Effects of CI-914 in Congestive Heart Failure Due to Coronary Artery Disease or Idiopathic Cardiomyopathy

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The hemodynamic effects of CI-914, a phosphodiesterase inhibitor, were studied in 12 patients with left ventricular (LV) dysfunction who were undergoing diagnostic cardiac catheterization. CI-914 was infused intravenously at a rate of 0.8 to 7.0 μg/kg/min for 30 to 60 minutes; hemodynamic values were measured every 10 minutes. No effect was seen in the patient receiving 0.8 μg/kg/min. At infusion rates of 1.2 to 2.4 μg/kg/min, cardiac index increased by 14% ($p < 0.025$). At infusion rates of 4.5 to 7.0 μg/kg/min, cardiac index increased by 21% ($n = 8$, difference not significant [NS]). Among 4 patients (group B) with an initial pulmonary artery wedge pressure greater than 20 mm Hg and cardiac index less than 2.5 liters/min/m^2, cardiac index increased by 50% ($p < 0.001$); it did not change among the 4 patients with an initial pulmonary artery wedge pressure of less than 20 mm Hg and cardiac index of more than 2.5 liters/min/m^2 (group A). Although systemic vascular resistance decreased in all 8 patients by 26% ($p < 0.01$), the reduction was greater in group B (33%, $p < 0.01$) than in group A (16%, NS). Peak +dP/dt increased in all 8 patients by 13% ($p < 0.01$). Mean stroke work index increased from 29 ± 15 to 34 ± 13 g-m/m^2; the double product fell from 101 ± 31 to 91 ± 23 (NS). In all 12 patients, a linear correlation between peak venous blood concentration and peak effect on cardiac index, systemic vascular resistance and pulmonary artery wedge pressure was observed. The increase in cardiac index associated with a decrease in systemic vascular resistance suggests that part of the favorable hemodynamic effect is attributable to afterload reduction. Nonetheless, the increase in peak +dP/dt in all patients suggests that CI-914 also has a positive inotropic effect. This combination of effects may be of value in the treatment of severe congestive heart failure.

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Phosphodiesterase inhibitors have vasodilator and positive inotropic effects and are of value in the acute therapy of congestive heart failure (CHF).[1–7] Like β-adrenergic agonists,[8] phosphodiesterase inhibitors increase intracellular cAMP, enhance Ca^{++} flux across the slow channel and Ca^{++} release from the sarcoplasmic reticulum,[9–12] exerting a combination of beneficial mechanical effects on myocardium.[8] These drugs increase the peak force developed, the rate of force development and the relaxation velocity, thereby shortening total contraction time and maintaining diastolic function despite the tachycardia often associated with CHF. Because they act distal to the β-adrenergic receptor, these agents are active even in patients with CHF who are relatively insensitive to catecholamines.[13] Moreover, their prolonged use does not appear to be associated with development of tachyphylaxis, usually associated with β-adrenergic therapy.[14]

CI-914 is a new phosphodiesterase inhibitor selective for cAMP.[15] It is equipotent with amrinone in increasing peak developed tension in rabbit right ventricular papillary muscle and guinea pig left atrium, and is 10 times more potent than amrinone in increas-

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TABLE I Peak Change in Hemodynamic Measurements After Infusion of CI-914

