JACC Vol. 3, No. 4
April 1984:1044–50

Beneficial Hemodynamic Effects of Intravenous and Oral Diltiazem in Severe Congestive Heart Failure

RICHARD W. WALSH, MD, FACC, CHARLES B. PORTER, MD, MARK R. STARLING, MD, FACC, ROBERT A. O'ROURKE, MD, FACC

San Antonio, Texas

Concern persists about the potential negative inotropic effects of calcium channel blockers in patients with severely depressed myocardial function. Therefore, intravenous diltiazem (100 to 200 μg/kg per min infusion) was administered for 40 minutes followed by oral diltiazem (90 to 120 mg/8 hours) for 24 hours to patients with advanced congestive heart failure (New York Heart Association class III to IV, mean ejection fraction 26 ± 4 [SD]). Intravenous diltiazem (eight patients) increased cardiac index 20% (2.05 ± 0.8 to 2.47 ± 0.8 liters/min per m^2, $p < 0.01$), stroke volume index 50% (22 ± 9 to 33 ± 12 ml/m^2, $p < 0.001$) and stroke work index 27% (19 ± 10 to 24 ± 10 g-m/m^2, $p < 0.05$); while reducing heart rate 23% (97 ± 18 to 75 ± 11 beats/min, $p < 0.01$), mean arterial pressure 18% (95 ± 13 to 78 ± 7 mm Hg) and pulmonary wedge pressure 34% (29 ± 9 to 19 ± 7 mm Hg), without altering maximal first derivative of left ventricular pressure (dP/dt_{max}). Oral diltiazem (seven patients) produced equivalent hemodynamic effects. Transient junctional arrhythmias were observed in three of eight patients with intravenous diltiazem and one of seven patients with oral diltiazem.

It is concluded that intravenous and short-term oral diltiazem improve left ventricular performance and reduce myocardial oxygen demand by heart rate and afterload reduction without significantly depressing contractile function in severe congestive heart failure. Caution should be exercised to avoid potential adverse, drug-induced electrophysiologic effects in such patients.

Appropriate concerns persist regarding the potential negative inotropic properties of the calcium channel blocking drugs, particularly when used in patients with depressed left ventricular performance. These structurally heterogeneous compounds share three basic hemodynamic characteristics: peripheral and coronary artery vasodilation, reflex sympathetic stimulation and myocardial depression (1). The first two properties tend to augment left ventricular performance and mitigate or abrogate drug-induced negative inotropism under usual circumstances (1,2). However, the net cardiocirculatory response to such agents may differ depending on the calcium channel blocking agent employed (3,4), the dose, the use of concomitant cardioactive drugs (5,7) and the hemodynamic status of the patient (8).

Several clinical investigations detailing the beneficial effects of nifedipine as vasodilator therapy for congestive heart failure have been reported (8–11). However, problems regarding patient selection and the use of a single acute dose of nifedipine preclude extrapolation of these data to subacute or chronic administration of calcium blocking agents to patients with heart failure because of depressed myocardial function. In addition, acute pulmonary edema and hypotension with reduced cardiac output after parenteral and oral verapamil and oral nifedipine have been reported (12–14). By contrast, there have been no investigations detailing the hemodynamic actions of diltiazem, the calcium blocking agent with the least negative inotropic effects (1,15), in patients with severe heart failure.

Previously we demonstrated (3) that diltiazem produced the least myocardial depression of the available calcium blockers when given in equimolar, equihypotensive doses by either the intravenous or intracoronary route in the awake, preinstrumented dog with normal cardiovascular function. However, more recently we observed (16) that this drug substantially reduced the rate of left ventricular pressure development (dP/dt_{max}) in an animal model of high output congestive heart failure with enhanced left ventricular function, when given in a dose which produced no negative

From The Department of Medicine, Division of Cardiology, The University of Texas Health Science Center at San Antonio, San Antonio, Texas. This study was supported in part by Grants HL 07350 and IF32 HL6539 from the National Institutes of Health and the Veterans Administration, Bethesda, Maryland. The data were presented in part at the 55th Annual Scientific Sessions of the American Heart Association, Dallas, Texas, November 1982. Manuscript received July 25, 1983; revised manuscript received September 27, 1983, accepted October 21, 1983.

Address for reprints: Richard A. Walsh, MD, Department of Medicine/Cardiology, The University of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, Texas 78284.

0735-1097/84/$3.00

inotropic effect in the same animal before the induction of congestive heart failure. Accordingly, we designed the present investigation to assess the effects of intravenous diltiazem on left ventricular performance and evaluate the hemodynamic effects of high dose oral diltiazem in patients with severe congestive heart failure due to myocardial depression.

