Hemodynamic effects of intravenous butopamine in congestive heart failure

Butopamine is chemically similar to dobutamine but, unlike dobutamine, it is not a catecholamine. Preclinical studies on dogs show that butopamine is inotropic intravenously and orally. We gave butopamine intravenously to eight patients with congestive heart failure using a progressive dose-response protocol ranging from 0.02 to 0.17 mcg/kg/min. The mean cardiac index and stroke volume index increased at doses ≥ 0.06 mcg/kg/min; there was also an increase in heart rate at ≥0.06 mcg/kg/min. At ≥0.08 mcg/kg/min the augmented stroke volume tended to plateau so that additional increases in the cardiac index were secondary to the elevated heart rate. Improved ventricular performance, measured by systolic time intervals, left ventricular stroke work index, and the calculated mean rate of left ventricular pressure development during isovolumetric contraction ($\Delta P/\Delta t$/PCWP), was noted at ≥0.06 mcg/kg/min. Systemic systolic blood pressure increased at ≥0.04 mcg/kg/min but diastolic and mean arterial pressures and pulmonary artery and pulmonary capillary wedge pressures did not change. The progressive increase in cardiac output was accompanied by a reduction in pulmonary and systemic vascular resistances. Although mean premature ventricular contractions per minute did not change, two patients experienced a substantial increase in ventricular ectopy at 0.10 and 0.12 mcg/kg/min. Butopamine induces a positive inotropic response in patients with congestive heart failure but for equal increments in cardiac output, butopamine increases heart rate more than dobutamine.

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Catecholamines (dopamine, norepinephrine, epinephrine, isoproterenol) are not generally used to treat most patients suffering from low-output heart failure because there is little separation between the dose that improves cardiac contractility and that causing either tachycardia or blood pressure changes. Furthermore, enzymatic inactivation by either catechol-*O*-methyltransferase or monoamine oxidase is so rapid that catecholamines must be given by intravenous infusion to maintain effect. Tuttle and Mills[11] systematically modified the catecholamine molecule; their efforts resulted in the development of a relatively safe and effec-

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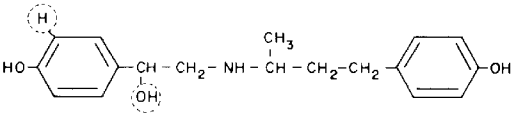
tive catecholamine, dobutamine. The selective preference of dobutamine for ventricular beta-1 receptors results in improvement in ventricular performance and cardiac output with minimal changes in heart rate and systemic blood pressure.[2-4, 6, 8, 11] As with other catecholamines, dobutamine is rapidly degraded by catechol-*O*-methyltransferase, so it must also be given intravenously to maintain an adequate blood level and pharmacodynamic effect. To overcome this, Tuttle et al.* recently modified the dobutamine molecule to produce butopamine, which differs from dobutamine only in the location of one hydroxyl group (Fig. 1). This shift renders butopamine refractory to the action of catechol-*O*-methyltransferase and makes it suitable for oral administration. Initial animal studies† indicate that the hemodynamic effects of butopamine are similar to those of dobutamine and that butopamine appears to be effective orally. We examined the hemodynamic effects of intravenous butopamine in patients with congestive heart failure and compared these effects with those of dobutamine and dopamine in a comparable group of patients.[7]

Methods

Our subjects were eight patients with moderately severe to severe congestive heart failure. Mean age was 55 yr (range, 30 to 66 yr); five were male and three, female. All patients underwent a diagnostic cardiac catheterization within a month of study. Each patient had a form of cardiomyopathy (five idiopathic, one familial, one after ostium primum repair, and one chronic valvular disease). None of the patients had occlusive coronary atherosclerosis. Five patients were classified as functional class IV and three as functional class III (New York Heart Association). One patient had atrial fibrillation. Two patients had demand-mode ventricular pacemakers.

Seven patients were on a digitalis preparation (daily oral digitoxin dose of 0.1 mg in two patients, digoxin 0.25 mg in two, 0.125 mg in two, and 0.125 mg every other day in one); the digitalis was continued throughout the experiment. None of the patients took antiarrhythmics. All vasodilators were discontinued at least 72 hr before experiments.

BUTOPAMINE



DOBUTAMINE

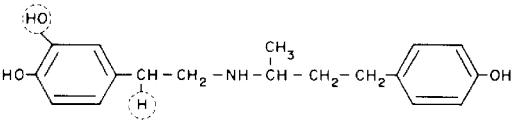


Fig. 1. Structure of butopamine and dobutamine.

