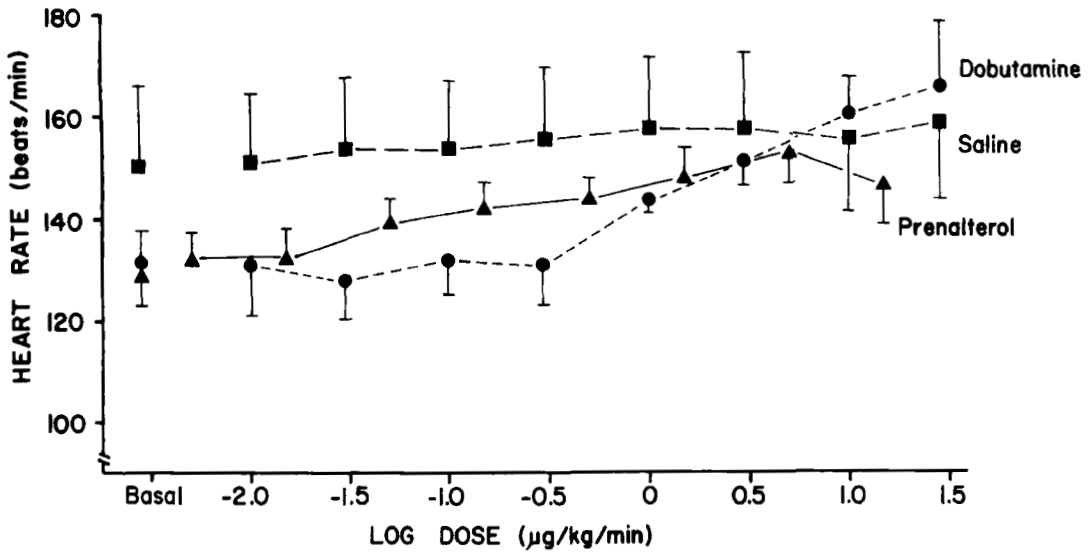


Figure 3. Effect of prenalterol and dobutamine on heart rate. Neither inotropic agent significantly increased heart rate compared to saline controls. Dobutamine tended to cause greater increases than prenalterol ( $p < 0.10$ ). (Reprinted with permission from *J Cardiovasc Pharmacol* 3:896-905, 1981.)

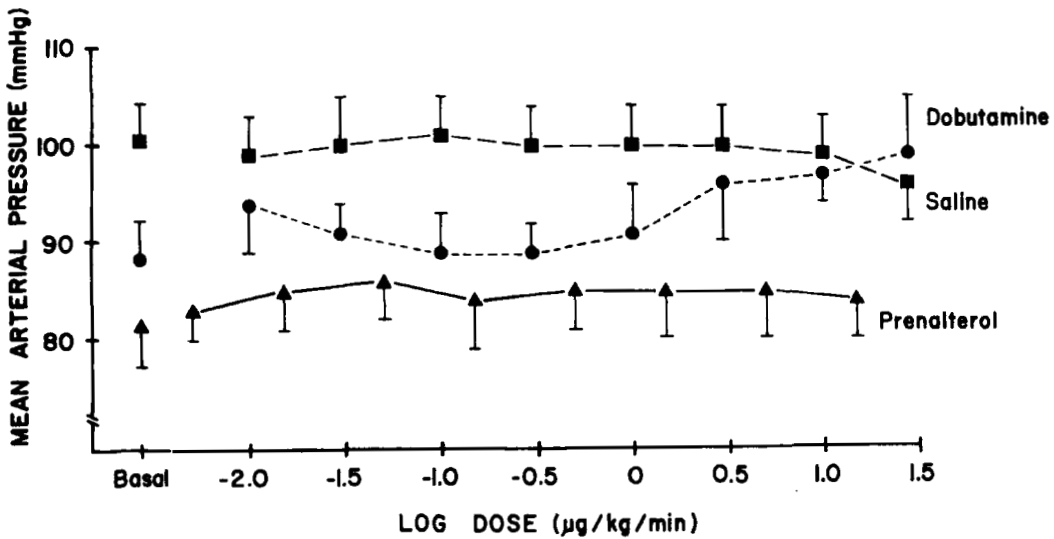


Figure 4. Effect of prenalterol and dobutamine on mean arterial pressure. Dobutamine caused significant elevations compared to saline controls ( $p < 0.02$ ); prenalterol caused no change. (Reprinted with permission from *J Cardiovasc Pharmacol* 3:896-905, 1981.)

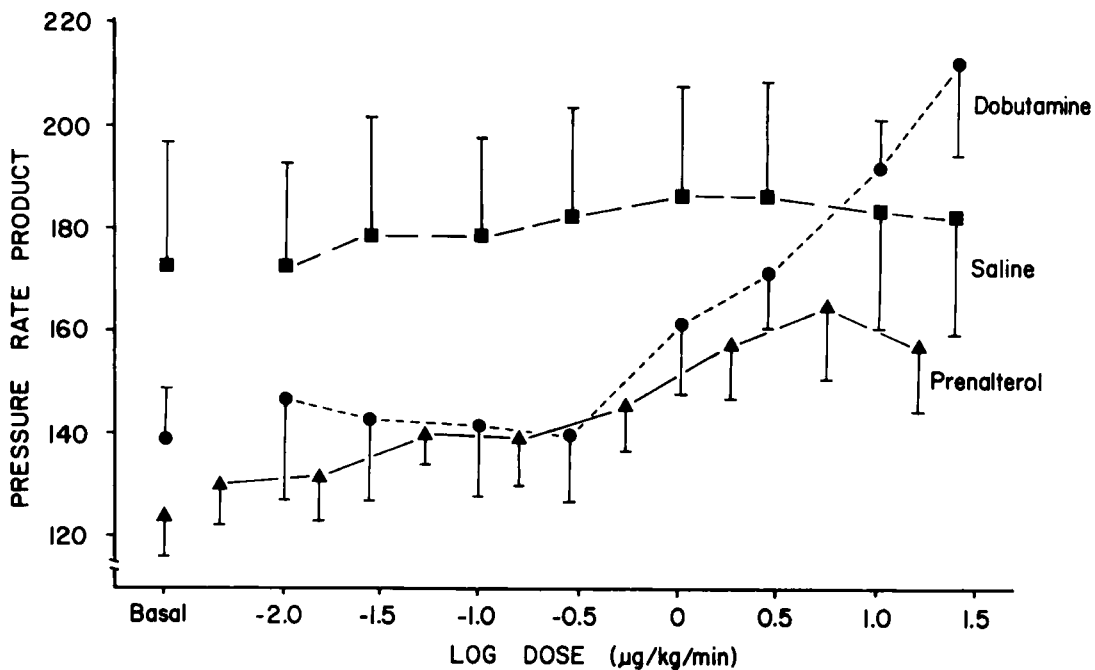


Figure 5. Effects of prenalterol and dobutamine on pressure rate product. Dobutamine caused significant elevations compared to saline controls ( $p < 0.03$ ) and prenalterol ( $p < 0.03$ ). No significant changes resulted from prenalterol compared to saline.