Methods

Study patients. Patients referred for cardiac catheterization for routine diagnostic purposes were invited to participate in the study. Eight patients (five men and three women), mean age 49 years (range 31 to 56), consented to the experimental protocol, which was approved on April 21, 1981, by the Institutional Review Board of The University of Texas Health Science Center at San Antonio. All patients had New York Heart Association functional class III or IV heart failure, despite conventional medical treatment which included digoxin and furosemide in all cases and vasodilator therapy in five. All cardioactive medications were withheld at least 24 bours before and for the entire duration of the study. Additional criteria included the absence of acute myocardial infarction within 6 months or valvular heart disease. Four of the subjects had ischemic cardiomyopathy and four had idiopathic dilated cardiomyopathy (Table 1).

Cardiac catheterization procedure. Catheterization was performed in the fasting state, without premedication, using the brachial artery approach. All eight patients had systemic arterial pressure monitored by a percutaneous cannula. Balloon flow-directed catheters were employed to measure right heart pressures, and cardiac output was recorded in triplicate by computer-derived indicator-dilution technique (Lyons Instruments). Both systemic arterial and right-sided pressures were measured by fluid-filled catheter systems utilizing Statham P23Db strain gauges and recorded on an Electronics for Medicine VR16 recorder. Left-sided pressure and first derivative of left ventricular pressure (dP/dt) were obtained in six patients using an 8 French high fidelity micromanometer-tipped angiographic catheter. Electronic calibration, differentiation and correction for zero drift were accomplished by methods previously reported for this laboratory (17).

Simultaneous biplane left ventricular cineangiography was performed in the 30° right anterior oblique and 60° left anterior descending/20 cranially angulated projections (CGR Double Angiomax) after the injection of 40 and 70 ml, respectively, of radiopaque contrast (Renografin-76) at 10 to 20 ml/s, at a frame rate of 60/s. Image analysis was performed on one of the first three sinus beats after contrast injection when the effects of contrast material on myocardial performance are negligible. Left ventricular end-diastolic and end-systolic volumes were calculated using a modified biplane formula (18).

Experimental protocol. *Intravenous phase.* The experimental protocol was divided into two phases: an intravenous phase in the catheterization laboratory and an oral phase in the coronary care unit. All eight patients underwent the intravenous phase. Control measurements (C_1) were recorded when systemic arterial and pulmonary wedge pressures were unchanged for a minimum of 15 minutes. Diltiazem (Marion Laboratories) was then administered in either a 100 (four patients) or a 200 (four patients) μg/kg intravenous bolus infusion (dissolved in normal saline solution), with a drug infusion sufficient to produce a 15 to 20% decrease in steady state mean systemic arterial pressure (mean diltiazem dose 13 $\pm$ 2 μg/kg per min). Steady state measurements were made during 5, 10, 20 and 40 minutes of drug administration. Diagnostic coronary arteriography and biplane left ventriculography were performed 20 minutes after cessation of the intravenous drug infusion when all hemodynamic variables had returned to baseline.

Oral phase. Seven of these eight patients consented to the oral phase of the study. This involved transfer to the coronary care unit, intravenous saline solution administration and a mean delay of 2.5 hours postcatheterization for the osmotic effects of iodinated contrast medium to dissipate and hemodynamic profiles to return to prediltiazem baseline

Table 1. Characteristics of Patients With Severe Congestive Heart Failure Given Diltiazem

Patient	Age (yr)	Diagnosis	Functional Class*	LVEDVI† (cc/m^2)	Ejection Fraction‡ (%)
1	56	PMD	III	300	30
2	52	IHD	IV	189	30
3	53	PMD	IV	198‡	15‡
4	51	IHD	IV	184	26
5	31	PMD	III	173	28
6	62	IHD	III	142	32
7	37	PMD	IV	180	11
8	53	IHD	IV	204	25
Mean $\pm$ SD	49 $\pm$ 10			196 $\pm$ 46	24 $\pm$ 6

*New York Heart Association criteria; †biplane left ventriculography; ‡radionuclide ventriculography. IHD = ischemic cardiomyopathy; LVEDVI = left ventricular end-diastolic volume index; PMD = primary myocardial disease.