Pt	Age (yr) & Sex	Cause	EF (%)	Dose (μg/kg/min)	HR (beats/min) C	HR D	LVSP (mm Hg) C	LVSP D	MAP (mm Hg) C	MAP D	CI (liters/min/m²) C	CI D	SVR (dynes s cm⁻⁵) C	SVR D	PAP (mm Hg) C	PAP D	PVR (dynes s cm⁻⁵) C	PVR D	LVEDP (mm Hg) C	LVEDP D	PCW (mm Hg) C	PCW D	+dP/dt (mm Hg/s) C	+dP/dt D	−dP/dt (mm Hg/s) C	−dP/dt D	τ (sec⁻¹) C	τ D	SWI (g-m/m²) C	SWI D	DP C	DP D
1	56M	CAD	34	0.8	63	66	120	139	92	102	2.5	2.3	1,183	1,598	13	18	70	148	19	18	9	10	766	820	909	980	62	78	37	39	81	93
2	67M	CAD	42	1.2	59	68	160	176	110	104	2.6	2.8	1,781	1,584	15	12	154	95	22	12	15	13	814	946	814	—	60	42	42	55	119	108
3	24M	IDC	9	2.0	122	130	95	86	85	77	2.2	2.5	1,760	1,440	36	31	228	315	29	25	26	22	700	725	725	675	50	52	13	13	139	127
4	59M	CAD	23	2.4	77	83	94	88	77	84	1.6	1.9	1,455	1,280	30	38	72	220	34	27	27	30	572	682	572	638	76	47	12	16	78	87
5	55F	CAD	30	4.5	87	88	111	108	93	84	1.6	2.3	1,749	1,241	48	33	350	221	28	17	28	20	748	819	676	765	76	64	16	24	107	90
6	42M	IDC	36	7.0	60	69	103	98	85	74	3.5	3.0	800	844	36	21	185	110	26	16	18	10	725	899	580	783	—	—	47	36	72	69
7	55M	IDC	42	7.0	60	66	135	115	94	89	2.9	2.6	1,400	1,393	21	12	78	117	20	3	16	5	805	917	850	939	67	45	49	57	77	87
8	47M	IDC	18	7.0	60	84	90	80	72	62	3.4	4.1	943	734	34	18	200	107	27	8	20	4	437	453	534	583	86	33	35	43	60	71
9	57M	CAD	27	7.0	84	90	150	116	120	95	2.5	2.8	1,583	992	22	13	139	31	23	2	14	6	967	1,136	967	1,136	70	40	39	45	134	101
10	44M	IDC	29	7.0	108	96	108	101	107	101	1.8	2.8	1,806	1,076	50	38	411	234	27	18	32	17	530	629	811	712	73	51	16	24	117	96
11	40M	IDC	10	7.0	105	90	86	68	79	69	1.4	2.0	2,074	1,566	35	19	296	122	28	18	25	11	594	709	517	594	80	51	9	15	94	71
12	58M	IDC	11	7.0	117	123	124	130	101	92	2.4	3.7	1,666	1,034	43	30	251	181	32	21	30	15	1,144	1,258	897	1,095	72	53	20	28	146	130
Mean (patients 5–12)					85	88	114	102	94	83†	2.4	2.9	1,502	1,110*	36	23*	239	140	26	13*	23	11*	744	852	729	826†	75	48*	29	34	101	91
±SD					±23	±18	±22	±20	±16	±14	±0.8	±0.7	±436	±277	±11	±10	±111	±67	±34	±7	±7	±6	±232	±263	±175	±211	±6	±10	±15	±14	±31	±23
% Change					+7±17		−8±9		−11±5		+19±27		−23±17*		−37±8*		−35±38		−53±25*		−54±16*		+15±7*		+14±13†		−35±16*		+30±28		−10±15	
Group A (patients 6–9)																																
Mean					66	77	120	102	93	80†	3.1	3.1	1,182	991	28	16	151	91	24	7*	17	6	734	851*	732	860†	75	39	42	43	86	82
±SD					±12	±12	±28	±17	±20	±15	±0.5	±0.7	±370	±288	±8	±4	±55	±40	±3	±6	±3	±3	±222	±286	±209	±235	±10	±6	±7	±5	±33	±15
Group B (patients 5, 10–12)																																
Mean					104	99	108	102	95	87	1.8	2.7*	1,823	1,229*	44	25	327	190	29	19*	29	16*	754	853†	725	792	75	55*	15	23*	116	97*
±SD					±13	±16	±16	±26	±12	±14	±0.4	±0.7	±176	±242	±7	±14	±69	±50	±2	±8	±3	±4	±276	±281	±166	±215	±3	±6	±4	±5	±22	±25

Level of statistical significance was determined by paired *t* test on the difference between peak response and baseline: * $p < 0.01$; † $p < 0.05$.

CAD = coronary artery disease; CI = cardiac index; DP = double product; HR = heart rate; IDC = idiopathic dilated cardiomyopathy; LV = left ventricular; LVEDP = LV end-diastolic pressure; LVSP = LV systolic pressure; MAP = mean arterial pressure; PCW = pulmonary artery wedge pressure; SD = standard deviation; SVR = systemic vascular resistance; SWI = stroke work index; τ = time constant of LV isovolumic pressure fall.

ing peak +dP/dt after infusion into anesthetized dogs despite significant reduction of mean arterial pressure.[15] As a pyridazinone derivative, chemically distinct from the bipyridines, amrinone and milrinone, it may not be associated with thrombocytopenia.[16] We report here the acute hemodynamic effects of CI-914 on patients with moderate to severe LV dysfunction.

Methods

Patients: Twelve patients with symptomatic LV dysfunction were studied at diagnostic cardiac catheterization (Table I). No patient had primary valvular disease, myocardial infarction in the past 2 weeks, unstable angina, left main coronary artery stenosis or clinically significant hepatic or renal disease. All had given informed consent to a study protocol approved by the University of Michigan Hospital Human Subject Review Committee.

