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Direct Myocardial Effects of OPC-18790 in Human Heart Failure: Beneficial Effects on Contractile and Diastolic Function Demonstrated by Intracoronary Infusion With Pressure–Volume Analysis

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Objectives. **We sought to determine the precise myocardial effects of OPC-18790 as demonstrated by intracoronary administration.**

Background. **Although previous studies have determined the cardiovascular effects of a novel intravenous inotrope, OPC-18790, the observed benefits on contractile and diastolic function may have been confounded by the marked changes in peripheral loading associated with this drug when given intravenously.**

Methods. **Eight heart failure patients received intracoronary OPC-18790 at 31.25 μg/min for 20 min, and then at 62.5 μg/min for another 20 min. Hemodynamic variables and pressure–volume indexes using the conductance catheter method were determined at baseline and then after the two doses.**

Results. **There were no significant effects on heart rate, cardiac output or loading conditions, including afterload as determined by systemic vascular resistance and arterial elastance (E_a) and preload as determined by end-diastolic volume (EDV). There were significant increases in end-systolic elastance (E_{es}) from 0.74 ± 0.11 to 0.90 ± 0.16 mm Hg/ml at 31.25 μg/min and to 1.37 ± 0.33 mm Hg/ml at 62.5 μg/min ($p < 0.05$ by analysis of variance [ANOVA]). Diastolic function improved, as determined by the time constant for isovolumetric relaxation tau, which decreased significantly from baseline to 31.25 μg/min (94 ± 9 to 79 ± 9 ms, $p < 0.05$), and did not shorten further at 62.5 μg/min (78 ± 8 ms, p = NS). There were significant decreases in right atrial pressure (9 ± 1 to 7 ± 1 mm Hg, $p < 0.01$ by ANOVA) and mean pulmonary artery wedge pressure (21 ± 3 to 16 ± 2 mm Hg, $p < 0.05$ by ANOVA). This fall in filling pressures was not accompanied by any change in EDV. Inspection of the diastolic portion of the pressure–volume curve confirmed a downward shift consistent with pericardial release in five of the eight patients.**

Conclusions. **Intracoronary administration of OPC-18790 demonstrates that the direct myocardial effects of this agent include a modest increase in inotropy and improvement in diastolic function, both of which occur without increases in heart rate, indicating that this agent may be beneficial for the intravenous treatment of congestive heart failure.**

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OPC-18790 has been shown to increase contractility (1), which is thought to be mediated in part by phosphodiesterase inhibition (2). However, unlike other phosphodiesterase inhibitors, these effects occur without any change in heart rate (1,3), which is thought to be the consequence of inhibition of inward potassium and delayed rectifier currents (4). We previously studied the effects of intravenous OPC-18790 on pressure–volume relations in human heart failure, demonstrating that OPC-18790 increased end-systolic elastance (E_{es}), a relatively load-independent measure of contractility, by up to 172%, and decreased the time constant for isovolumetric relaxation tau by 20% (1). These effects were also accompanied by a 30% fall in atrial and pulmonary artery pressures and a 40% reduction in afterload. As a result, OPC-18790 has been classified as a positive inotrope with potent venous and arterial vasodilator properties.

However, the profound changes in vascular loading may have confounded the observed effects on diastolic and contractile function. The significant decrease in tau may have been produced by the reduction in afterload. Tau is known to be afterload-dependent, particularly in heart failure (5–7). Also, marked decreases in loading may have falsely elevated the improvement in E_{es} (Fig. 1). In a canine model, Kass et al. (8) have shown that the slope of the end-systolic pressure–volume relation is nonlinear, being concave away from the volume axis, and as contractility is depressed this relation becomes more linear (9). The investigators concluded that E_{es} is accurate to assess contractility only in limited load ranges and may not be