JACC Vol. 3, No. 4
April 1984:1044–50

Table 2. Systemic Hemodynamic Effects of Diltiazem in Patients With Left Ventricular Failure (mean ± standard deviation)

	Intravenous (n = 8, 150 ± 53 μg/kg bolus, 13 ± 2 μg/min infusion)						Oral (n = 7, 116 ± 11 mg/8 h)			
	C_1	5 min	10 min	20 min	40 min	C_2	8 h	16 h	24 h
Heart rate (beats/min)	97 ± 18	85 ± 14*	80 ± 13*	75 ± 11*	72 ± 12*	88 ± 18	80 ± 14*	74 ± 9*	77 ± 10*
Mean systemic arterial pressure (mm Hg)	95 ± 13	86 ± 10*	86 ± 11*	78 ± 7*	75 ± 8*	93 ± 18	85 ± 14	87 ± 13	89 ± 16
Cardiac index (liters/min per m^2)	2.05 ± 0.8	2.48 ± 1*	2.48 ± 0.8*	2.47 ± 0.8*	2.44 ± 0.8*	1.89 ± 0.6	2.20 ± 0.6‡	2.53 ± 0.9*	2.67 ± 0.6*
Stroke volume index (cc/m^2)	22 ± 9	31 ± 13†	32 ± 12†	33 ± 12†	35 ± 15†	23 ± 9	28 ± 9‡	34 ± 12†	35 ± 8†
Pulmonary wedge pressure (mm Hg)	29 ± 9	24 ± 9†	23 ± 12†	21 ± 9†	19 ± 7†	25 ± 7	17 ± 4‡	19 ± 5	22 ± 6
Stroke work index (g-cm^2·m^2)	19 ± 10	26 ± 15‡	26 ± 13‡	24 ± 10‡	27 ± 17‡	20 ± 10	28 ± 15‡	34 ± 18†	33 ± 12†
Systemic resistance (dynes·s·cm^{-5})	2,465 ± 410	1,824 ± 307†	1,868 ± 266†	1,637 ± 460†	1,708 ± 375†	2,466 ± 437	1,986 ± 331‡	1,869 ± 588*	1,794 ± 271*
Mean pulmonary artery pressure (mm Hg)	44 ± 7	35 ± 9†	32 ± 11†	31 ± 8†	31 ± 7†	42 ± 6	28 ± 10‡	31 ± 8‡	34 ± 12‡
Pulmonary resistance (dynes·s·cm^{-5})	382 ± 144	237 ± 110*	206 ± 70*	216 ± 89*	277 ± 116*	435 ± 143	256 ± 200‡	291 ± 168‡	278 ± 81‡
Plasma diltiazem (ng/ml)	0	259 ± 135	341 ± 212	430 ± 103	444 ± 188	30 ± 17	210 ± 134	148 ± 95	307 ± 72

*, †, ‡probability (versus control) ≤ 0.01, 0.001 and 0.05, respectively, by analysis of variance. C_1 = control pre-intravenous diltiazem; C_2 = control pre-oral diltiazem.

levels. Control measurements (C_2) were then performed when systemic arterial and pulmonary wedge pressures were stable for a minimum of 30 minutes. Oral diltiazem was administered to one patient in a dose of 90 mg every 8 hours, and to six patients in a dose of 120 mg every 8 hours. Serial measurements of hemodynamic variables were made for a 24 hour period. Plasma diltiazem levels were assessed concomitantly with hemodynamic measurements during intravenous and oral drug administration by high pressure liquid chromatography.

Data analysis. Mean systemic and pulmonary artery pressures were determined by electronic filtration. Derived hemodynamic variables were determined as follows: CI = CO/body surface area (liters/min per m^2), PVR = 80 × (MAP − PCWP)/CO (dynes·s·cm^{-5}), SVI = CI/HR (ml/beat per m^2), SVR = 80 × MAP/CO (dynes·s·cm^{-5}), and SWI = SVI × (MAP − PCWP) × 0.0136 (g-m/m^2), where CI = cardiac index; CO = cardiac output; HR = heart rate; PVR = pulmonary vascular resistance; SVI = stroke volume index; SVR = systemic vascular resistance; and SWI = stroke work index.

Statistical analyses. These were performed using a repeated measures one-way analysis of variance (Program BMDP 2V) for intragroup interaction. Dunnet's *t* test was then used to assess statistical significance among group mean values. The level of significance was chosen as probability [p] ≤ 0.05. Results are expressed as the mean ± 1 standard deviation (SD).

Results

Control hemodynamic data (Tables 1 and 2; Fig. 1 to 4). Control data (C_1) for the group before intravenous diltiazem included heart rate 97 ± 18 beats/min, mean arterial pressure 95 ± 13 mm Hg, pulmonary capillary wedge pressure 29 ± 9 mm Hg and cardiac index 2.05 ± 0.8 liters/min per m^2. The left ventricular end-diastolic volume index was 196 ± 46 ml and the mean ejection fraction was 24 ± 6%. Left ventricular volumes and ejection fraction were determined by biplane angiography in seven patients and by radionuclide angiography in one patient. There were no significant differences in control hemodynamic values between the intravenous and oral phases of the investigation.