Catheterization protocol: Topical nitrates, calcium channel blockers and afterload reducing agents, but not diuretic drugs or digoxin, were stopped 24 to 72 hours before cardiac catheterization. After routine right-sided cardiac catheterization and coronary arteriography, baseline hemodynamic variables (heart rate, LV pressure with a micromanometer-tip catheter, electronically differentiated dP/dt, pulmonary artery, pulmonary artery wedge, right atrial and arterial pressures, and cardiac output by thermodilution) were measured. CI-914 was administered to consecutive patients at rates of 0.8 (patient 1), 1.2 (patient 2), 2.0 (patient 3), 2.4 (patient 4), 4.5 (patient 5) and 7.0 μg/kg/min (patients 6 through 12) for 60 minutes or until there was a 50% reduction in pulmonary artery wedge pressure, a decrease in arterial pressure to less than 80 mm Hg or a plateau in hemodynamic response. The infusions lasted for 60 minutes in patients 1 to 5, 10 and 11; 50 minutes in patient 7; 40 minutes in patients 6, 9 and 12; and 30 minutes in patient 8. Cardiac output and pressures were measured and femoral arterial and venous blood samples obtained from the side arms of the femoral introducer sheaths every 10 minutes during the infusion, for 30 minutes after termination of infusion and 2, 4 and 24 hours after infusion. CI-914 concentration was determined by high-pressure liquid chromatography.[5]

Analysis of data: Stroke work index was calculated as: (mean arterial pressure − LV end-diastolic pressure) × (stroke volume index) × 0.0136. Double product was calculated as (LV systolic pressure) × (heart rate). The time constant of relaxation (τ) was calculat-

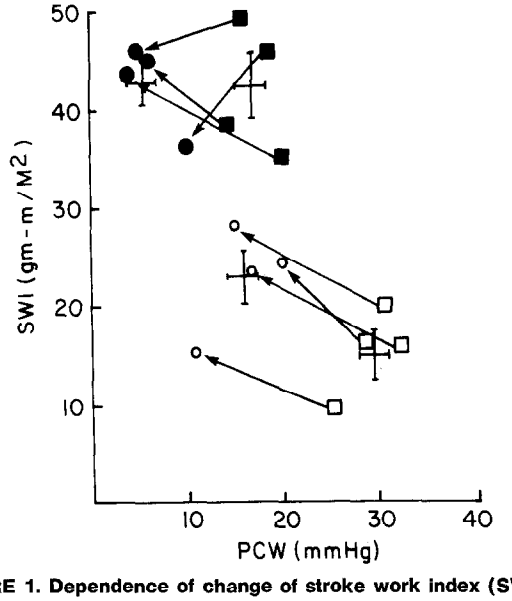

FIGURE 1. Dependence of change of stroke work index (SWI) on initial pulmonary artery wedge pressure (PCW). The mean ± standard error of the mean of the initial and final PCW and SWI are shown. *Closed squares* indicate group A control; *closed circles*, group A after drug; *open squares*, group B control; and *open circles*, group B after drug.