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Abbreviations and Acronyms

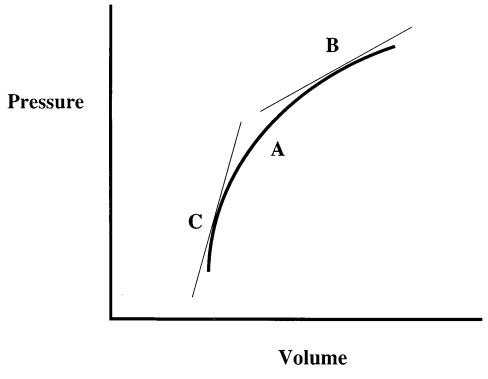
CO	=	cardiac output
dP/dt	=	rate of rise in left ventricular pressure
dV/dt	=	maximal rate of change of left vetricular volume
E_a	=	arterial elastance
EDV	=	end-diastolic volume
E_{es}	=	end-systolic elastance
MSW	=	preload recruitable stroke work
$M\dot{V}O_2$	=	myocardial oxygen consumption
PWR_{max}	=	maximal power index
SVR	=	systemic vascular resistance

accurate when there are significant changes in loading. Accordingly, we minimized the potentially confounding effects of vascular loading on diastolic and contractile variables by administering intracoronary OPC-18790 to eight patients with congestive heart failure, and we determined the direct myocardial effects of this drug using pressure–volume relations. We hypothesized that with intracoronary doses (31.25 to 62.5 μg/min) comparable to those used intravenously (5 to 10 μg/kg body weight per min), OPC-18790 would have a reduced positive inotropic effect and that an improvement in isovolumetric relaxation would persist despite the absence of changes in afterload, due to phosphodiesterase inhibition of OPC-18790.

Methods

Patients. Eight patients (mean age 57 ± 8 years) with congestive heart failure referred for elective cardiac catheterization at the University of Virginia were enrolled in this study. Four patients were in New York Heart Association functional class II and four patients were in class III. Congestive heart failure was due to idiopathic dilated cardiomyopathy in five patients, ischemic cardiomyopathy in two and hypertensive heart disease in one. All patients had a baseline pulmonary capillary wedge pressure ≥15 mm Hg and an ejection fraction ≤35%. Patients were excluded from the study if they had atrial fibrillation, received any inotropic agent other than digoxin within 4 weeks of the study or had symptomatic ventricular tachycardia, left ventricular apical thrombus or primary valvular heart disease. Six patients were taking captopril (mean daily dose 38.5 ± 19.5 mg); all patients were taking oral furosemide (mean daily dose 48.6 ± 38.0 mg); and three patients were taking digoxin (mean daily dose 0.21 ± 0.07 mg). All vasodilators were withheld for at least 24 h before cardiac catheterization. In a ninth patient, the study was terminated early due to patient restlessness. This patient's incomplete data were excluded from the analysis. Written informed consent was obtained from all patients, and the protocol was approved for use by the human investigational committee of the Hospital of the University of Virginia.

Figure 1. Diagram illustrating the curvilinear nature of the end-systolic pressure–volume relation (8). This figure demonstrates that by reducing loading conditions and not changing contractility, the assumed linear end-systolic pressure–volume relation (B) becomes steeper, implying greater contractility (C), due to the true curvilinear end-systolic pressure–volume relation (A).



Instrumentation and protocol. Patients underwent routine right and left heart catheterization, left ventriculography and coronary arteriography. Additional femoral artery access was obtained for the 5F left coronary catheter, which was used to infuse intracoronary OPC-18790 during the protocol. A nonionic contrast agent was used to minimize the potential negative inotropic effects of contrast. After the diagnostic study, conductance and micromanometer catheters were advanced to the left ventricular apex, as described previously (10). Baseline hemodynamic variables were recorded at least 30 min after the diagnostic catheterization and included heart rate, mean right atrial pressure, pulmonary artery pressure, pulmonary artery wedge pressure, aortic pressure, left ventricular end-diastolic and systolic pressures, thermodilution cardiac output and stroke volume. Transient balloon catheter (SP-9168, Cordis) obstruction of the inferior vena cava was performed to generate pressure–volume relations from beats at decreasing preloads. Steady state conditions were rapidly restored after balloon deflation. Data were digitized at 200 Hz by use of custom acquisition and display software. After baseline data were measured, OPC-18790 was infused into the left main coronary artery at a dose of 31.25 μg/min for 20 min and then at 62.5 μg/min for another 20 min. Hemodynamic measurements, including pressure–volume relations obtained at steady state and during transient inferior vena caval occlusion, were taken at the end of the 31.25-μg/min infusion and then again at the end of the 62.5-μg/min infusion. Peripheral venous samples were drawn at each time point and for up to 2 h after the beginning of the protocol (11). The intracoronary doses were calculated to produce coronary sinus concentrations similar to the venous concentrations produced by intravenous infusion by Feldman et al. (1), based on a coronary flow rate of 125 ml/min (12), so that the intracoronary dose of 31.25 μg/min corresponded to 5.0 μg/kg per min given intravenously and 62.5 μg/min corresponded to 10.0 μg/kg per min. There were no adverse events in any of the eight patients studied. Neither arrhythmias nor an increase in baseline atrial or ventricular ectopy was noted during OPC-18790 infusion.