Procedures and measurements. The experiment was divided into control, infusion, and postinfusion periods. The control period lasted 1.0 hr and baseline data were collected three times at 20-min intervals. Patients who did not demonstrate a coefficient of variance of less than 10% in their control cardiac indices (CIs) and pulmonary capillary wedge pressures (PCWPs) were excluded. The infusion period lasted 6 to 7 hr and consisted of a cumulative dose-response format. The intravenous infusions were performed with a calibrated Harvard pump. Successive infusion doses of 0.02, 0.04, 0.06, 0.08, 0.10, 0.12, and 0.17 mcg/kg/min were administered; each dose was administered for 1.0 hr. Experiments were performed 20, 40, and 60 min after the start of each dose increment of butopamine. The infusion was terminated if heart rate exceeded the control by 30%, or if premature ventricular contractions (PVCs) exceeded 15 per minute. All eight patients received an infusion of 0.08 mcg/kg/min and seven patients received doses of 0.10 and 0.12 mcg/kg/min. Only four patients received as much as 0.17 mcg/kg/min. The postinfusion period consisted of studies performed at 30 min and 1, 2, and 12 hr after the infusion.

On the day before the experiment, a flow directed triple-lumen thermodilution Swan-Ganz catheter was positioned in the pulmonary artery. This catheter provided the pulmonary arterial pressures (systolic, diastolic, and mean), PCWP (or pulmonary arterial occlusive pressure), and cardiac output (thermodilution technique[5]). Pressures were measured by Electronics for Medicine M2101 pressure amplification units. The cardiac outputs were computed with an In-

*Tuttle RR et al: Unpublished data.

†Tuttle RR: Unpublished data.

Table IA. *Effects of butopamine on hemodynamic and noninvasive measurement parameters in congestive heart failure ($\bar{x} \pm SD$)*

		Butopamine dose (mcg/kg/min)		
	Control	*0.02 (n = 8)*		
CI (l/min/m²)	2.36	2.58	2.61	2.50
	0.70	0.93	0.98	0.78
SVI (ml/beat/m²)	26.6	28.6	28.4	27.9
	9.3	10.8	11.1	8.9
Heart rate (beats/min)	91	92	94	91
	12	12	13	12
PVCs (PVCs/min)	0.5	0.1	0.8	0.2
	0.8	0.4	1.4	0.5
Systemic blood pressure				
Systolic (mm Hg)	111	116	116	114
	22	30	32	27
Mean (mm Hg)	88	90	90	89
	12	15	16	15
Diastolic (mm Hg)	76	76	77	77
	8	11	10	10
Systemic vascular resistance	1,733	1,688	1,635*	1,651*
(dynes-sec-cm^{-5})	547	672	584	536
Pulmonary artery pressure				
Systolic (mm Hg)	51	51	51	50
	21	21	22	23
Mean (mm Hg)	38	38	38	38
	16	16	16	16
Diastolic (mm Hg)	31	31	31	31
	13	13	13	13
PCWP (mm Hg)	23	22	24	23
	10	10	11	11
Pulmonary vascular resistance	291	278	248	257
(dynes-sec-cm^{-5})	171	134	121	120
LVSWI (gm-M-M²)	24.4	27.7	27.5	26.7
	12.5	15.1	16.1	14.1
ΔP/Δt/PCWP (mm Hg/sec/mm Hg)	34.6	38.8	39.4	44.2
	23.2	26.2	29.5	38.4
QS_2I (msec)	556	561	555	551
	30	34	34	34
LVETI (msec)	376	382	377	374
	33	37	33	34
PEPI (msec)	181	180	178	178
	32	39	34	35
PEP/LVET	0.68	0.68	0.66	0.67
	0.24	0.28	0.25	0.25

Abbreviations: See text.
*$p < 0.05$.

strumentation Laboratory 601 computer and 602 recorder. Each cardiac output value represents the mean of a minimum of three measurements when the measurements were within 10% variance; additional measurements were made when the three values exceeded this variance. Systemic blood pressure determinations were made with a calibrated sphygmomanometer. The electrocardiogram was monitored continuously throughout the study. Heart rate was obtained from the electrocardiographic monitor unit during the cardiac-output measurements. The frequency of premature ventricular contractions was determined from the Electronics for Medicine Echo Four recordings taken every 20 min (recording duration of 2.0 min).