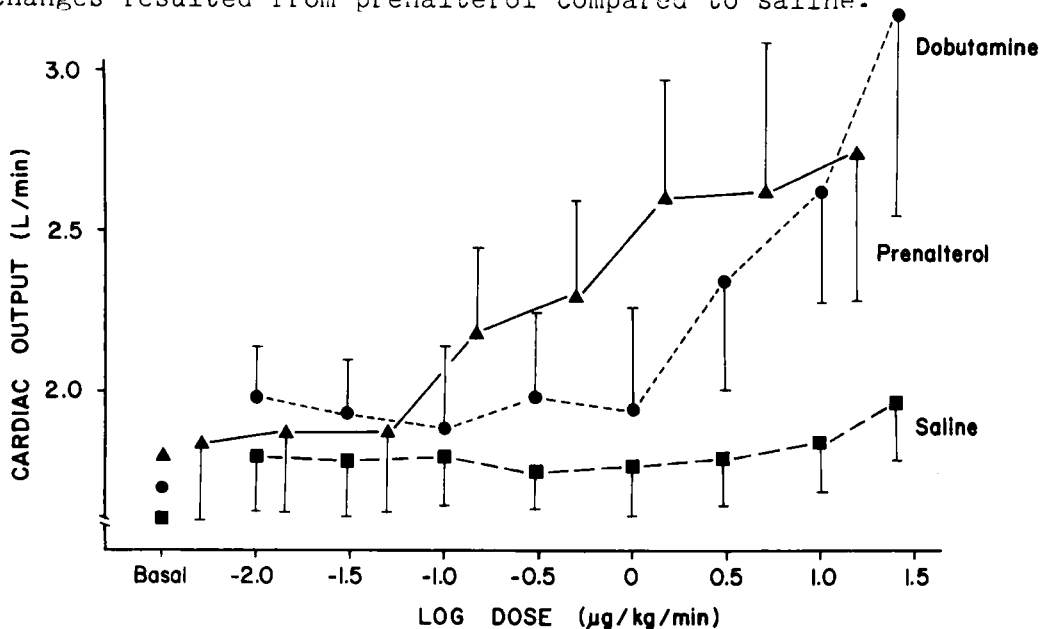


Figure 6. Effect of prenalterol and dobutamine on cardiac output. Compared to saline controls, cardiac output was significantly greater with both prenalterol ( $p < 0.02$ ) and dobutamine ( $p < 0.01$ ). At maximal dose, dobutamine caused a greater increase in cardiac output than prenalterol. (Reprinted with permission from *J Cardiovasc Pharmacol* 3:896-905, 1981.)

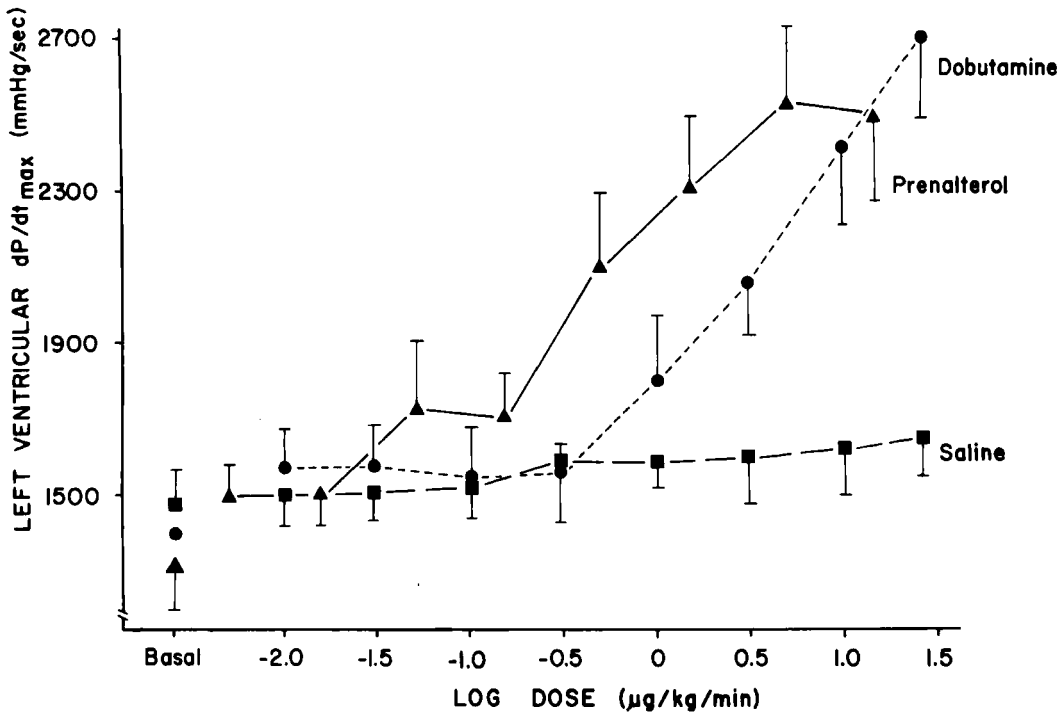


Figure 7. Effect of prenalterol and dobutamine on left ventricular  $dP/dt_{max}$ . Increases resulted with both prenalterol ( $p < 0.03$ ) and dobutamine ( $p < 0.001$ ) compared to saline controls. (Reprinted with permission from *J Cardiovasc Pharmacol* 3:896-905, 1981.)

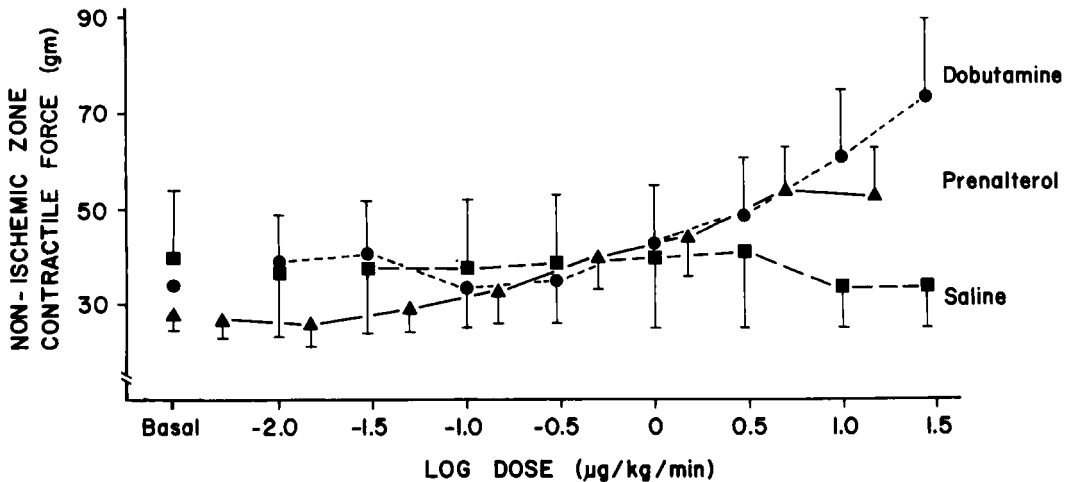


Figure 8. Effect of prenalterol and dobutamine on non-ischemic zone contractile force. Increases resulted with both prenalterol ( $p < 0.03$ ) and dobutamine ( $p < 0.005$ ) compared to saline controls. (Reprinted with permission from *J Cardiovasc Pharmacol* 3:896-905, 1981.)