Hemodynamic effects of diltiazem. Mean steady state hemodynamic alterations produced at each time period by intravenous and oral diltiazem appear in Table 2. Figures 2 through 4 compare changes in selected hemodynamic variables during 20 minutes and 24 hours of intravenous and oral diltiazem, respectively.

Rate of pressure development (Fig. 1). The effect of intravenous diltiazem on the rate of pressure development (dP/dt_{max}) in the left ventricle was evaluated in six patients. In two patients, dP/dt was unobtainable because of complete left bundle branch block (Case 1) or inability to advance

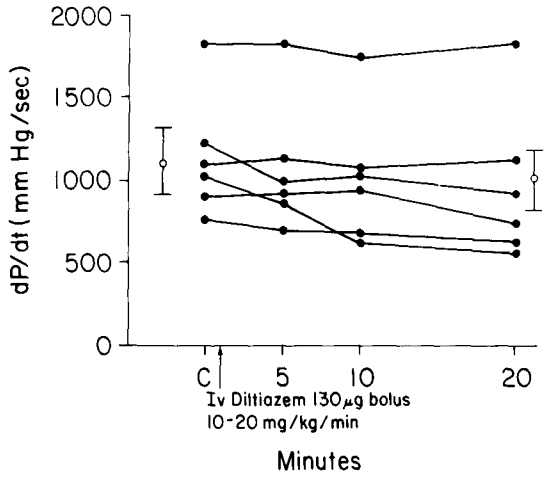

Figure 1. Effects of intravenous (Iv) diltiazem on maximal rate of size of left ventricular pressure (dP/dt_{max}) in six patients. There is no significant difference from control (C) at 5, 10 or 20 minutes of drug infusion.

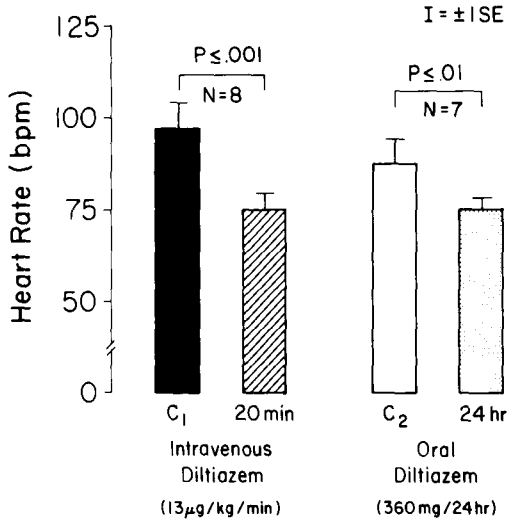

Figure 2. Effects of intravenous and oral diltiazem on heart rate at 20 minutes and 24 hours of drug administration, respectively. A significant negative chronotropic effect was present after both intravenous and oral diltiazem (T = SE).

the high fidelity catheter into the left ventricle (Case 3). There was no significant change in dP/dt_{max} from control for the group during 5, 10 or 20 minutes of drug infusion (for example, control = 1,165 ± 171 mm Hg/s versus 20 minute diltiazem infusion = 1,062 ± 191, p = NS). However, dP/dt_{max} was reduced in two of the six patients during intravenous diltiazem administration.

Heart rate, aortic and arterial pressure. Heart rate decreased significantly during 20 minutes of intravenous diltiazem from 97 ± 18 to 75 ± 11 beats/min (a decrease of 23%, $p < 0.001$) and from 88 ± 18 to 76 ± 10 beats/min (a decrease of 13%, $p < 0.01$) during 24 hours of oral diltiazem (Fig. 2). Mean aortic pressure also declined from 95 ± 13 to 78 ± 7 mm Hg (a decrease of 18%, $p < 0.01$), although there was no significant change in arterial pressure after the oral diltiazem (93 ± 18 versus 89 ± 16 mm Hg, p = NS) at the same time intervals.

Pulmonary capillary wedge pressure. The changes from control in mean pulmonary capillary wedge pressure produced by intravenous oral diltiazem are recorded in Table 2. For example, pulmonary wedge pressure was reduced from 29 ± 9 to 21 ± 9 mm Hg (a decrease of 28%, $p < 0.001$) during 20 minutes of intravenous diltiazem administration, but was not significantly altered during 24 hours of oral administration (25 ± 7 to 22 ± 6 mm Hg, p = NS).