Butopamine dose (mcg/kg/min)								
0.04 (n = 8)			*0.06 (n = 8)*			*0.08 (n = 8)*		
2.60	2.53	2.59	2.84*	3.02*	3.14*	3.14*	3.14*	3.12*
0.97	0.80	0.87	1.01	0.89	1.04	1.09	1.08	1.06
27.8	28.5	28.3	30.5*	31.6*	32.6*	32.1*	31.6*	31.0*
10.9	11.2	10.0	11.9	10.1	11.8	11.8	11.6	10.2
96*	92	93	96	98*	98*	100*	102*	102*
16	15	15	17	16	16	14	18	18
0.0	0.2	0.1	1.2	1.1	1.4	1.9	1.9	1.0
0.0	0.7	0.4	2.5	1.8	2.8	2.9	2.9	2.4
120	120*	118	124*	125*	124*	123*	127*	127*
33	31	29	34	35	34	33	32	38
92	92	91	93	93	91	94*	93	93
18	16	16	18	18	17	17	18	20
78	77	78	78	77	74	77	76	76
12	11	12	13	11	11	11	12	12
1,691	1,710	1,663	1,548*	1,419*	1,381*	1,395*	1,438	1,402*
658	642	619	540	438	535	451	663	481
49	50	51	51	51	51	50	52	54
22	22	23	21	22	23	23	24	24
38	38	39	39	39	38	38	41	41
17	17	17	16	18	18	18	20	19
30	30	30	31	31	30	30	32	32
14	14	14	14	15	15	15	16	15
22	22	23	23	23	22	22	23	24
10	10	11	11	12	11	11	12	12
279	286	262	249	230	234*	223*	243	242
144	141	130	104	117	124	123	124	114
27.6*	28.2*	27.6	31.2*	31.6*	32.0*	32.8*	31.8*	30.9*
14.3	14.5	14.5	18.1	15.4	15.9	16.9	16.9	16.2
46.7	57.3	44.4	46.5	46.8*	49.8*	50.6*	50.0*	48.3
46.3	70.4	38.7	39.8	35.4	41.2	38.0	39.4	41.3
552	548	552	550	550	547	548	548	553
38	40	38	43	41	39	44	37	33
376	376	379	378	380	380	380	381	383
37	37	36	36	32	35	37	36	37
176	173	174*	173	171*	168*	168*	168*	171*
38	38	35	34	35	34	35	34	32
0.66	0.65	0.64	0.65	0.64	0.61*	0.62*	0.63	0.64
0.25	0.26	0.23	0.23	0.23	0.22	0.23	0.24	0.24

CI was obtained by dividing the cardiac output by the body surface area. CI divided by the heart rate provided the stroke volume index (SVI). Pulmonary and systemic vascular resistances were calculated according to the formulas: pulmonary vascular resistance = mean pulmonary artery pressure (MPAP) − PCWP × 80/cardiac output; and systemic vascular resistance = mean systemic arterial blood pressure ($\overline{BP}$) × 80/cardiac output. Left ventricular stroke work index (LVSWI) was derived from the formula: $LVSWI = (\overline{BP} - PCWP) \times SVI \times 13.6 \times 10^{-3}$. The calculated mean rate of left ventricular pressure development during isovolumetric contraction, $\Delta P/\Delta t/PCWP$, was determined[1]; in this formulation, ΔP represents the pressure generated by the left ventricle during isovolumetric contraction and was calculated

Table IB. *Effects of butopamine on hemodynamic and noninvasive measurement parameters in congestive heart failure (x ± SD)*