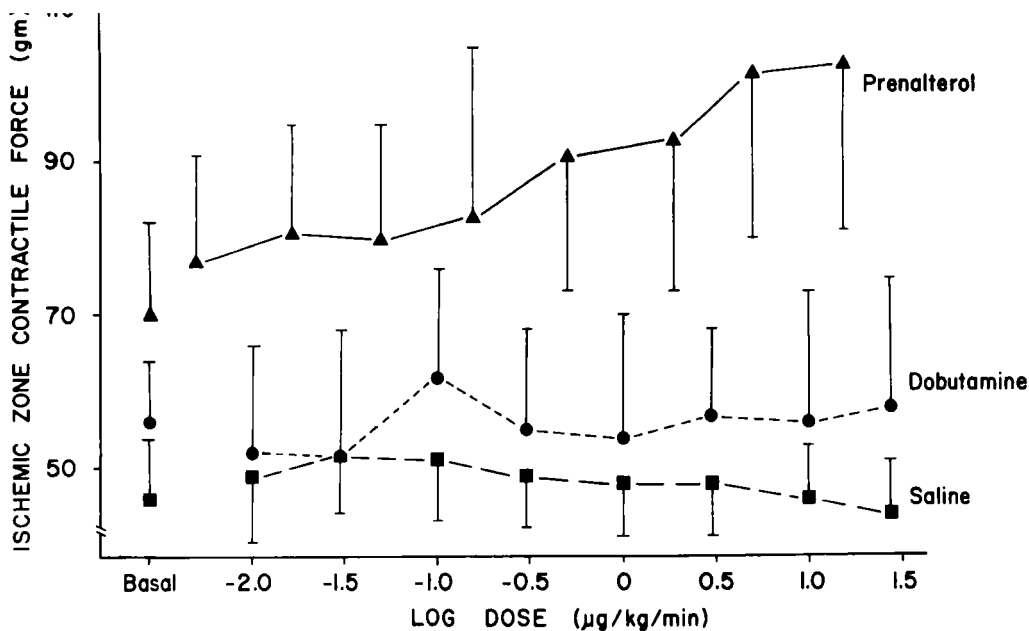


Figure 9. Effect of prenalterol and dobutamine on ischemic zone contractile force. No significant changes resulted after prenalterol ( $p > 0.25$ ) or dobutamine ( $p > 0.4$ ) compared to saline controls. (Reprinted with permission from *J Cardiovasc Pharmacol* 3:896-905, 1981.)

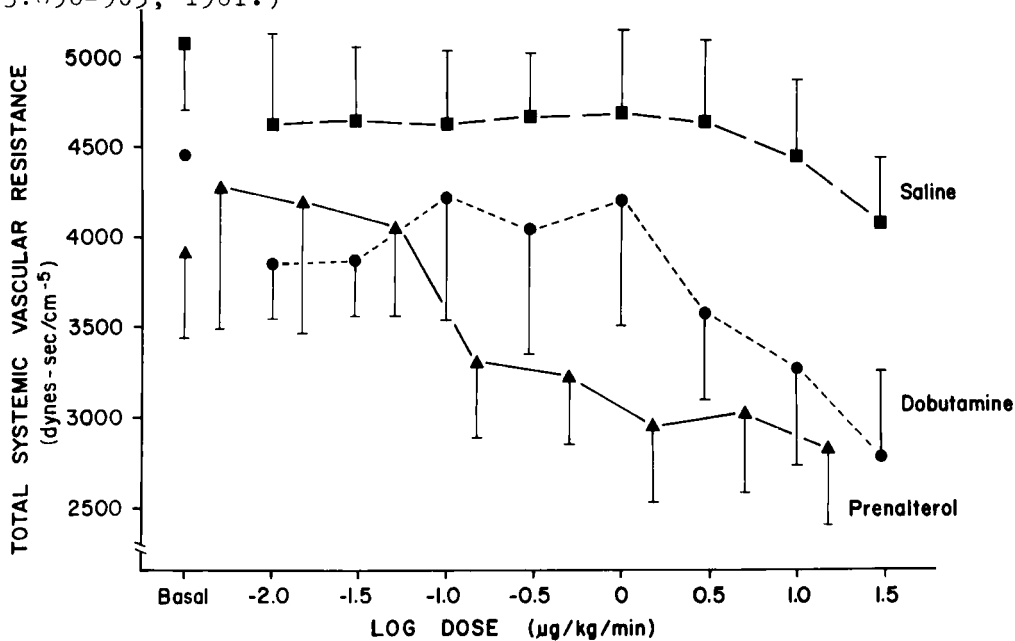
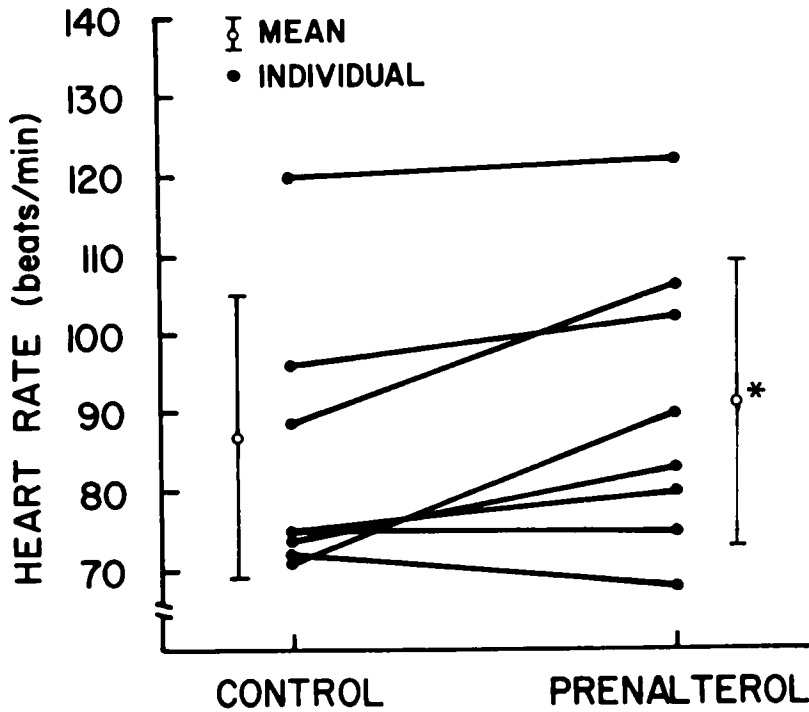