Conductance catheter technique. The conductance catheter technique and its principles have been fully described previously (10). A 7F or 8F conductance catheter (Webstar

Labs), with a 2F micromanometer (Millar Instruments) placed within its lumen, was used. Under fluoroscopic guidance, catheters were placed along the long axis of the left ventricle and connected to a digital stimulator microprocessor (Sigma V, Leycom [dual-field system]). An excitation current was applied to electrodes at the apex and the aortic root, and resistance differences were measured between intervening electrode pairs. The inverse of each resistance is proportional to segmental volume, and the sum of these segments yielded total volume. It has been previously demonstrated that the conductance catheter accurately measures changes in left ventricular volume during the cardiac cycle in normal and abnormal ventricles (13). The conductance catheter signal gain was calibrated with the thermodilution-derived stroke volume. This correction was made at each drug dose. The calibration offset (parallel conductance) was corrected by matching the conductance catheter signal at end-diastole with the end-diastolic volume (EDV) measured by ventriculography. Using the Kennedy-Dodge regression (14), single-plane ventriculographic volumes were obtained which have been shown to correlate well with biplane ventriculographic volumes, even in patients with dyskinetic or depressed ventricles (15). Left ventriculography was performed at baseline and at the end of the 62.5-μg/min infusion.

Data analysis. Using custom software, digitized hemodynamic data were analyzed off-line. To eliminate any 60-Hz noise, pressure–volume data were smoothed with a three-point moving average. Steady state hemodynamic measurements were determined from signal-averaged cardiac cycles, combining 5 to 10 sequential beats. Pressure–volume relations were obtained from a set of cardiac cycles during preload reduction, starting at the beat just before the onset of the left ventricular pressure decline and ending with the nadir of the pressure decline, or before a reflex increase of >5% in heart rate for three consecutive beats. Extrasystolic beats and at least two post-extrasystolic beats were excluded from the analysis.

Hemodynamic variables. 1) *Preload* was defined as EDV and was measured by left ventriculography. 2) *Arterial loading* was determined by systemic vascular resistance (SVR = [mAoP − mRAP]/CO), where mAoP = mean aortic pressure; mRAP = mean right atrial pressure; and CO = cardiac output, and by arterial elastance (E_a = ESP/SV), where ESP = end-systolic pressure; and SV = stroke volume. SVR quantifies mean resistance, whereas E_a incorporates both mean and pulsatile components of the arterial load (16). 3) *Systolic pump function* variables included CO, stroke volume and stroke work. Stroke work was defined as the area enclosed by the pressure–volume relation. 4) *Contractility* was assessed by four methods: the ratio of maximal rate of rise in left ventricular pressure (dP/dt) to EDV (17), the slope of the end-systolic pressure–volume relation (E_{es}) (18), the slope of the stroke work to EDV relation (Msw) (19) and the ratio of the maximal power index (PWR_{max}) to EDV^2 (20). 5) *dP/dt* was derived digitally by the use of a five-point weighted slope. 6) *End-systolic pressure–volume points* were fit by perpendicular regression to derive E_{es}. 7) *Stroke work* and 8) *EDV* were measured for the same set of beats, and the relation was fit by linear regression, to yield the slope (Msw). 9) PWR_{max} was the product of peak instantaneous pressure and flow (left ventricular pressure and dV/dt). PWR_{max} was divided by EDV^2 to minimize load dependence, as previously described and validated (20).

Diastolic function. Diastolic variables included the diastolic pressure–volume relation and the time constant for isovolumic relaxation (tau). Tau was calculated by regressing left ventricular pressure versus dP/dt during the isovolumic relaxation phase (21). Other variables measured included minimal left ventricular pressure, the driving pressure for left ventricular filling (expressed as the difference between the V wave of the pulmonary artery wedge pressure and minimal left ventricular pressure), left ventricular end-diastolic pressure (the lower right-hand corner of the pressure–volume loop), peak positive dV/dt and peak negative dP/dt.