Cardiac index and stroke volume index (Table 2, Fig. 3). The cardiac index increased from 2.05 ± 0.8 to 2.47 ± 0.8 liters/min per m^2 (+ 21%, $p < 0.01$) during intravenous diltiazem, and from 1.89 ± 0.6 to 2.67 ± 0.6 liters/min per m^2 (+ 46%, $p < 0.01$) during oral diltiazem. The stroke volume index increased from 22 ± 9 to 33 ± 12 ml/m^2 (+ 55%, $p < 0.001$) after intravenous diltiazem,

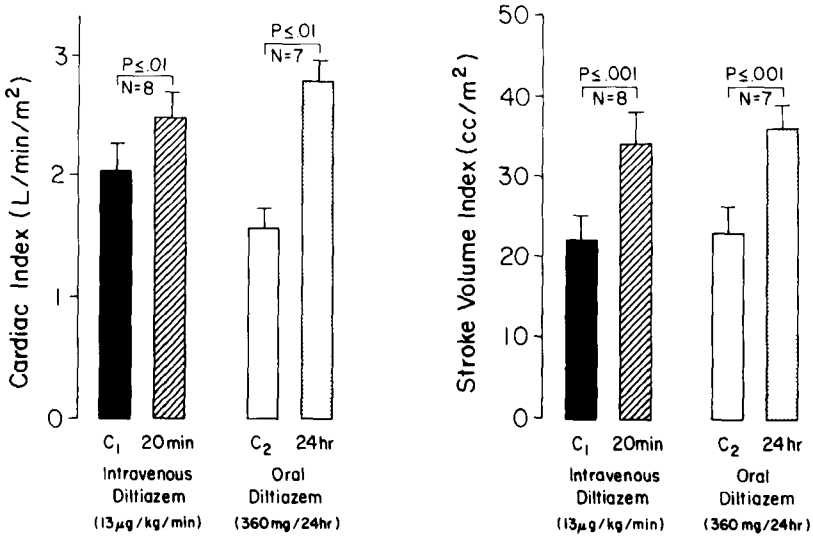

Figure 3. Relative effects of intravenous and oral diltiazem on cardiac index **(left)** and stroke volume index **(right)**. Both variables were significantly increased by both modes of administration. The relative increase in stroke volume was greater than the increase in cardiac output as a consequence of the concomitant negative chronotropic effect of diltiazem (T = SE).

and from 23 ± 9 to 35 ± 8 ml/m^2 (+ 57%, $p < 0.001$) with oral drug administration. Because heart rate declined significantly after both intravenous and oral administration, the observed increases in cardiac index are entirely a function of the substantial drug-induced augmentation of stroke volume. The observed alteration in stroke volume index, plus arterial and pulmonary capillary wedge pressure, resulted in significant increases in stroke work index during both intravenous (19 ± 10 to 24 ± 10 g-m/m^2, $p < 0.05$) and oral (20 ± 10 to 33 ± 12 g-m/m^2, $p < 0.05$) diltiazem (Table 2) at 20 minutes and 24 hours of drug administration, respectively.

Systemic and pulmonary vascular resistances (Table 2, Fig. 4). Systemic vascular resistance declined by 34% from 2,465 ± 410 to 1,637 ± 460 dynes·s·cm^{-5} ($p < 0.001$) during 20 minutes of intravenous diltiazem, while 24 hours of oral diltiazem administration reduced systemic resistance by 27% from 2,466 ± 437 to 1,794 ± 271 ($p < 0.01$). Pulmonary vascular resistance declined similarly by 43% during intravenous diltiazem (382 ± 144 to 216 ± 89 dynes·s·cm^{-5}, $p < 0.01$) and 39% (435 ± 143 to 278 ± 81 dynes·s·cm^{-5}, $p \leq 0.05$) during oral drug administration.

Plasma diltiazem levels (Table 2). The mean plasma diltiazem level that occurred after 20 minutes of intravenous diltiazem infusion was 430 ± 103 ng/ml (range 150 to 846). A mean plasma concentration of 307 ± 72 ng/ml (range 66 to 650) was measured after 24 hours of oral drug administration. These levels are considerably above the 50 to 150 ng/ml range, which has previously been shown to be clinically effective in the management of stable angina pectoris and coronary arterial spasm (19).

Adverse effects. During the intravenous phase of diltiazem administration three of four patients who were given the 200 μg bolus infusion developed a transient junctional rhythm. One of these three patients developed relative hypotension consequent to the bradyarrhythmia and was withdrawn from further study. No patient had any arrhythmia after the 100 μg/kg bolus. One of the seven patients receiving 360 mg/day of oral diltiazem had an intermittent, hemodynamically insignificant junctional rhythm which occurred during oral diltiazem administration and abated after drug withdrawal.