Figure 10. Effects of prenalterol and dobutamine on total systemic vascular resistance. A significant reduction occurred after prenalterol ( $p < 0.03$ ) compared to saline controls. Dobutamine caused a significant reduction in mean total systemic vascular resistance ( $p < 0.001$ ) compared to saline controls without changing profile parallelism significantly ( $p > 0.15$ ). (Reprinted with permission from *J Cardiovasc Pharmacol* 3:896-905, 1981.)

or IV, and the remaining patient was in Functional Class II. All patients had received chronic diuretic therapy and seven had received vasodilator therapy for persistent heart failure symptoms despite digitalis and diuretics. Five of the nine patients were chronically digitalized with oral digoxin in doses of 0.125 or 0.25 mg daily, with serum digoxin levels obtained within six days of study ranging from 0.26 to 1.05 ng/ml (mean 0.74 ng/ml). Patients were studied in the post-absorptive state at least 24 hours after discontinuation of all vasodilator therapy and at least four hours after administration of all other cardiovascular medications. Two patients received antiarrhythmic therapy (disopyramide 100 mg orally four times daily and quinidine sulfate 200 mg orally four times daily) at the time of the investigation.

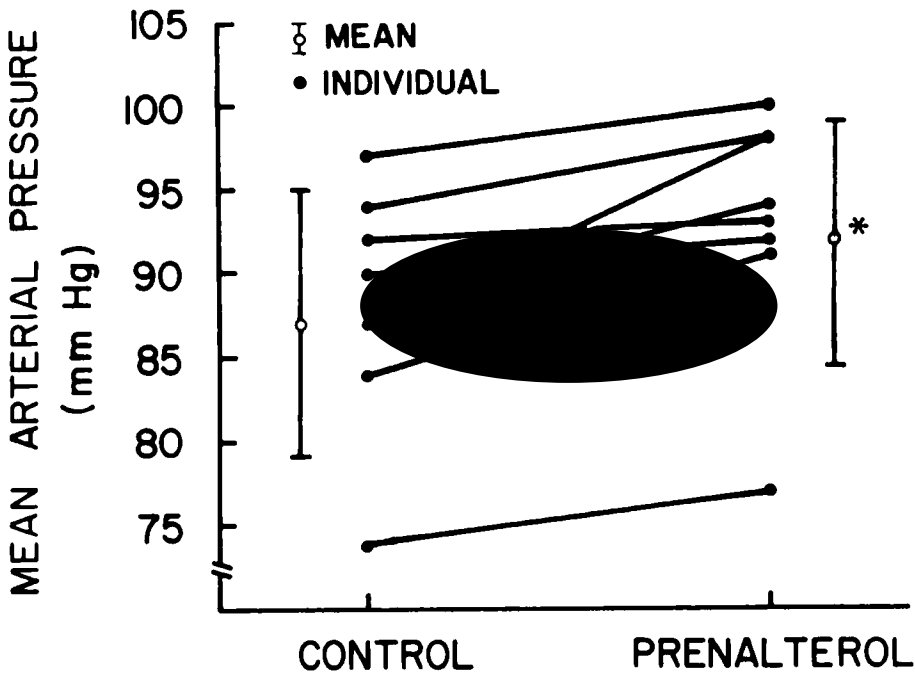
Hemodynamic data were obtained from a triple lumen thermodilution flow directed pulmonary artery catheter inserted through an antecubital vein and from a peripheral arterial catheter (7 patients) or blood pressure cuff (2 patients). In addition, left ventricular ejection fraction (LVEF) was obtained by radionuclide ventriculography employing 10-20 mCi of technetium 99m for in vivo red cell labelling. Equilibrium gated cardiac blood pool imaging was performed in the modified left anterior oblique position with a gamma camera. All studies were obtained in the supine position. Directly measured hemodynamic parameters included systemic arterial pressure, right atrial pressure, pulmonary artery pressure, pulmonary artery wedge pressure used as an estimate of left ventricular filling pressure (LVFP), cardiac output (thermodilution technique in 8 patients, indocyanine green dye curves in 1 patient), and radionuclide LVEF. Standard hemodynamic formulae were used for derived parameters. An Electronics for Medicine VR12 recorder was used to record measurements.

Intravenous prenalterol was administered in doses of 1, 4, and 8 mg at 30 min intervals by infusion pump into a peripheral vein and hemodynamic measurements were obtained at 10 min and 25 min after 1 and 4 mg and 10, 25, and 55 min after 8 mg. Peak hemodynamic effects are presented in Figures 11-18.



\*p < .05

Figure 11. Effect of prenalterol on heart rate in patients. A slight but significant change ( $p < 0.05$ ) occurred.



\*p < .01

Figure 12. Effect of prenalterol on mean arterial pressure in patients. Significant elevation occurred ( $p < 0.01$ ).

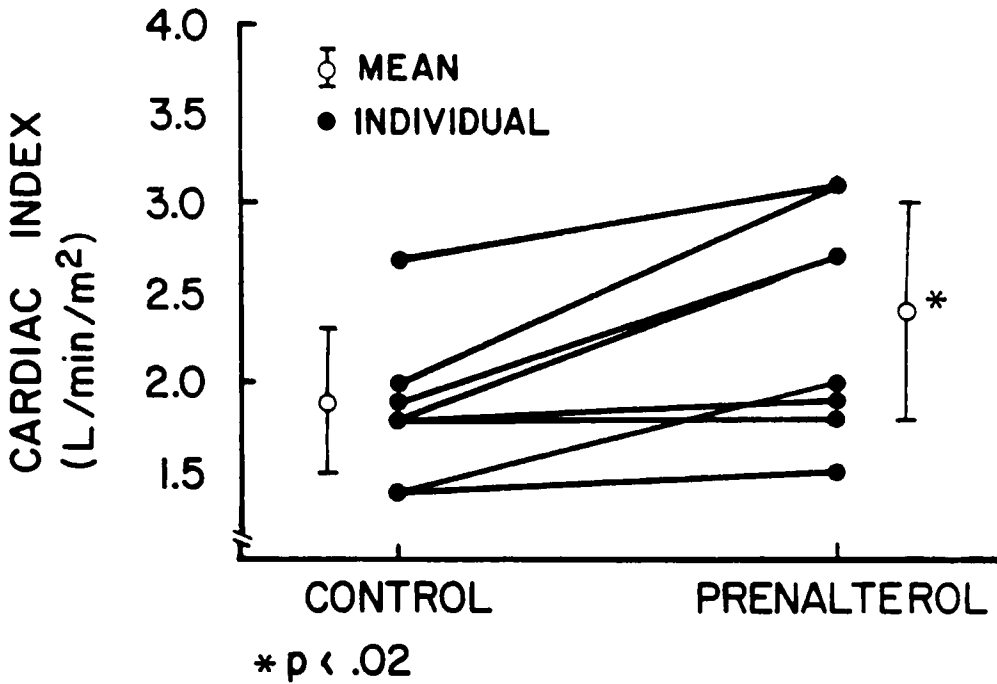


Figure 13. Effect of prenalterol on cardiac index in patients. A significant increase ( $p < 0.02$ ) occurred.