Ventriculoarterial coupling and myocardial efficiency. Ventriculoarterial coupling was determined by the E_{es}/E_a ratio. This ratio reflects the matching of left ventricular contractility to arterial loading. In normal subjects, this ratio is typically ≥1.5, and it declines to <0.5 in patients with congestive heart failure (22). Such reduced ratios reflect a depressed left ventricular contractile state (low E_{es}) coupled with a high vascular resistance (high E_a). An increase in this ratio would be predicted to increase ventricular work and efficiency (stroke work/$M\dot{V}O_2$) (23). Myocardial oxygen consumption ($M\dot{V}O_2$) was estimated by the pressure–work index (PWI) of Rooke and Feigl (24), calculated by $PWI = 4.08 * 10^{-4} * (sAoP * HR) + 3.25 * 10^{-4} * (0.8\ sAoP - 0.2\ dAoP) * (HR * SV/BW) + 1.43$, where sAoP and dAoP = systolic and diastolic aortic pressure; HR = heart rate; and BW = body weight (kg). This method has been shown to correlate reasonably well with directly measured $M\dot{V}O_2$ (25). Both stroke work and $M\dot{V}O_2$ were expressed in joules.

Statistical analysis. Data are expressed as the mean value ± SEM. Drug-induced changes were tested for by repeated measures analysis of variance, and multiple comparisons were performed by using a *t* test with the Bonferroni correction.

Results

Effect of intracoronary OPC-18790 on heart rate and vascular load (Table 1). Heart rate was not significantly altered by either dose of OPC-18790. There was a small but significant effect on right heart load as determined by a fall in right atrial pressure, and a more pronounced effect on mean pulmonary artery wedge pressure. These effects were greater at 62.5 μg/min than at 31.25 μg/min. There were no significant effects on arterial load as determined by SVR index and E_a, or preload as determined by left ventricular EDV.

Effect of intracoronary OPC-18790 on systolic function, ventriculoarterial coupling and efficiency (Table 2). There were no significant effects on stroke volume, CO or stroke work. Among the more load-insensitive measures of contrac-

Table 1. Effects of Intracoronary OPC-18790 on Heart Rate and Vascular Load

	Baseline	31.25 μg/min	62.5 μg/min	p Value
HR (beats/min)	88 ± 4	87 ± 4	86 ± 4	NS
mRAP (mm Hg)	9 ± 1	8 ± 1	7 ± 1*	< 0.01
mPAP (mm Hg)	32 ± 3	27 ± 2	26 ± 3	0.05
sPAP (mm Hg)	43 ± 4	37 ± 3	34 ± 4	< 0.005
dPAP (mm Hg)	23 ± 3	20 ± 2	19 ± 3	0.07
mPAW (mm Hg)	21 ± 3	18 ± 2	16 ± 2*	< 0.05
EDV (ml)	177 ± 12		173 ± 12	NS
mAoP (mm Hg)	101 ± 6	101 ± 6	100 ± 6	NS
sAoP (mm Hg)	142 ± 9	142 ± 9	145 ± 10	NS
dAoP (mm Hg)	78 ± 4	80 ± 4	80 ± 4	NS
SVR (dynes·s·cm^{-5})	1,802 ± 161	1,870 ± 205	1,991 ± 235	NS
PVR (dynes·s·cm^{-5})	203 ± 22	191 ± 32	223 ± 45	NS
E_a (mm Hg/ml)	3.1 ± 0.3	3.1 ± 0.3	3.3 ± 0.4	NS

*$p < 0.05$ versus 31.25-μg/min dose. Data are presented as mean value ± SEM. dAoP = diastolic aortic pressure; dPAP = diastolic pulmonary artery pressure; E_a = arterial elastance; EDV = end-diastolic volume; HR = heart rate; mAoP = mean aortic pressure; mPAP = mean pulmonary artery pressure; mPAW = mean pulmonary artery wedge pressure; mRAP = mean right atrial pressure; PVR = pulmonary vascular resistance; sAoP = systolic aortic pressure; sPAP = systolic pulmonary artery pressure; SVR = systemic vascular resistance.

tile function, there was a significant increase in the ratio of maximal dP/dt to EDV by 74% and an increase in E_{es} by 85% (Fig. 2). Msw and PWR_{max}, both of which are dependent on changes in stroke volume, end-systolic pressure and stroke work, were not affected by either dose. Ventriculoarterial coupling, defined by the ratio of E_{es}/E_a, significantly improved by 80%, as there was a significant increase in E_{es} without any change in E_a. Efficiency remained constant, as there was no significant change in either stroke work or estimated $M\dot{V}O_2$.