Discussion

Hemodynamic effects of diltiazem in congestive heart failure. The results of this investigation suggest that steady state intravenous and short-term oral diltiazem administration produced substantial improvement in left ventricular performance in a group of patients with severe congestive heart failure because of ischemic heart disease or cardiomyopathy. Beneficial hemodynamic effects included significant augmentation of cardiac stroke volume and stroke work indexes accompanied by decreases in heart rate and systemic and pulmonary vascular resistances during both intravenous and oral drug administration. Preload, as assessed by pulmonary capillary wedge pressure, was significantly reduced during the intravenous but not during the oral phase of the study. The reduction in left ventricular filling pressure occurred despite the decrease in heart rate with consequent increase in diastolic filling period. Although previous studies (1,16) failed to demonstrate direct effects of calcium channel inhibition on venous smooth mus-

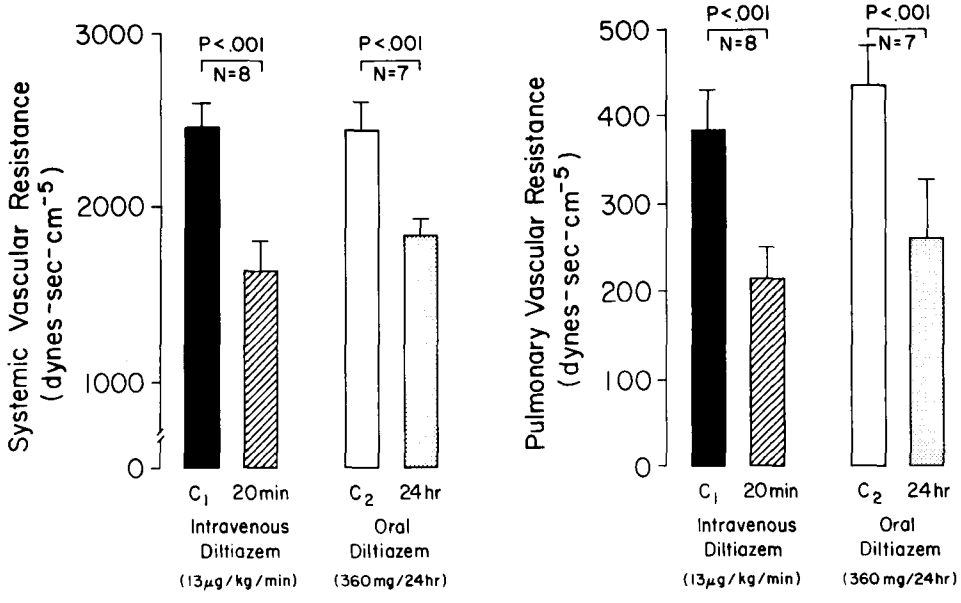

Figure 4. Effects of intravenous and oral diltiazem on systemic **(left)** and pulmonary **(right)** vascular resistance. Significant reductions in both variables were observed with both forms of administration (T = SE).

cle, reflex increases in venous capacitance or the large increases in stroke volume caused by drug induced afterload reduction may have decreased the pulmonary wedge pressure. Because left ventricular volumes were not measured after diltiazem, we cannot exclude an increase in diastolic chamber compliance as an alternative explanation for the observed reduction in left-sided filling pressures. Myocardial contractile state as assessed by left ventricular dP/dt_{max} was not significantly diminished for the group by the dose of diltiazem employed in this investigation. However, the sample size was small (six patients) and calcium blockade-induced reductions in dP/dt were observed in two patients (Fig. 1).

The mechanism responsible for the observed hemodynamic effects is undoubtedly diltiazem-induced afterload reduction, produced by systemic arteriolar vasodilation. Alternatively, coronary arterial vasodilation produced by diltiazem may have enhanced left ventricular systolic performance. This possibility seems less likely because no patient had clinical or electrocardiographic evidence of ischemia during the study and no difference was observed in the magnitude or direction of hemodynamic response between those patients with ischemic or idiopathic cardiomyopathy.