		Butopamine dose (mcg/kg/min)					
	Control	*0.10 (n = 7)*			*0.12 (n = 7)*		
CI (l/min/m²)	2.36	3.52*	3.61*	3.56*	3.39*	3.50*	3.49*
	0.70	0.69	0.99	0.92	1.35	1.46	1.45
SVI (ml/beat/m²)	26.6	33.9*	34.4*	35.5*	29.7*	30.8*	30.3*
	9.3	7.6	9.9	8.2	9.9	11.6	11.4
Heart rate (beats/min)	91	106*	108*	106*	112*	112*	114*
	12	20	23	19	15	13	14
PVCs (PVCs/min)	0.5	1.1	4.7	5.0	1.7	2.3	0.6
	0.8	3.0	8.0	7.9	4.5	4.5	1.1
Systemic blood pressure							
Systolic (mm Hg)	111	134*	137*	135*	129*	128*	130*
	22	32	34	38	44	41	39
Mean (mm Hg)	88	96	97	95	94	94	95
	12	17	18	20	24	23	20
Diastolic (mm Hg)	76	77	77	75	77	77	77
	8	11	13	12	14	14	13
Systemic vascular resistance (dynes-sec-cm^{-5})	1,733	1,208*	1,218*	1,206*	1,401*	1,366*	1,375*
	547	296	396	394	599	592	576
Pulmonary artery pressure							
Systolic (mm Hg)	51	53	53	55	59	57	58
	21	27	26	26	24	22	23
Mean (mm Hg)	38	39	40	40	44	42	44
	16	20	20	19	16	16	17
Diastolic (mm Hg)	31	31	31	31	33	34	34
	13	17	16	15	12	14	13
PCWP (mm Hg)	23	22	22	22	25	27	26
	10	13	12	11	10	10	10
Pulmonary vascular resistance (dynes-sec-cm^{-5})	291	204*	214*	217*	263	217	247
	171	97	96	117	133	105	107
LVSWI (gm-M/M²)	24.4	35.0*	36.4*	35.8*	29.5*	30.5*	30.4*
	12.5	14.4	16.5	14.0	16.1	18.7	17.5
ΔP/Δt/PCWP (mm Hg/sec/mm Hg)	34.6	67.6	64.4*	57.7	44.1	42.3	47.2
	23.2	59.1	50.4	40.8	32.8	37.6	42.2
QS_2I (msec)	556	551	547	547	561	559	562
	30	51	51	51	31	30	30
LVETI (msec)	376	390	390	400	391*	391*	394*
	33	45	46	42	40	36	40
PEPI (msec)	181	162*	158*	157*	170*	168*	167*
	32	35	35	36	33	29	30
PEP/LVET	0.68	0.58*	0.56*	0.54	0.64	0.63*	0.62*
	0.24	0.22	0.21	0.20	0.24	0.21	0.22

*$p < 0.05$.

by subtracting the PCWP from the systemic arterial diastolic pressure and Δt represents the time period during which isovolumetric contraction takes place and was calculated by subtracting the time interval from the onset of the electrocardiographic Q wave to the upstroke of the ventricular impulse (obtained from the apexcardiogram) from the preejection period (PEP) (obtained from the systolic time intervals).

The noninvasive determination of left ventricular performance was provided by the systolic time intervals. Systolic time intervals were

Butopamine dose (mcg/kg/min)			*After infusion (hr) (n = 8)*			
0.17 (n = 4)			*½*	*1*	*2*	*12*
4.00*	3.83*	3.86	3.08*	2.71*	2.69*	2.57
1.38	1.16	1.28	0.79	1.00	0.90	0.46
34.4*	33.1*	33.4*	29.7	27.6	27.2	29.4
10.5	7.7	8.5	5.1	9.4	8.4	6.0
116*	116*	114*	104	99	99	88
15	16	13	18	14	14	10
0.5	0.8	1.2	2.6	2.4	3.9	0.3
1.0	1.5	2.5	4.7	3.8	8.5	0.8
125*	126*	129*	135*	124*	116*	119
22	21	21	33	37	33	27
91	91	93	100	94	91	92
10	12	9	18	21	18	17
74*	73*	75*	82	80	79*	77
4	9	7	12	14	11	12
1,157*	1,186*	1,228*	1,473	1,614	1,613	1,583
466	460	512	497	616	647	438
50	50	50	53	51	51	52
24	24	24	22	20	22	24
39	37	38	38	39	38	38
20	16	20	17	16	16	19
30	29	29	30	32	31	30
16	13	14	14	13	13	15
24	24	25	21	24	22	22
14	13	14	10	11	10	11
194*	176*	186	245	259	269	279
124	98	147	145	137	139	191
31.7*	30.1*	31.2*	32.3	28.7	27.3	28.6
14.0	10.2	12.3	11.7	16.9	15.1	10.7
51.6	45.8	46.3	52.3*	44.8	46.8	42.7
49.5	32.9	35.3	31.8	35.4	35.0	31.5
558	562	562	549	544	546	558
44	46	43	45	43	41	31
385	388	388	382	371	371	380
33	32	35	37	37	33	31
174*	174*	171*	168*	175	176	179
27	26	32	33	33	34	33
0.65*	0.66	0.66	0.63	0.69	0.70	0.65
0.15	0.13	0.14	0.23	0.25	0.25	0.23

performed with an Electronics for Medicine Echo Four unit using techniques and specifications outlined previously.[9] The systolic time intervals consist of total electromechanical systole (QS_2), left ventricular ejection time (LVET), and PEP; each of these intervals was corrected for heart rate and designated QS_2I, LVETI, and PEPI, respectively. Lengthening of the LVET and/or shortening of the PEP with a decrease in the PEP/LVET ratio was used as a measure of improved ventricular performance.[9] Analysis of the results was made with analysis of variance;