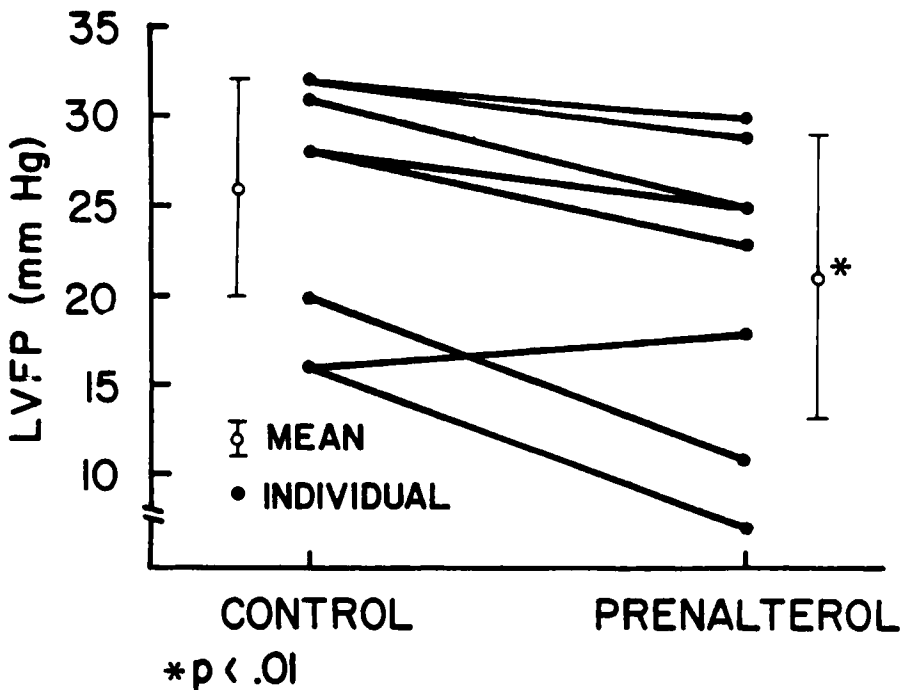


Figure 14. Effect of prenalterol on left ventricular filling pressure (LVFP) in patients. A significant reduction ( $p < 0.01$ ) occurred.

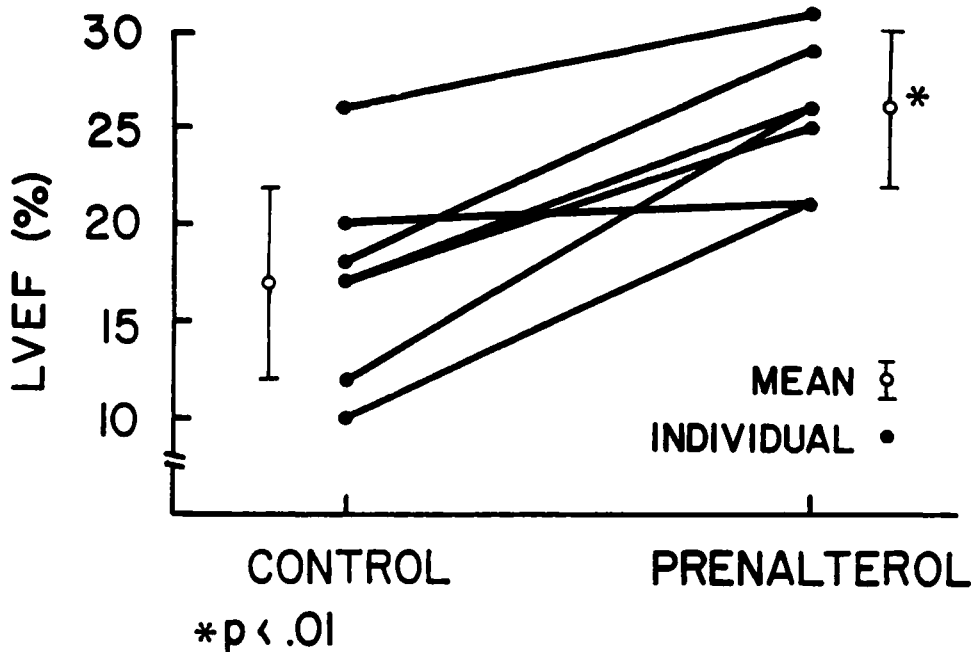


Figure 15. Effect of prenalterol on left ventricular ejection fraction (LVEF) in patients. A significant increase ( $p < 0.01$ ) occurred. In one patient there was no response.

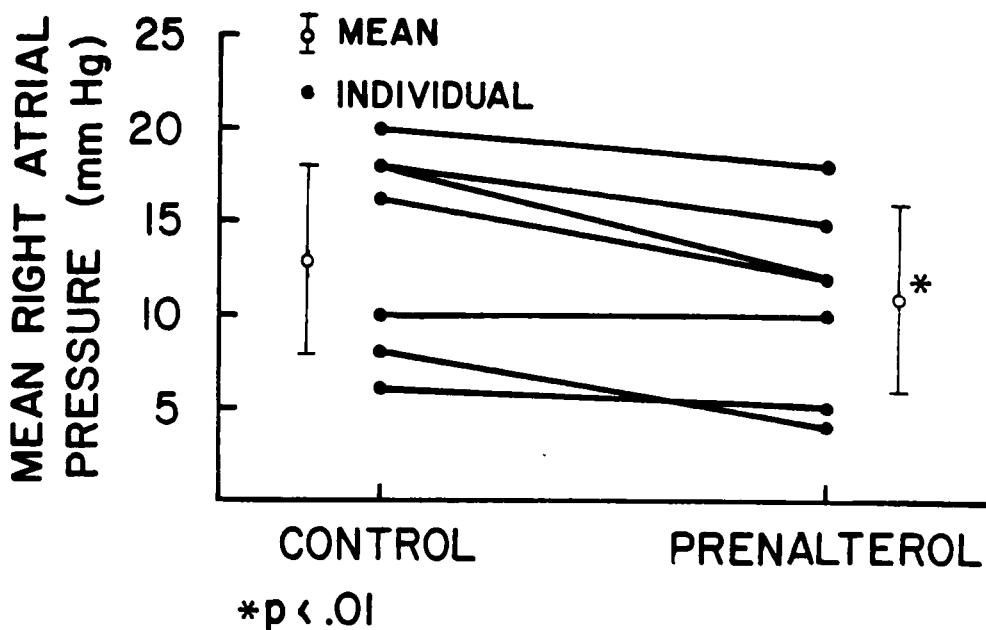


Figure 16. Effect of prenalterol on mean right atrial pressure in patients. A significant reduction ( $p < 0.01$ ) occurred.