Chronotropic effects of diltiazem in congestive failure. We observed significant decreases in heart rate in these patients after intravenous (23% decrease) and oral (13% decrease) administration of diltiazem. Each of the calcium antagonists has been shown to directly reduce the frequency of sinoatrial depolarization after injection of the agents into the sinoatrial nodal artery (20,21). However, during systemic administration this direct negative chronotropic effect is usually partially or completely offset by baroreceptor-mediated reflex increases in beta-adrenergic tone in response to the systemic vasodilation produced by these drugs (3,4). The negative chronotropic response produced by diltiazem in this study may be due to the blunted baroreceptor function, coupled with the high resting level of sympathetic tone observed in chronic congestive heart failure, which amplified the direct effect of this drug on sinus node function. The transient junctional rhythm disturbances noted in some of our patients may have been an extension of these electrophysiologic properties. Alternatively, the direct effect of calcium entry blockade on the proximal conduction system may have been augmented by the elevated plasma diltiazem levels achieved in these patients (Table 2). These levels are clearly in excess of those reported after similar dosages of oral diltiazem in human beings without heart failure (19). Further investigation is indicated to determine the reason(s) for the apparent altered drug pharmacokinetics of this agent in patients with circulatory congestion.

Comparison with nifedipine. The salutory effects of diltiazem on left ventricular performance in severe congestive heart failure observed in this investigation are similar to those previously reported after acute single dose oral administration of nifedipine in patients with variably diminished cardiac function of multiple causes (8–11). In contrast, Matsui et al. (22) were unable to demonstrate sustained hemodynamic improvement after 24 hours of oral nifedipine given at 4 hour intervals in patients with depressed left ventricular performance, although afterload reduction with increased cardiac output was noted after the initial dose. Nifedipine administration was associated with either no change or modest increases in heart rate in each of the aforementioned studies, in contrast to the significant decrease in heart rate observed after acute intravenous and short-term oral diltiazem in our investigation. These data suggest that, at least acutely, administration of nifedipine can produce beneficial hemodynamic effects by afterload reduction and reflex beta-adrenergic stimulation, even in patients with clinically advanced congestive heart failure. Whether these effects are sustained after subacute or short-term drug therapy is uncertain and reports of cardiac failure associated with nifedipine, and with (5,13) and without (14) concomitant beta-adrenergic blockade have appeared.

Comparison with verapamil. Verapamil in clinically relevant doses has been shown to impair left ventricular performance in conscious dogs with normal cardiac function (3,4,23). The negative inotropic properties of this agent are augmented in the conscious animal (23) and in human beings (6,7), when sympathetic reflexes are blocked by prior beta-adrenergic blockade. By contrast, equihypotensive, equimolar doses of diltiazem produced no decrease in left ventricular function before or after beta-adrenergic blockade (3,4). Short-term studies dealing with the effects of verapamil in patients with normal or mildly reduced left ventricular function have demonstrated peripheral systemic vasodilation associated with modest improvement of systolic function (24); however, both Singh and Roche (25) and Lewis et al. (26) observed decreases in dP/dt associated with increases in left ventricular diastolic pressure after intravenous verapamil. More recently, Chew et al. (12) reported reductions in mean arterial pressure accompanied by a decrease in stroke volume index and an abrupt increase in mean pulmonary wedge pressure associated with clinical evidence of heart failure in three patients with severely reduced basal ejection fraction and mean pulmonary capillary wedge pressure greater than 20 mm Hg. These data suggest that in contrast to our findings with diltiazem, verapamil may cause frank deterioration of left ventricular performance in patients with severe congestive heart failure.

Conclusions. Intravenous and short-term oral diltiazem in maximally recommended therapeutic doses produces sustained improvement in global left ventricular performance in patients with severe cardiomyopathic congestive heart failure. The determinants of myocardial oxygen demand were favorably influenced in the absence of any significant, drug-induced negative inotropic effects. It should be em-

phasized that the favorable hemodynamic actions observed in our small patient group do not preclude the possibility of adverse hemodynamic or electrophysiologic effects in an individual patient. Until more experience is gained, all calcium blocking agents should be used with caution in patients with left ventricular dysfunction. Clearly, additional studies are needed to demonstrate potential long-term hemodynamic benefits and further delineate the pharmacokinetics of these agents in congestive heart failure.

We acknowledge Marion Laboratories, Kansas City, Missouri, for supplying diltiazem and measuring diltiazem blood levels. We also appreciate the secretarial assistance of Louise Williams.