Table II. *Individual responses to butopamine (B) (0.12 mcg/kg/min*) vs control (C)*

	Patient 1		*Patient 2*		*Patient 3*	
	C	*B*	*C*	*B*	*C*	*B*
CI (l/min/m^2)	1.25	1.29	1.78	2.67	2.54	3.74
SVI (ml/beat/m^2)	13.6	12.7	21.4	30.2	31.0	31.1
Heart rate (beats/min)	92	101	83	88	82	120
PVCs (PVCs/min)	0	0	0	0	1	9
Systemic blood pressure						
Systolic (mm Hg)	73	78	99	107	115	129
Mean (mm Hg)	67	70	84	84	86	86
Diastolic (mm Hg)	64	66	77	72	71	65
Systemic vascular resistance (dynes-sec-cm^{-5})	2,308	2,321	2,597	1,719	1,360	911
Pulmonary artery pressure						
Systolic (mm Hg)	44	50	37	42	57	68
Mean (mm Hg)	38	45	30	33	38	49
Diastolic (mm Hg)	34	38	24	23	31	34
PCWP (mm Hg)	30	34	20	21	21	27
Pulmonary vascular resistance (dynes-sec-cm^{-5})	265	353	287	246	264	232
LVSWI (gm-M/M^2)	6.80	6.23	18.7	26.0	26.9	25.2
$\Delta P/\Delta t$/PCWP (mm Hg/sec/mm Hg)	10.1	11.2	31.2	34.6	38.3	34.2
QS_2I (msec)	561	544	505	508	549	557
LVETI (msec)	351	349	311	331	401	410
PEPI (msec)	210	194	193	177	148	145
PEP/LVET	0.93	0.93	0.96	0.76	0.44	0.47

Abbreviations: See text.

*Values obtained for patient 5 were at a dose of 0.10 mcg/kg/min (see text).

mean values with $p < 0.05$ gave the level of significant change.

Results

The effects of butopamine on hemodynamic and noninvasive parameters are presented in Table I. The values of the study parameters obtained at the 0.12-mcg/kg/min dose for each patient are presented in Table II. Although increases in the mean CI and SVI were observed with the initial infusion rates, the changes were not significant until the dose of 0.06 mcg/kg/min was reached. Mean CI continued to increase with further increase in dose while the mean SVI tended to plateau between 0.08 and 0.12 mcg/kg/min. Although an increase in mean heart rate was noted 20 min after infusing 0.04 mcg/kg/min, consistent increases were not observed until doses ≥0.06 mcg/kg/min were infused. At infusion rates of 0.10 and 0.12 mcg/kg/min the augmented heart rate accounted for a major portion of the increase in CI; this coincided with the plateau phase of the SVI. In the four patients who received 0.17 mcg/kg/min there were further, although small, increases in the mean CI and SVI. The mean CI remained elevated above control 0.5, 1, and 2 hr after the infusion was discontinued; this was attributable to the persistent elevation of mean heart rate. Individual changes in the CI and SVI and heart rate to intravenous butopamine varied considerably (Fig. 2). Patients 2, 5, and 7 had a substantial increase in CI attributable to an increase in stroke volume. Patient 5 also had complete atrioventricular conduction block (treated with a permanent ventricular pacemaker), and thereby had a fixed ventricular rate. The CI of patients 4 and 6 also improved during the infusion period; in both the improvement was secondary to an increased stroke volume only at lower doses; as the infusion rate was increased, the stroke volume either plateaued or decreased so that most of the augmented CI was then attributable to elevated heart rate. In patients 3 and 8 CI improved primarily by increased heart rate. In patient 1 the CI, SVI, and heart rate did