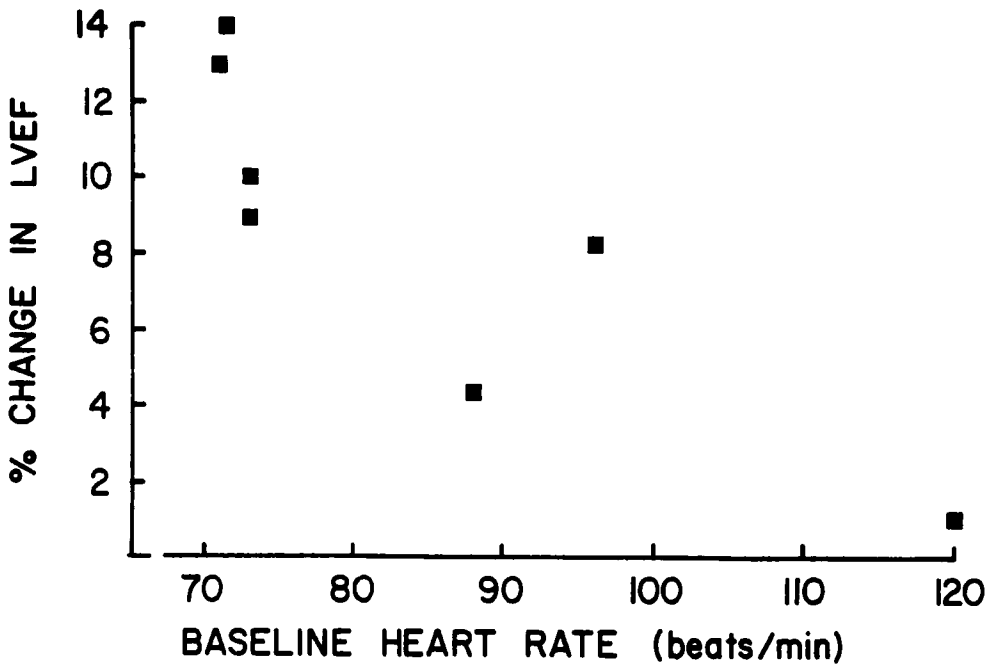


Figure 17. Correlation in patients between increase in left ventricular ejection fraction (LVEF) with prenalterol and baseline heart rate prior to drug administration. A significant inverse correlation was present ( $r = -0.89$ ,  $p < 0.01$ ).

**Prenalterol**

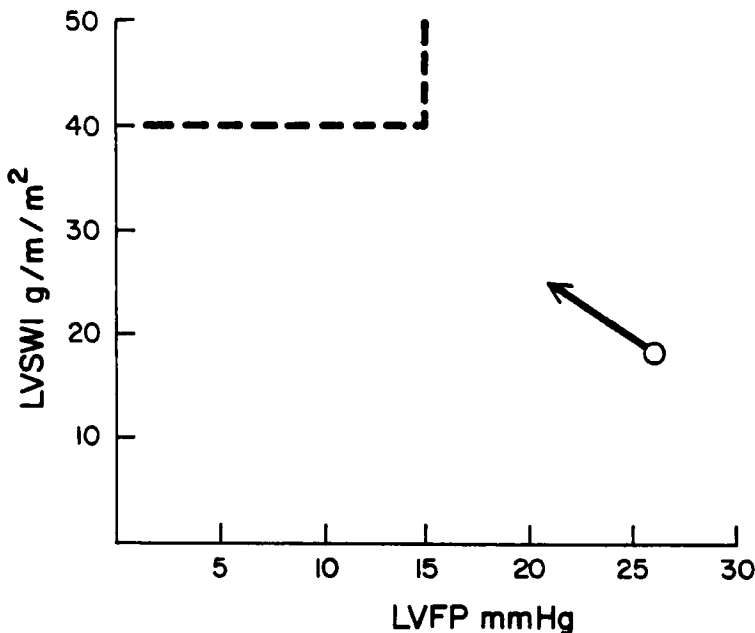


Figure 18. Net effect of prenalterol on left ventricular stroke work index (LVSWI) plotted against left ventricular filling pressure (LVFP) in patients. Values represent mean before (open circle) and after (arrow) prenalterol. Normal values are represented by dotted lines.

Arrhythmia analysis was obtained from continuous ECG (Holter) monitoring for at least 8 hours prior to prenalterol administration, as well as during and several hours after drug administration.

Statistical analysis was performed by t-test for paired data, comparing control measurements and peak effect. Values are expressed as mean±SD.

## RESULTS

### I. Experimental acute ischemic heart failure

An acute ischemic low output state was present after two vessel coronary artery constriction, with significant decreases in cardiac output (from  $2.3 \pm 0.2$  to  $1.7 \pm 0.1$  l/min), LV  $dP/dt_{\max}$  (from  $1654 \pm 58$  to  $1395 \pm 60$  mm Hg/s), ischemic zone contractile force (from  $96 \pm 7$  to  $58 \pm 7$  g), non-ischemic zone contractile force (from  $38 \pm 5$  to  $34 \pm 5$  g) and mean arterial pressure (from  $95 \pm 4$  to  $90 \pm 3$  mm Hg) and significant increases in LVEDP (from  $7 \pm 1$  to  $17 \pm 2$  mm Hg) and total peripheral resistance (from  $3461 \pm 234$  to  $4470 \pm 300$  dyn·s·cm<sup>-5</sup>).

Dose-response curve analysis demonstrates that both intravenous prenalterol and dobutamine cause significant dose-dependent increases in cardiac output (Figure 6), LV  $dP/dt_{\max}$  (Figure 7) and non-ischemic zone contractile force (Figure 8) compared to saline controls, as well as a significant dose-dependent decrease in systemic vascular resistance (Figure 10). However, ischemic zone contractile force did not change significantly after either inotropic agent compared to saline controls (Figure 9). Increases in mean arterial pressure were significantly greater during dobutamine infusion (but not prenalterol infusion) than in control animals (Figure 4). Dobutamine tended to cause greater increases in heart rate at higher doses than saline (Figure 3) but this difference did not achieve statistical significance. Prenalterol caused no significant changes in heart rate. The greater increase in heart rate associated with dobutamine, however, largely accounts for the significantly higher cardiac output during high dose

dobutamine infusion, as stroke volume was not different in the two groups of animals treated with inotropic agents ( $p > 0.22$ , not graphed). Pressure rate product, an index of myocardial oxygen consumption [4], was calculated by multiplying systolic arterial pressure by heart rate, divided by 100. As shown in Figure 5, dobutamine caused significantly greater increases than either saline or prenalterol. LVEDP did not change significantly after either inotropic agent.