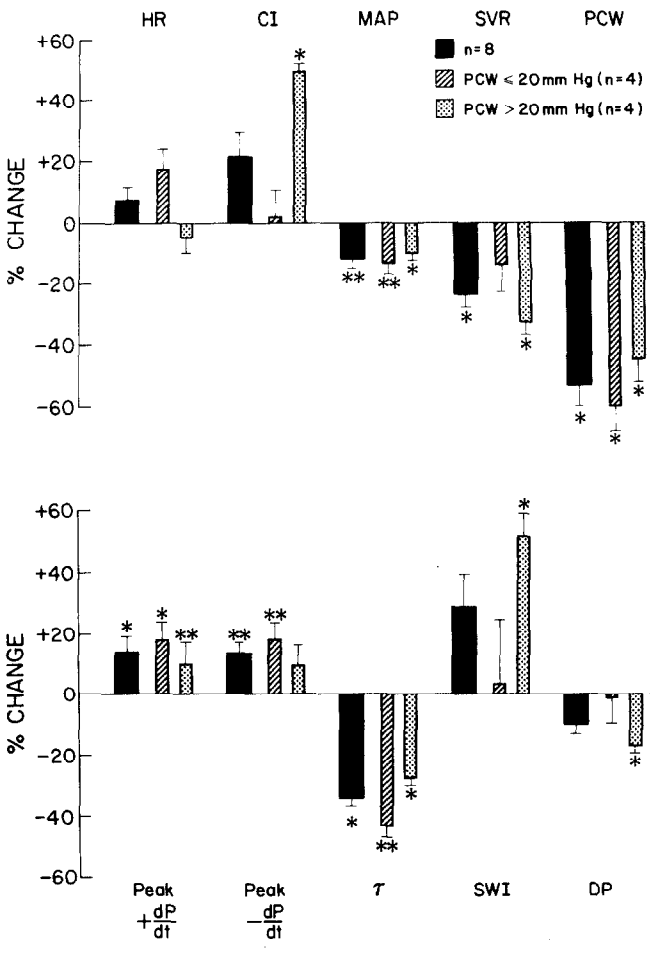

FIGURE 2. Systemic and cardiac effects of CI-914. The peak effect of CI-914 on systemic and cardiac hemodynamic variables are expressed as mean percent change from baseline ± standard error. The hemodynamic effects on patients in groups A and B are shown. Level of statistical significance was determined by paired *t* test on the difference between peak change and baseline. *p <0.01; **p <0.05. CI = cardiac index; DP = double product; HR = heart rate; MAP = mean arterial pressure; PCW = pulmonary capillary wedge pressure; SVR = systemic vascular resistance; SWI = stroke work index; τ = time constant of relaxation.

ed as the inverse slope of a plot of log pressure vs time during isovolumic relaxation beginning at the time of peak −dP/dt.[17] Because the hemodynamic response of patients receiving between 1.2 and 2.4 μg/kg/min differed from that of patients receiving a larger dose, these patients were analyzed separately. Data are expressed as peak response (Table I). In general, the peak change in all hemodynamic values occurred toward the end of the infusion.

Results

No significant hemodynamic effects were observed at an infusion rate of 0.8 μg/kg/min. At infusion rates of 1.2 to 2.4 μg/kg/min, cardiac index increased by 14% (n = 3, p <0.025), and systemic vascular resistance was reduced to the same degree (n = 3, p <0.05). Peak +dP/dt did not increase significantly (Table I). At infusion rates of 4.5 to 7.0 μg/kg/min, cardiac index of the 8 patients increased from 2.4 ± 0.8 to 2.9 ± 0.7 liters/min/m^2 and stroke work index from 29 ± 15 to 34 ± 14 g-m/m^2; however, these effects were not uniform. In 4 patients with a pulmonary artery wedge pressure of less than 20 mm Hg (patients 6 through 9, group A), cardiac index and stroke work index did not change significantly (from 3.1 ± 0.5 to 3.1 ± 0.7 liters/m/m^2 and from 42 ± 7 to 43 ± 5 g-m/m^2, respectively) (Fig. 1 and 2, Table I). In contrast, in 4 patients with a pulmonary artery wedge pressure of more than 20 mm Hg (patients 5, 10, 11 and 12, group B), both cardiac and stroke work indexes increased (from 1.8 ± 0.4 to 2.7 ± 0.7 liters/min/m^2, p <0.01, and 15 ± 4 to 23 ± 5 g-m/m^2, p <0.01). In group B systemic vascular resistance fell more than in group A (32% vs 16%, p <0.01), as did LV end-diastolic pressure (71% vs 36%, p <0.01). The double product decreased more among patients in group B (16%, p <0.01) than in group A (4%, difference not significant [NS]). Ejection fraction was 30 ± 11% in group A and 20 ± 11% in group B (NS).

Peak +dP/dt increased from 744 ± 232 to 852 ± 263 mm Hg/s in the 8 patients in groups A and B (p <0.01), despite variable changes in heart rate and despite a decrease in diastolic arterial pressure. Peak −dP/dt rose from 729 ± 175 to 826 ± 211 mm Hg s^{-1} (n = 7, p <0.05), and τ was reduced from 75 ± 6 to 48 ± 10 s^{-1} (n = 8, p <0.01).

Among all 12 patients receiving the drug, the peak increase in cardiac index correlated with peak venous drug concentration (Fig. 3) (r = 0.58, p <0.01). There was a better correlation of peak venous plasma level with the decrease in pulmonary artery wedge pressure (r = −0.69, p <0.01) than with the decrease in systemic vascular resistance (r = −0.52, p <0.01). The peak values of other parameters (pulmonary artery pressure, peak +dP/dt and −dP/dt, and τ) did not significantly correlate with venous plasma level. The change in venous levels of the drug after infusion did not follow first-order kinetics. In 2 patients with venous drug concentrations of less than 100 ng/ml, the drug concentration dropped to half its initial value at the end of infusion over the next 2 hours. In 10 patients with venous drug levels above 100 ng/ml, drug concentration fell to half its initial value after 5 hours.