Effect of intracoronary OPC-18790 on diastolic function (Table 3). There was a significant reduction in tau, reflecting enhanced active relaxation, without any significant difference between the two doses. Although preload as determined by EDV was not affected, there was a small fall in right atrial pressure and a larger fall in pulmonary artery wedge pressure (Table 1). There was also a significant decrease in minimal left ventricular end-diastolic pressure. Consistent with this fall in pressure, without any change in volume, inspection of the pressure–volume relations revealed a downward shift, consistent with pericardial release in five of the eight patients studied (Fig. 3).

Plasma concentrations of OPC-18790. Despite the intracoronary route of delivery, systemic levels were detectable. Plasma concentrations of OPC-18790 peaked at 54 ± 7 ng/ml at the end of the second 20-min infusion and fell thereafter to 12 ± 4 at 2 h. These levels are much lower than the peripheral levels from the equivalent dose of 10.0 μg/kg per min administered intravenously by Feldman et al. (1), who reported levels of 782 ± 50 ng/ml at this dose after 45 min of infusion.

Discussion

The present study demonstrates that in the absence of a reduction in preload (EDV) and afterload (E_a), intracoronary OPC-18790 is a modest inotrope. The rise in E_{es} in the current study, using intracoronary administration, was much less than that found with comparable intravenous doses used previously (1), consistent with curvilinearity of the end-systolic pressure–volume relation (Fig. 1). Improvement of isovolumic relaxation was also demonstrated in the absence of a reduction of afterload. In addition, the small fall in right atrial pressure results in a marked reduction in pulmonary artery wedge pressure, without any change in EDV, due to pericardial release. These effects are accompanied by improved ventriculoarterial coupling, constant efficiency and no increase in heart rate. These results imply that OPC-18790 is a favorable agent for the intravenous treatment of congestive heart failure.

Inotropic effects. The current study confirms that OPC-18790 is a weak inotrope. When intracoronary OPC-18790 was administered at 31.25 and 62.5 μg/min, there was a significant increase in E_{es} of 22% to 85% and an increase in the ratio of

Table 2. Effects of Intracoronary OPC-18790 on Systolic Function, Ventriculoarterial Coupling and Myocardial Efficiency

	Baseline	31.25 μg/min	62.5 μg/min	p Value*
SV by td (ml)	47 ± 4	49 ± 5	47 ± 5	NS
CI by td (liters/min per m^2)	2.4 ± 0.1	2.4 ± 0.2	2.3 ± 0.2	NS
SW (mm Hg/ml)	5,168 ± 700	5,381 ± 842	5,627 ± 725	NS
$dP/dt_{max}/EDV$ (mm Hg·s^{-1}·ml^{-1})	3.5 ± 0.5	4.2 ± 0.6	6.1 ± 0.8	< 0.005
E_{es} (mm Hg/ml)	0.74 ± 0.11	0.90 ± 0.16	1.37 ± 0.33	< 0.05
Msw (mm Hg)	42 ± 8	55 ± 8	47 ± 6	NS
PWR_{max}/EDV^2 (W/ml^2·1,000)	2.95 ± 0.76	3.49 ± 0.91	3.47 ± 1.16	NS
E_{es}/E_a ratio	0.25 ± 0.05	0.30 ± 0.06	0.45 ± 0.12	< 0.05
$M\dot{V}O_2$	2.12 ± 0.12	2.14 ± 0.13	2.17 ± 0.12	NS
Efficiency† (%)	31.8 ± 2.6	32.6 ± 2.8	34.0 ± 2.7	NS

*By repeated measures analysis of variance. †Myocardial efficiency (stroke work/myocardial oxygen consumption). Data are presented as mean value ± SEM. CI = cardiac index; $dP/dt_{max}/EDV$ = preload-adjusted peak rate of rise in left ventricular pressure; E_{es} = end-systolic elastance; E_{es}/E_a = ratio of end-systolic elastance to arterial elastance; Msw = preload recruitable stroke work; $M\dot{V}O_2$ = predicted myocardial oxygen consumption (ml O_2/beat per 100 g); PWR_{max}/EDV^2 =maximal power index; SV = stroke volume; SW = stroke work; td = thermodilution method.