Arrhythmia analysis revealed that neither dobutamine nor prenalterol increased the number of isolated ectopic beats. Both inotropic agents, however, caused sustained ventricular tachyarrhythmias. One animal suffered ventricular fibrillation during 5  $\mu\text{g}/\text{kg}/\text{min}$  prenalterol infusion, and one animal developed ventricular tachycardia during 3  $\mu\text{g}/\text{kg}/\text{min}$  dobutamine infusion. Saline treated animals had no ventricular tachyarrhythmias.

The duration of the hemodynamic effect was substantially longer after discontinuation of prenalterol than dobutamine, with hemodynamic half-lives (change in non-ischemic zone contractile force) of 3 hours and 1.7 min respectively.

## II. Chronic heart failure in patients

Baseline hemodynamic measurements prior to drug administration confirmed severe heart failure in all patients (Table I, Figures 11-16). Left ventricular ejection fraction ranged from 10-26% with a mean of  $17 \pm 5\%$ ; cardiac index ranged from 1.4 to 2.7  $\text{l}/\text{min}/\text{m}^2$  with a mean of  $1.7 \pm 0.4 \text{ l}/\text{min}/\text{m}^2$ ; left ventricular stroke work index ranged from 12-28  $\text{g m}/\text{m}^2$  with a mean of  $18 \pm 6 \text{ g m}/\text{m}^2$ ; and left ventricular filling pressure ranged from 16-32 mm Hg (mean  $26 \pm 6 \text{ mm Hg}$ ). Elevated systemic arteriolar resistance (mean  $1872 \pm 493 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ ) and pulmonary arteriolar resistance (mean  $338 \pm 129 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ ) were also present.

Peak hemodynamic effects after prenalterol administration are shown in Figures 11-16 and Table I. Significant increases in left ventricular ejection fraction (to  $26 \pm 4\%$ ), cardiac index (to  $2.4 \pm 0.6 \text{ l}/\text{min}/\text{m}^2$ ) and left ventricular stroke work index (to  $25 \text{ g}\cdot\text{m}/\text{m}^2$ )



TABLE I. Characteristics of Patients and Response to Prenalterol

Pt #	Age	Sex	Diagnosis	Heart Rate (beats/min)		Systolic Arterial Pressure (mmHg)		Mean Arterial Pressure (mmHg)	
				Baseline	Maximum	Baseline	Maximum	Baseline	Maximum
1	63	M	Ischemic	75	80	116	120	90	92
2	53	F	Alcoholic	74	83	110	130	94	98
3	64	F	Ischemic	39	106	135	140	84	91
4	56	F	Idiopathic	120	122	118	130	87	98
5*	60	F	Ischemic	110	-	102	-	74	-
6	48	M	Idiopathic	71	90	128	135	92	93
7	64	M	Ischemic	96	102	135	140	97	100
8	55	M	Ischemic	75	75	108	120	88	94
9	70	M	Ischemic	72	68	104	107	74	77
<b>Mean ± SD</b>	<b>59 ± 7</b>			<b>87 ± 18</b>	<b>91 ± 18</b>	<b>117 ± 13</b>	<b>128 ± 11</b>	<b>87 ± 8</b>	<b>92 ± 7</b>
<b>P vs Baseline</b>					<b>0.05</b>		<b>0.004</b>		<b>0.007</b>

\*Pt #5 experienced ventricular tachycardia after 1 mg infusion and was excluded from further analysis.

Pt#	Diastolic Arterial Pressure (mmHg)		LVEF (%)		LVSWI (gm·m/m <sup>2</sup> )		Cardiac Index (L/min/m <sup>2</sup> )	
	Baseline	Maximum	Baseline	Maximum	Baseline	Maximum	Baseline	Maximum
1	78	78	17	26	21	28	1.9	2.7
2	86	88	**	**	22	21	1.8	1.8
3	62	67	26	31	28	30	2.7	3.1
4	71	85	20	21	12	17	1.8	1.9
5	62	-	12	-	12	-	2.0	-
6	78	75	18	29	27	40	2.0	3.2
7	78	82	17	25	16	22	1.8	2.7
8	75	76	10	21	17	28	1.4	2.0
9	60	65	12	26	12	15	1.4	1.5
<b>Mean ± SD</b>	<b>72 ± 9</b>	<b>77 ± 8</b>	<b>17 ± 5</b>	<b>26 ± 4</b>	<b>18 ± 6</b>	<b>25 ± 8</b>	<b>1.9 ± 0.4</b>	<b>2.4 ± 0.6</b>
<b>P vs Baseline</b>		<b>0.09</b>		<b>0.002</b>		<b>0.008</b>		<b>0.015</b>

\*\*Technically unsatisfactory radionuclide cardiac blood pool scan

LVEF = Left Ventricular Ejection Fraction

LVSWI = Left Ventricular Stroke Work Index

Pt #	LVFP (mmHg)		PAP (mmHg)		Systemic Arterial Resistance (dynes·sec·cm <sup>-5</sup> )		Mean Right Atrial Pressure (mmHg)	
	Baseline	Minimum	Baseline	Minimum	Baseline	Minimum	Baseline	Minimum
1	31	25	54	41	-	-	10	NA
2	28	25	42	40	2229	2289	16	12
3	16	18	34	36	1460	1280	10	10
4	28	23	34	30	1786	2075	18	15
5	26	-	34	-	1449	-	12	-
6	20	11	31	22	1446	903	6	5
7	32	30	51	49	2133	1413	18	12
8	16	7	26	17	2802	2071	8	4
9	32	29	45	40	1780	1692	20	18
<b>Mean ± SD</b>	<b>26 ± 6</b>	<b>21 ± 8</b>	<b>39 ± 9</b>	<b>34 ± 11</b>	<b>1872 ± 493</b>	<b>1674 ± 502</b>	<b>13 ± 5</b>	<b>11 ± 5</b>
<b>P vs Baseline</b>		<b>0.01</b>		<b>0.02</b>		<b>0.11</b>		<b>0.01</b>

LVFP = Left Ventricular Filling Pressure

PAP = Mean Pulmonary Artery Pressure

NA = Not Available

occurred with significant decreases in left ventricular filling pressure (to  $21 \pm 8$  mm Hg), pulmonary arteriolar resistance (to  $215 \pm 85$  dyn $\cdot$ s $\cdot$ cm $^{-5}$ ) and mean right atrial pressure (to  $11 \pm 5$  mm Hg). Systemic arteriolar resistance declined (to  $1674 \pm 502$  dyn $\cdot$ s $\cdot$ cm $^{-5}$ ) without achieving significance ( $p > 0.11$ ). Heart rate increased significantly (from  $87 \pm 18$  to  $91 \pm 18$  beats/min) as did mean arterial pressure (from  $87 \pm 8$  to  $92 \pm 7$  mm Hg).

Variable hemodynamic responses were noted (Table I, Figures 11-16) and no significant differences among peak effects at different doses were present. Correlation between response (as measured by increase in LVEF) with several baseline parameters revealed that basal heart rate was inversely correlated with increase in ejection fraction following prenalterol ( $r = -0.89$ ,  $p < 0.01$ , Figure 17).