Discussion

These findings suggest that CI-914 administered at rates of 1.2 μg/kg/min or more improves the hemodynamic state of patients with severe CHF primarily by reducing systemic vascular resistance. Among patients who responded, systemic vascular resistance fell by 33%, LV end-diastolic pressure remained optimal, and, consequently, stroke volume index increased 32%. Among patients who did not respond, the initial systemic vascular resistance was not significantly elevated; LV end-diastolic pressure decreased to levels not optimal to maintain LV filling; and stroke volume index decreased by 16%. The fact that the group with a

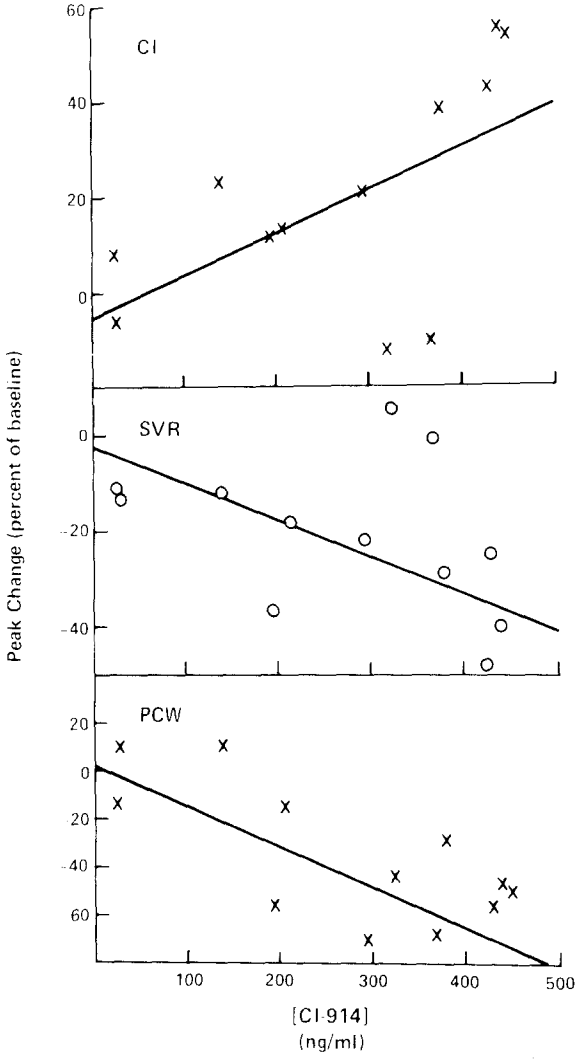

FIGURE 3. Peak changes of cardiac index (CI), systemic vascular resistance (SVR) and pulmonary artery wedge pressure (PCW) as a percent of the baseline value vs peak venous plasma concentration of CI-914. Regression equations are: Percent change of CI = 0.092 [CI-914] − 5.46; r = 0.58; n = 12; p <0.01. Percent change of systemic vascular resistance = −0.60 [CI-914] − 1.46; r = 0.52; n = 12; p <0.05. % change of pulmonary artery wedge = −0.13 [CI-914] + 0.067; r = −0.67; n = 12; p <0.01.

worse ejection fraction (group B) responded better to the drug underscores the value of the drug as a vasodilator; those with a poorer ejection fraction had an initial hemodynamic state that was more responsive to vasodilatation than those of the nonresponders.

The positive inotropic effect of CI-914 contributed to its beneficial effect. Peak +dP/dt increased in all patients receiving at least 1.2 μg/kg/min, without an effect on heart rate or on arterial diastolic pressure, variables that may themselves alter peak +dP/dt,[18] and despite a significant reduction in LV end-diastolic pressure, suggesting an upward shift in the Starling curve. Systolic function may have improved as a result of improved diastolic function, as observed with milrinone treatment.[6] These effects are comparable to those reported by Jafri et al[7] and those reported for other phosphodiesterase inhibitors.[2-5]

The reduction in the systolic double product observed among responders reflects a reduction in myocardial oxygen consumption.[19] The effect of reduction of the range of working LV pressure on myocardial oxygen consumption more than offset the higher energy cost of an increase in volume work.[20,21]

Thus, similar to other vasodilators, CI-914 converts pressure work to volume work and thereby improves cardiac index while reducing myocardial oxygen consumption.

Although CI-914 and other phosphodiesterase inhibitors have acute beneficial effects in patients with CHF, the long-term effectiveness and safety must be questioned.[22,23] Nonetheless, the results of the present investigation and of studies of other phosphodiesterase inhibitors suggest that these agents will play an important role in the therapy of patients with severe LV dysfunction.

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