Patient 4		*Patient 5**		*Patient 6*		*Patient 7*		*Patient 8*	
C	*B*	*C*	*B*	*C*	*B*	*C*	*B*	*C*	*B*
2.58	4.84	2.58	3.32	3.68	5.50	2.32	3.43	2.17	2.75
27.2	37.3	35.0	44.8	42.5	47.8	21.3	28.8	20.4	23.9
95	130	74	74	87	115	109	119	106	115
0	0	2	19	0	0	0	0	1	3
144	202	105	134	121	119	97	106	131	165
99	134	81	87	94	86	86	85	105	117
76	99	69	63	80	70	80	75	92	93
1,563	1,131	1,193	988	1,058	649	1,733	1,133	2,051	1,802
78	81	20	21	30	19	67	59	74	86
57	64	14	15	23	14	55	45	52	57
49	52	12	12	18	12	41	37	42	39
21	26	7	7	14	7	40	33	32	35
630	324	98	91	93	50	297	151	397	340
28.7	54.9	35.2	48.5	45.9	51.8	13.2	20.3	20.1	26.7
28.8	60.2	84.1	134.8	44.5	121.7	11.6	21.0	27.9	28.9
547	568	539	454	590	583	601	603	560	562
387	436	383	340	389	401	368	391	416	424
160	132	162	120	201	181	233	212	144	138
0.52	0.35	0.51	0.42	0.71	0.67	0.99	0.83	0.43	0.41

not deviate from control. (This subject died 2 mo after study because of refractory low-output congestive heart failure.)

There were progressive increases in systolic blood pressure at infusion rates of ≥0.04 mcg/kg/min (Table I). These changes in systolic pressure persisted for an hour after the infusion was discontinued. Diastolic and mean pressures were not altered in any but the four subjects who received the 0.17-mcg/kg/min dose. Mean total systemic vascular resistance decreased at ≥0.06 mcg/kg/min. The total systemic vascular resistance returned to baseline by 0.5 hr after discontinuation of butopamine.

Intravenous butopamine did not alter pulmonary artery pressures or mean PCWP but there was a reduction in pulmonary vascular resistance. The decrease in the calculated pulmonary vascular resistance occurred in concert with the increase in cardiac output and without accompanying changes in mean PCWP or pulmonary artery pressure.

There were significant increases in LVSWI at ≥0.04 mcg/kg/min and the changes plateaued at ≥0.06 mcg/kg/min; these findings coincide with those for the SVI. There were similar results with ΔP/Δt/PCWP but significant changes were limited to the 0.06- to 0.10-mcg/kg/min dose range.

Butopamine tended to lower the QS_2I below control but the changes were not significant. Mean LVETI increased only at 0.12 mcg/kg/min. Progressive shortening of the PEPI occurred in response to increasing doses of butopamine and the changes became significant at ≥0.06 mcg/kg/min. There was reduction of the PEP/LVET, indicating improved ventricular performance, at the initial infusion rate of 0.02 mcg/kg/min, but it became significant only at doses ≥0.08 mcg/kg/min.

Mean premature ventricular contractions (PVCs) per minute did not change from control during the infusion period. Three of the eight patients had ventricular ectopy during the control period; of these three, two (patients 3 and 5) had a substantial increase in PVCs per minute with butopamine. In patient 3, who also had frequent premature atrial contractions (PACs)