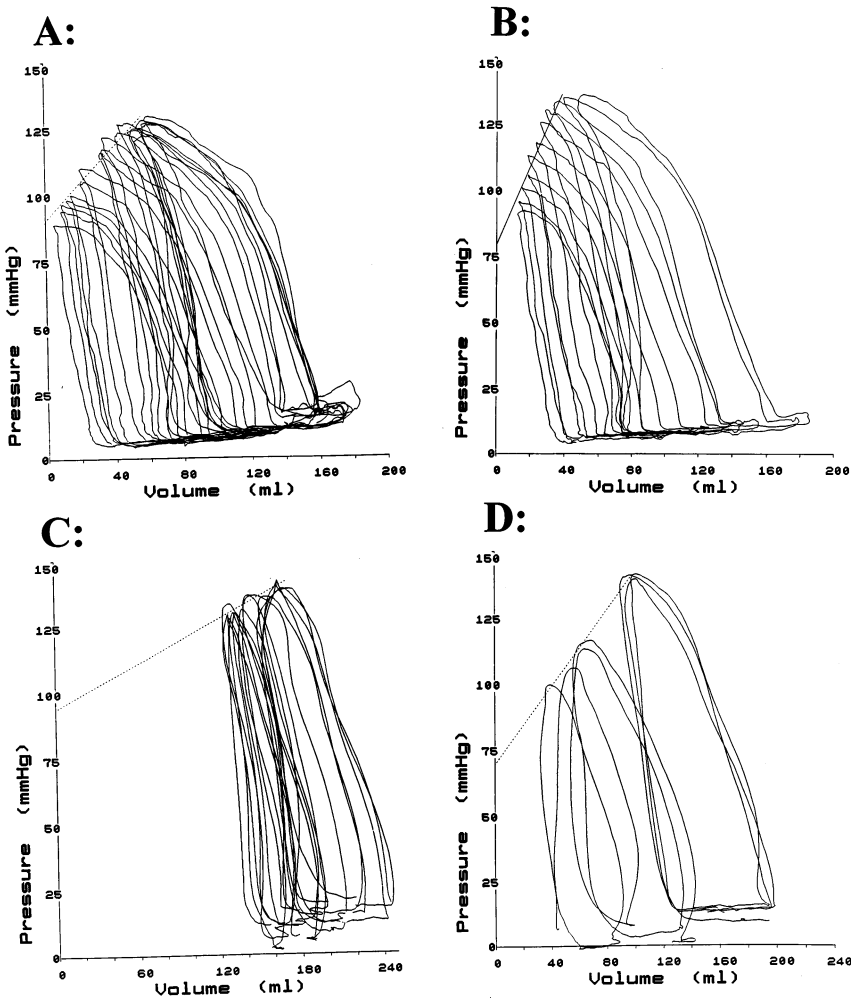


Figure 2. Examples of pressure–volume loops during inferior vena caval occlusion from patients receiving intracoronary OPC-18790 **(top)** and intravenous OPC-18790 **(bottom)** at baseline **(A and C)** and at either 62.5 μg/min by intracoronary infusion **(B)** or the equivalent intravenous dose of 10 μg/kg per min **(D).** Note that with intracoronary infusion the end-diastolic and end-systolic volumes do not change (first loop of the ramp), whereas with intravenous infusion there are marked decreases in both end-diastolic and end-systolic volumes, which may lead to an overestimation of the improvement in E_{es}.

maximal dP/dt to EDV of 20% to 74%. Other indexes of contractility, such as Msw and PWR_{max}, were not significantly affected by either dose. These changes in contractility are much less than those found with the equivalent intravenous doses of 5 to 10 μg/kg per min of OPC-18790, which increased E_{es} by 124% to 172% in the study of Feldman et al. (1). The effects of intravenous OPC-18790 on E_{es} may have been overestimated (1). It has been shown in animal studies (8,9) that the slope of the end-systolic pressure–volume relation is concave away from the volume axis. With reduced loading conditions and no change in contractility, the end-systolic pressure–volume relation would have moved to a steeper part of the curve (Fig. 1), giving the false appearance of an inotropic effect. Because this curvilinear relation is further enhanced by an increase in contractility, the 124% to 172% increase in E_{es} with intravenous OPC-18790 administration is an overestimation, as confirmed in the present study.

