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 \( \mu \text{g/kg/min} \) for 30 to 60 minutes; hemodynamic values were measured every 10 minutes. No effect was seen in the patient receiving 0.8 \( \mu \text{g/kg/min} \). At infusion rates of 1.2 to 2.4 \( \mu \text{g/kg/min} \), cardiac index increased by 14% \( (p < 0.025) \). At infusion rates of 4.5 to 7.0 \( \mu \text{g/kg/min} \), cardiac index increased by 21% \( (n = 8, \text{difference not significant [NS]}) \). 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/\text{min/m}^2, cardiac index increased by 58\% \( (p < 0.001) \); 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/\text{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.

(Please note that the rest of the text is not transcribed due to its length and complexity.)
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<th>Age (yrs)</th>
<th>Sex</th>
<th>Cause (%)</th>
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<th>HR (beats/min)</th>
<th>LVSP (mm Hg)</th>
<th>MAP (mm Hg)</th>
<th>CI (l/min/m²)</th>
<th>SVR (dynes x cm⁻²)</th>
<th>PAP (mm Hg)</th>
<th>PVR (dynes x cm⁻²)</th>
<th>LVEDP (mm Hg)</th>
<th>PCW (mm Hg)</th>
<th>+dP/dt (mm Hg/s)</th>
<th>-dP/dt (mm Hg/s)</th>
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<td>Mean (patients 5-12)</td>
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<td>102 94 83</td>
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</table>

**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 ±386 | ±209 ±236 | ±10 ±6 | ±7 ±5 | ±93 ±15 |

**Group B (patients 5, 10-12)**

| Mean | 104 99 | 100 102 | 95 07 | 1.0 2.7 1,023 1,229* | 44 25 | 227 199 | 20 10 | 20 16 | 754 830 | 725 792 | 75 55 | 15 23 | 116 97 |
| ±SD | ±13 ±16 ±16 ±06 ±12 ±14 ±0.4 ±0.7 ±178 ±242 | ±7 ±14 | ±59 ±50 ±2 ±8 | ±3 ±4 | ±276 ±281 | ±166 ±215 | ±3 ±6 | ±4 ±8 | ±20 ±25 |

Level of statistical significance was determined by paired t test on the differences 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; r = time constant of LV isovolumic pressure fall.
ing peak +dP/dt after infusion into anesthetized dogs despite significant reduction of mean arterial pressure. As a pyridazinone derivative, chemically distinct from the bipyridines, amrinone and milrinone, it may not be associated with thrombocytopenia. 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.

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

\[
\tau = \frac{1}{\text{double product}}
\]

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 \(-dP/dt\). Because the hemodynamic response of patients receiving between 1.2 and 2.4 \(\mu g/kg/min\) 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 \(\mu g/kg/min\). At infusion rates of 1.2 to 2.4 \(\mu g/kg/min\), 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 \(\mu g/kg/min\), cardiac index of the 8 patients increased from 2.4 ± 0.8 to 2.9 ± 0.7 liters/min/m² and stroke work index from 29 ± 15 to 34 ± 14 g-m/m²; 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 \((P = 0.5 ± 0.7 liters/min/m² and from 42 ± 7 to 43 ± 5 g-m/m², respectively)\) (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 \((P = 1.8 ± 0.4 to 2.7 ± 0.7 liters/min/m², p <0.01, and 15 ± 4 to 23 ± 5 g-m/m², p <0.01)\). 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 \(\tau\) 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 \(\tau\)) 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 \(\mu g/kg/min\) 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...
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 $\mu$g/kg/min, with an effect on heart rate or on arterial diastolic pressure, variables that may themselves affect peak $+dP/dt$, 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. These effects are comparable to those reported by Jafri et al and those reported for other phosphodiesterase inhibitors.

The reduction in the systolic double product observed among responders reflects a reduction in myocardial oxygen consumption. 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.

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. 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.

References