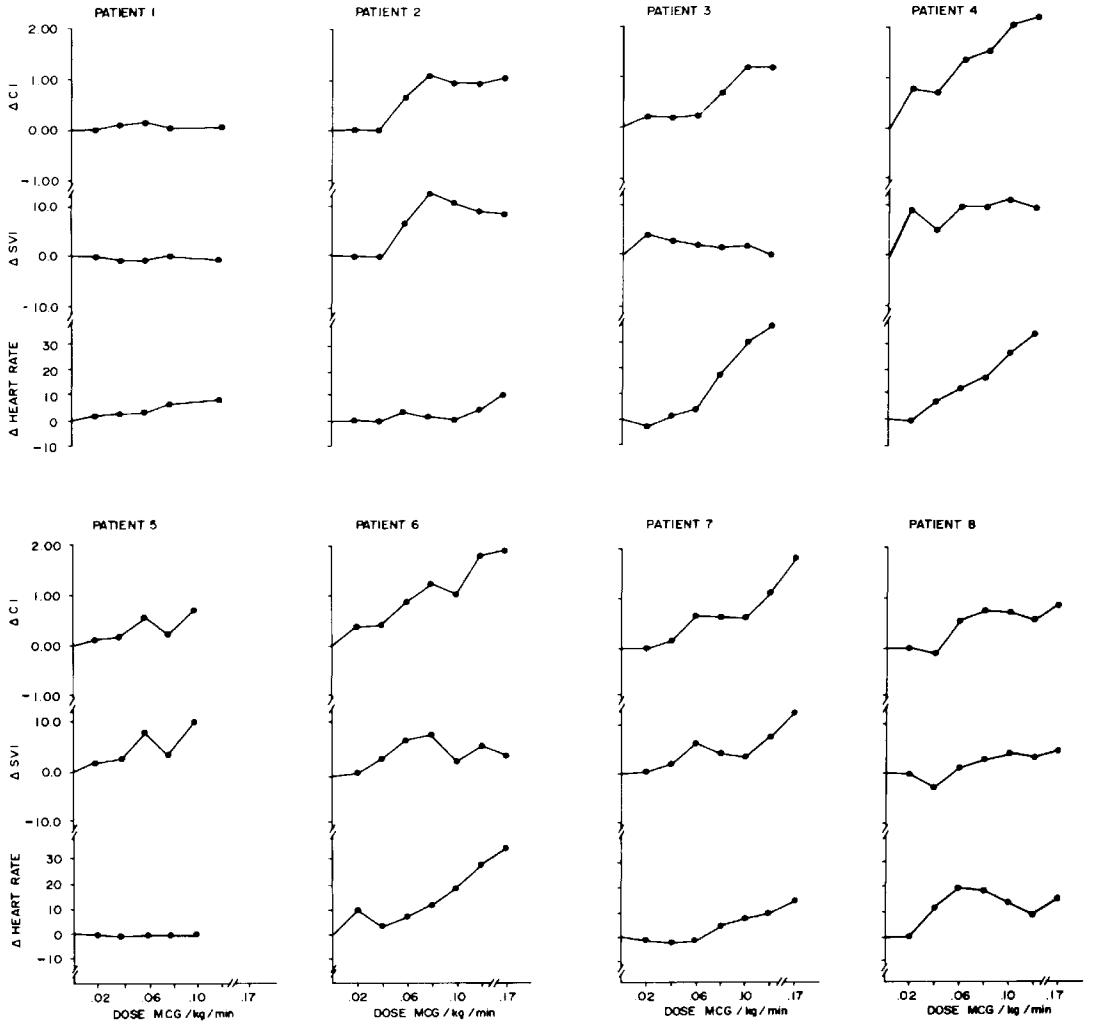


Fig. 2. Individual responses to butopamine. ΔCI = change in cardiac index (*l*/min/m^2); ΔSVI = change in stroke volume index (ml/min/m^2).

during control, there was an increase of 8 PVCs/min and 14 PACs/min during the 0.10-mcg/kg/min infusion. In patient 3, the increased frequency of PVCs was present for 2 hr after drug was discontinued, while PAC frequency returned to control within an hour of stopping the infusion. At 0.10 mcg/kg/min, there was an increase in the frequency of PVCs in patient 5 (13/min above control). The increase in ventricular ectopy was sustained up to 2 hr after discontinuation of butopamine. The other patients did not have increases in ventricular or atrial ectopy during the infusion.

Butopamine was well tolerated by all subjects. Except for heart-rate changes (four subjects) and increased ventricular ectopy (two subjects), no other adverse effects or symptoms developed during the 6- to 7-hr infusion.

Discussion

Butopamine inproved cardiac performance in patients with ventricular dysfunction and congestive heart failure; this property was retained (actually enhanced based on comparative doses) when the dobutamine molecule was altered slightly to generate the compound butopamine. The paucity of effects on systemic and pulmonary arterial pressures reflects, in part, the unal-