Despite being a weak inotrope, OPC-18790 develops less

Table 3. Effects of Intracoronary OPC-18790 on Diastolic Function

	Baseline	31.25 μg/min	62.5 μg/min	p Value
Tau (ms)	94 ± 9	79 ± 9*	78 ± 8	< 0.05
$-dP/dt_{min}$ (mm Hg·s^{-1})	−1,063 ± 93	−1,183 ± 102	−1,197 ± 119	0.06
LV_{min} (mm Hg)	15 ± 1	13 ± 1	11 ± 2	< 0.05
PAW(V) − LV_{min} (mm Hg)	7 ± 2	5 ± 2	5 ± 2	NS
LVEDP (mm Hg)	23 ± 1	20 ± 2	20 ± 2	< 0.05
dV/dt (ml·s^{-1})	440 ± 42	396 ± 29	485 ± 38	0.06

*$p < 0.05$ compared with baseline value. Data are presented as mean value ± SEM. $-dP/dt_{min}$ = peak negative rate of rise in left ventricular pressure; dV/dt = peak early diastolic first derivative of volume; LV_{min} = minimal left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; PAW(V) = V wave of pulmonary artery wedge pressure.

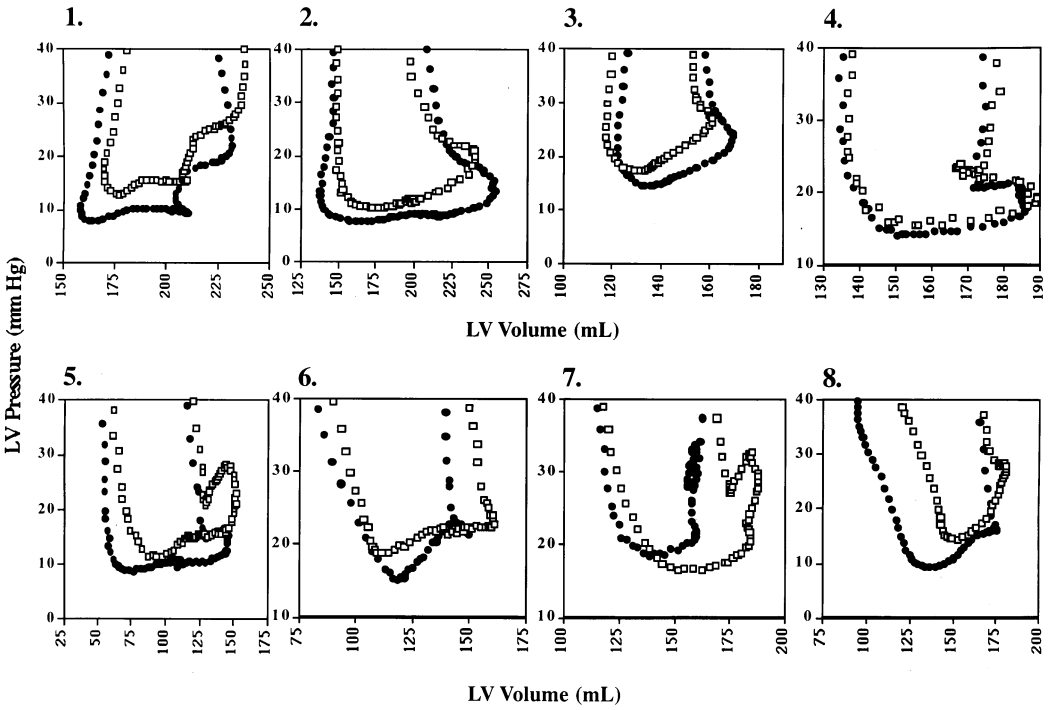


Figure 3. The diastolic portions of the pressure–volume loops in all eight patients are shown. In Patients 1 to 5, there is evidence of pericardial release with OPC-18790, with a reduction in left ventricular (LV) pressure without a change in volume. **Open squares** = baseline; **solid circles** = 62.5-μg/min dose (the 31.25-μg/min dose is excluded to aid in clarity).

tachyphylaxis and decrease in adenylate cyclase activity than with dobutamine (26), which results in sustained elevations in the cardiac index and dP/dt over 1 week in animals treated with dobutamine. We hypothesize that these effects are caused by some of the unique cellular features of OPC-18790 compared with more traditional agents. The inotropic effects of OPC-18790 are due primarily to inhibition of phosphodiesterase-III (2), although other electrophysiologic effects that result in a prolonged action potential and reduced potassium repolarization currents may also contribute to the inotropic effects (4). Although phosphodiesterase inhibitors generally increase heart rate, the inotropic effects of OPC-18790 are not accompanied by changes in heart rate. The increase in heart rate found with traditional beta-agonists and phosphodiesterase inhibitors partly explains their less favorable effects on efficiency compared with OPC-18790 (27). Illustrating the importance of the chronotropic effects on $M\dot{V}O_2$, Yamakawa et al. (28) demonstrated that the negative chronotropic effects of beta-blockade offset the mechanoenergetic deterioration resulting from negative inotropic effects. This absence of heart rate effects has also been shown to minimize changes in high energy phosphate metabolites when OPC-18790 is administered to a globally ischemic guinea pig heart model, and these results were in contrast to those in studies with amrinone or dobutamine (29).