Holter monitor analysis demonstrated that two patients developed increased numbers of ectopic ventricular complexes during prenalterol administration and two other patients developed unsustained ventricular tachycardia. Both of the latter patients had ischemic cardiomyopathy treated with digoxin at the time of study without antiarrhythmic therapy.

No subjective adverse effects were noted and no electrocardiographic evidence of worsening ischemia was seen.

## DISCUSSION

The present studies demonstrate that intravenous prenalterol causes significant hemodynamic improvement in both acute and chronic low output states, and that its effects are comparable to those of dobutamine in a canine model of acute ischemic heart failure. Previous investigations of prenalterol indicate that its inotropic action is due to myocardial  $\beta_1$ -receptor stimulation [1, 5], although the drug binds non-selectively to other  $\beta$ -receptors [5, 6] and it possesses  $\beta_2$ -adrenergic antagonistic activity [6, 7]. Isolated tissue preparation studies have demonstrated that prenalterol has less intrinsic  $\beta$ -agonist effect than isoproterenol [5, 6]. Thus, prenalterol could be classified as a partial  $\beta$ -agonist with relatively selective myocardial  $\beta_1$ -stimulating

properties and inherent  $\beta$ -adrenergic antagonistic effect in some other tissues. It is of interest that prenalterol does not elevate myocardial adenylate cyclase levels [5], as would be anticipated with catecholamines. This fact, in addition to its non-catecholamine structure and its prolonged hemodynamic effect raises the possibility that prenalterol's mechanism of action and route of metabolism may, in part, differ from those of catecholamine inotropic agents.

Results from this study are in agreement with previous investigations of prenalterol in normal experimental animals [1] and normal volunteers [2, 3], as well as patients with ventricular dysfunction [8, 9]. Hemodynamic improvement appears to result from both inotropic stimulation and a reduction in left ventricular outflow resistance (afterload reduction). Although difficulties exist in distinguishing afterload reduction from inotropic stimulation in the intact subject, a predominant inotropic effect of prenalterol is suggested by [1] its relatively selective  $\beta_1$ -stimulating effect with  $\beta_2$ -blocking activity consistent with myocardial ( $\beta_1$ ) stimulation but little or no peripheral arteriolar ( $\beta_2$ ) stimulation and [2] an increase in mean systemic arterial pressure despite a decrease in systemic arteriolar resistance (Table I) in contrast to the decline in blood pressure or minimal blood pressure effect associated with vasodilators [10]. It is possible that the decrease in peripheral vascular resistance caused by prenalterol is in part reflexively mediated by baroreceptor stimulation due to blood pressure elevation. The net hemodynamic effect of prenalterol is a shift in the ventricular function curve upward and to the left (Figure 18), as noted with other inotropic agents.

In addition to its positive inotropic and afterload reducing properties, prenalterol appears to possess a preload reducing (venodilating) effect, as evidenced by a reduction in left ventricular filling pressure (Figure 14) and a reduction in mean right atrial pressure (Figure 16) in patients with heart failure. Similar results have been reported following dobutamine administration [10, 11]. The failure of dobutamine and prenalterol to lower left ventricular end-diastolic pressure compared to saline

controls in the present animal investigation may be related to differences between the acute ischemic canine model of heart failure and the more chronic, stable left ventricular failure present in the patients studied.

Also of interest is prenalterol's ability to reduce elevated pulmonary vascular resistance in heart failure (Table I), similar to the effect of dobutamine as reported by Mikulic et al. [10]. This may be an additional contributing factor to the patients' hemodynamic improvement.

In the canine model of acute ischemic heart failure prenalterol and dobutamine caused similar increases in LV  $dP/dt_{max}$  and non-ischemic zone contractile force and similar reductions in systemic vascular resistance. Differences existed, however, in prenalterol's markedly longer duration of action and the greater increases in cardiac output, mean arterial pressure and pressure rate product associated with dobutamine.

Prenalterol's longer duration of action represents a potential advantage over dobutamine if sustained inotropic effect after discontinuation of infusion is desirable, but it could be disadvantageous in the presence of an adverse reaction. The greater cardiac output associated with high doses of dobutamine may be an advantage relative to prenalterol, but it is primarily due to greater increases in heart rate and is associated with significantly greater increases in pressure rate product indicative of higher myocardial oxygen demand, a potentially deleterious effect in acute ischemia. A possible explanation for this difference in pressure rate product changes is the partial  $\beta$ -agonistic property of prenalterol, which may limit heart rate and blood pressure increases at higher doses.

The extent of ischemic injury following prenalterol and dobutamine was not assessed in this animal study, but previous investigations with dobutamine indicate that it is not associated with increased infarct size in either experimental [12] or clinical [13] myocardial infarction. Because prenalterol causes less blood pressure and heart rate increase than dobutamine, it is even less

likely to be associated with increased ischemic damage.

The administration of both inotropic agents was associated with ventricular arrhythmias in the acute ischemic canine model and two prenalterol treated patients with ischemic cardiomyopathy developed ventricular tachycardia. While arrhythmias due to catheterization or ischemia per se cannot be excluded, their occurrence during drug administration and the absence of sustained rhythm disturbances in saline control animals suggest a cause and effect relationship between dobutamine and prenalterol administration and ventricular arrhythmias. This finding is consistent with prior experience with adrenergic inotropic agents [14]. Both prenalterol treated patients with ventricular tachycardia were chronically digitalized, raising the possibility that the combination of digoxin and adrenergic stimulation in the presence of severe ischemic heart disease may induce arrhythmias.

The considerable variation in response to prenalterol and the lack of significant differences among peak hemodynamic responses to varying doses in the patient study may be related to the drug's intrinsic  $\beta$ -adrenergic blocking effect, which could inhibit further response at higher doses. This may also account for the lower plateau compared to dobutamine in dose-response curves noted in the animal study (Figures 5-7). The inverse correlation between baseline heart rate and increase in left ventricular ejection fraction with prenalterol (Figure 17) may also explain in part the variability of patient response, and suggests that increased resting sympathetic tone (as manifested by tachycardia) may limit the response to further stimulation by adrenergic inotropic agents.

In conclusion, intravenous prenalterol results in hemodynamic improvement in patients with severe chronic heart failure and in a canine model of an acute ischemic low output state. The drug's hemodynamic effects are equivalent to those of dobutamine in the canine model except for prenalterol's longer duration of action and greater increases in heart rate and blood pressure at high dose dobutamine, resulting in higher pressure rate product and cardiac output. The primary mechanisms of prenalterol's beneficial hemodynamic effect appear to be an increase in contractile force,

greater in non-ischemic than in severely ischemic tissue, and a reduction of systemic vascular resistance. Reductions in pulmonary vascular resistance and systemic venous pressure may also contribute to its beneficial effect. However, ventricular arrhythmias may be associated with prenalterol, as with other inotropic stimulants, and the drug should be administered with careful electrocardiographic monitoring.

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