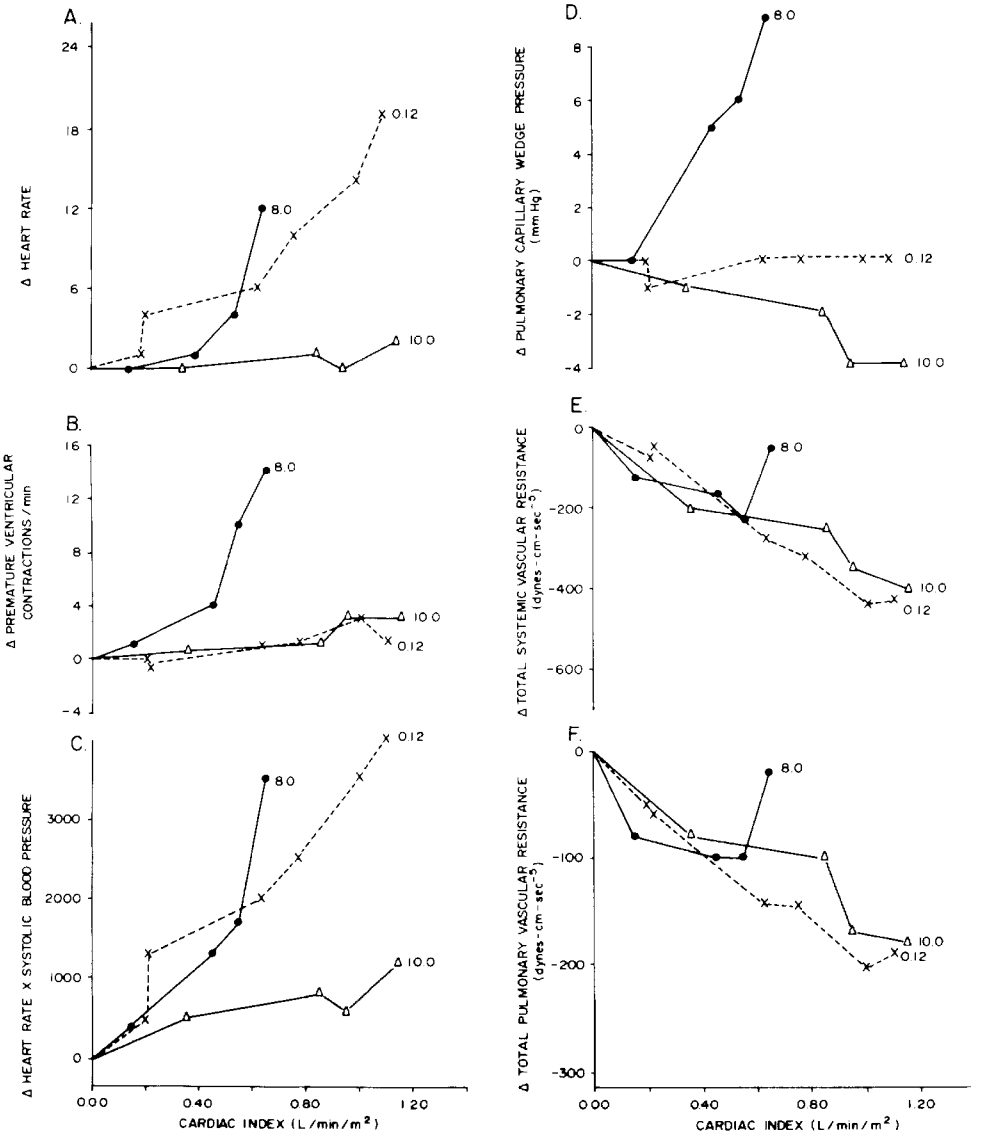


Fig. 3. Relationship between an index of improved cardiac function *(abscissa:* change in cardiac index) and some undesirable effects *(ordinate)* for butopamine (x---x), dopamine (•——•), and dobutamine (△——△). The number located to the right of the last datum point of each line represents the highest dose (mcg/kg/min) for that drug.

tered aralkyl-amine portion of the molecule. Moving the hydroxyl group from the ortho position of the phenyl portion to the beta position of the ethylamine group (Fig. 1) resulted in a chronotropic response. Chronotropic stimulation is a characteristic feature of catecholamines with a beta hydroxyl group (e.g., epinephrine, isoproterenol). The accompaniment of positive inotropy by positive chronotropy is in exchange for resistance to degradation by catechol-*O*-methyltransferase and application as an oral drug.

By plotting a beneficial parameter of an inotropic drug (e.g., improvement of CI) against its potential undesirable features (e.g., increase in heart rate, ventricular ectopy) the graphs of Fig. 3 are developed; in similar patient populations, the cumulative dose responses of butopamine are compared with those of the popular vasopressor, dopamine, and to those of

dobutamine.[7] The frequency of PVCs and the changes in pulmonary and systemic vascular resistances in relation to CI due to butopamine were similar to those of dobutamine. Butopamine effects resembled those of dopamine on heart rate and the double product (heart rate × systolic blood pressure): these two parameters increased considerably relative to the increase in cardiac output for butopamine and dopamine. PCWP did not change with butopamine and thus fell between the increase due to dopamine and the reduction due to dobutamine. Of the six undesirable effects noted above, after butopamine two were more frequent, three less frequent, and one was without effect; after dopamine four were more frequent and two were less frequent; and after dobutamine one was aggravated (mild increase of the double product), three were less frequent, and two were unchanged. In general, butopamine has less vasopressor effects than dopamine and elicits more chronotropy than dobutamine.

The acute chronotropic properties of butopamine are undesirable in the therapeutics of heart failure but oral administration in man warrants further investigation.

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