Diastolic effects. In isolated muscle, OPC-18790 shortens relaxation (2). In human heart failure, previous investigators have demonstrated that intravenous OPC-18790 shortens tau. However, tau, which reflects the active portion of ventricular relaxation, is known to be afterload-dependent (5–7), so a concomitant reduction in afterload may also reduce tau. Ishikaza et al. (5) have shown, in a canine pacing tachycardia-induced heart failure model, that there is a steeper relation between tau and end-systolic force after development of heart failure. Eichorn et al. (7) have made the same observations in patients with heart failure. These studies imply that in heart failure, the afterload sensitivity of tau is even greater. Other investigators have suggested that this does not mean enhanced load sensitivity in heart failure, but rather that the relation between end-systolic force and tau is J shaped, with the steep portion of the curve seen when end-systolic forces are markedly elevated in heart failure (6). Because no significant changes in afterload were seen in this study, the observed decrease in tau reflects improved diastolic function. In humans, Hoit et al. (3) have shown that OPC-18790 improves early diastolic filling. They demonstrated that the posterior wall thinning rates were increased and also that early diastolic transmitral flow was unchanged despite a reduction in pulmonary artery wedge pressure, suggesting that the early diastolic transmitral gradient was maintained by a beneficial effect on isovolumic left ventricular relaxation. They also demonstrated that the pulmonary artery wedge pressure was lower, although EDV was unchanged, which was attributed to a change in the passive diastolic chamber compliance. However, we also observed a similar decrease in pulmonary artery wedge pressure and no change in EDV. We interpreted this to be due to pericardial release in five of eight patients (Fig. 3). This

demonstrates how the use of pressure–volume loops allows a more mechanistic interpretation of these interrelating factors, which are not appreciable with other methods.

Tau, as calculated from the semilogarithmic slope of pressure versus time, as described by Weiss et al. (30), is dependent on transmural pressures (31) and could be affected by release of the pericardium observed in this study. However, the calculation of tau in this study involves plotting the first derivative of pressure against pressure (21) and is independent of pericardial pressures. Despite the shortening of active relaxation, as measured by tau, and the associated fall in minimal left ventricular pressure, there was only a borderline increase in dV/dt ($p = 0.06$). The driving gradient for left ventricular filling (the difference between the V wave of the pulmonary artery wedge pressure and minimal left ventricular pressure) was not significantly changed, which explains the absence of a significant increase in dV/dt. Inspection of the diastolic portion of the pressure–volume curves demonstrates that in five of the eight patients there was a parallel downward translation of the relation, consistent with pericardial release. Dauterman et al. (32) have shown that the pericardium can contribute significantly to filling pressures, so that when the diastolic pressure at rest is >6 mm Hg, almost 38% of the pressure is due to external factors. The phenomenon of pericardial release is seen early after decreases in preload (32,33), equivalent to the small decrease in right atrial pressure, with no change in left ventricular EDV, seen in this study. This resulted in a fall in both pulmonary artery wedge pressure and left ventricular diastolic pressures, with the result that the driving pressure across the mitral valve (V wave of pulmonary artery wedge pressure − minimal left ventricular pressure) did not increase as expected. Because the driving gradient across the mitral valve is a major determinant of dV/dt (34), the absence of change in mitral driving gradient shown in Table 3 would attenuate the predicted increase in dV/dt.

Conclusions. Intracoronary administration of OPC-18790 demonstrates that the direct myocardial effects of this drug include a modest increase in inotropy, improvement in diastolic function and no change in heart rate. These effects result in lowered left heart filling pressures, (partly due to pericardial release), improved ventriculoarterial coupling, constant $M\dot{V}O_2$ and myocardial efficiency, without provoking arrhythmias. These results indicate that this agent may be a useful alternative to more traditional agents for intravenous treatment of congestive heart failure.

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