References

1. Fleckenstein A. Specific pharmacology of calcium in myocardium, cardiac pacemakers, and vascular smooth muscle. Ann Rev Pharmacol Toxicol 1977;17:149–65.
2. Fabiato A, Fabiato F. Calcium and cardiac excitation contraction coupling. Ann Rev Physiol 1979;41:473–84.
3. Walsh RA, Badke FR, O'Rourke RA. Differential effects of systemic and intracoronary calcium channel blocking agents on global and regional left ventricular function in conscious dogs. Am Heart J 1981;102:341–50.
4. Nakaya H, Schwartz A, Millard R. Reflex chronotropic and inotropic effects calcium channel blocking agents in conscious dogs. Circ Res 1983;52:302–11.
5. Joshi PI, Dalal JJ, Ruttky MS, Sheridan DJ, Henderson AH. Nifedipine and left ventricular function in beta blocked patients. Br Heart J 1981;45:457–9.
6. Packer M, Miller J, Medina R, et al. Hemodynamic consequences of combined beta adrenergic and slow calcium channel blockade in man. Circulation 1982;65:660–70.
7. Kieval J, Kirotein E, Kessler K, Mallon SM, Myerburg RJ. The effects of intravenous verapamil on hemodynamic status of patients with coronary artery disease receiving propranolol. Circulation 1982;65:653–8.
8. Ludbrook PA, Tieffenbrunn A, Reed FR, Sobel B. Acute hemodynamic responses to sublingual nifedipine: dependence of left ventricular function. Circulation 1982;65:489–98.
9. Klugman S, Salvi A, Camerini F. Hemodynamic effects of nifedipine in heart failure. Br Heart J 1980;43:440–6.
10. Polese A, Fiorentini C, Olivari M, Guazzi M. Clinical use of a calcium antagonistic agent in acute pulmonary edema. Am J Med 1979;66:825–30.
11. Matsumoto S, Takashi I, Sada T, et al. Hemodynamic effects of nifedipine in congestive heart failure. Am J Cardiol 1980;46:476–80.
12. Chew C, Hecht H, Colett J, McCallister R, Singh B. Influence of severity of ventricular dysfunction on hemodynamic responses to intravenously administered verapamil in ischemic heart disease. Am J Cardiol 1981;47:917–22.
13. Robson RH, Vishivanath MC. Nifedipine and beta blockade as a cause of cardiac failure (abstr). Br Med J 1982;284:104.
14. Gillmer D, Kark P. Pulmonary edema precipitated by nifedipine. Br Med J 1980;280:1420–1.
15. Henry PD. Comparative pharmacology of calcium antagonists: nifedipine, verapamil, diltiazem. Am J Cardiol 1980;46:1047–58.
16. Porter CB, Walsh RA, Badke Fr, O'Rourke RA. Differential effects of calcium, diltiazem and nitroprusside on left ventricular function in chronic volume overload. Circulation 1983;68:685–92.
17. Walsh RA, Crawford NM, O'Rourke RA. Relative sensitivity of echocardiography and systolic time intervals for assessing acute positive inotropic interventions in normal human subjects. Am Heart J 1982;104:1061–70.
18. Dodge HT, Sandler H, Ballew DW, Lord J. Use of biplane angiography for measurement of left ventricular volumes in man. Am Heart J 1960;60:762–76.
19. Piepho RW, Bloedov DC, Lacz FP, Runser DJ, Dimmit DC, Browne RK. Pharmacokinetics of diltiazem in selected animal species and human beings. Am J Cardiol 1982;49:525–32.
20. Zipes DP, Fischer JC. Effects of agents which inhibit the slow channel on sinus node automaticity and atrioventricular conduction in the dog. Circ Res 1974;34:184–92.
21. Kawai C, Konishi T, Matsuyama E, Okazaki H. Comparative effects of three calcium antagonists, diltiazem, verapamil, and nifedipine, on sinoatrial and atrioventricular nodes: experimental and clinical studies. Circulation 1981;63:1035–42.
22. Matsui S, Marakami E, Takekoshi N, et al. Hemodynamic effects of sublingual nifedipine in congestive heart failure. Jpn Circ J 1979;43:1081–8.
23. Newman RK, Bishop VS, Peterson DF, Leroux EJ, Horowitz LD. Effects of verapamil on left ventricular performance in conscious dogs. J Pharmacol Exp Ther 1977;201:723–30.
24. Ferlinz J, Easthope J, Aronow W. Effects of verapamil on myocardial performance in coronary disease. Circulation 1979;59:313–9.
25. Singh B, Roche AH. Effects of intravenous verapamil on hemodynamics in patients with heart disease. Am Heart J 1977;94:593–9.
26. Lewis BS, Mitha AS, Gotsman MS. Immediate hemodynamic effects of verapamil in man. Cardiology 1976;60:366–76.
27. Factor SM, Minase T, Cho S, Dominitz R, Sonnenblick EH. Microvascular spasm in the cardiomyopathic Syrian hamster: a preventable cause of focal myocardial necrosis. Circulation 1982;66:342–54.
28. Unverferth D, Magorien RD, Lewis RB, Leier C. The role of subendocardial ischemia in perpetuating myocardial failure in patients with nonischemic congestive cardiomyopathy. Am Heart J 1983;105:176–80.