Differential effects of diltiazem and nitroprusside on left ventricular function in experimental chronic volume overload

Charles B. Porter, M.D., Richard A. Walsh, M.D., Frederick R. Badke, M.D., and Robert A. O'Rourke, M.D.

ABSTRACT To compare the hemodynamic effects of a calcium-channel blocker with those of a conventional vasodilator in the awake preinstrumented dog, diltiazem and nitroprusside were administered in equihypotensive infusions before (decrease in mean aortic pressure by 10%; p < .001, n = 6) and after (decrease in mean aortic pressure by 12%; p < .001) chronic volume overload (CVO) produced by an infrarenal aortocaval fistula. Diltiazem had no effect on preload either before or after CVO. The maximal rate of change in left ventricular pressure (dP/dt\textsubscript{max}) was unaffected by diltiazem before the aortocaval fistula (decrease in dP/dt\textsubscript{max} by 6%; p = NS) but was significantly reduced by calcium-channel blockade after CVO (decrease in dP/dt\textsubscript{max} by 22%; p < .001). By contrast, at matched aortic pressures nitroprusside significantly reduced left ventricular end-diastolic dimension (LVEDD) and pressure (LVEDP) in the same animals before (decrease in LVEDP by 10%, p < .05; decrease in LVEDP by 7 ± 2 mm Hg, p < .001) and after CVO (decrease in LVEDP by 7%, p < .05; decrease in LVEDP by 5 ± 2 mm Hg, p < .001) without altering dP/dt\textsubscript{max}. We conclude that the calcium entry blocker diltiazem, unlike conventional vasodilators, may depress left ventricular function in CVO by direct negative inotropic properties in amounts that are without myocardial depressant effects in the presence of normal left ventricular performance.


DILTIAZEM, a calcium-channel blocker, has two major potential direct hemodynamic effects: coronary and peripheral arterial vasodilation and myocardial depression. In addition to these direct effects, reflex sympathetic stimulation, induced by peripheral vasodilation, may offset or mask the negative inotropic and chronotropic effects of calcium-channel blockade. However, net cardiocirculatory response to such drugs may be markedly different in the presence of congestive heart failure with its variable alterations in level of sympathetic reserve. Several clinical investigations detailing the beneficial effects of calcium-channel blockade as a means of vasodilator therapy for congestive heart failure have appeared. However, acute pulmonary edema after parenteral verapamil\textsuperscript{11} and severe hypotension with reduced cardiac output after 20 to 30 mg of oral nifedipine have been reported.\textsuperscript{12}

By contrast, there are no investigations detailing the hemodynamic actions of diltiazem, which in equimolar doses has the least negative inotropic effects in vivo\textsuperscript{13-15} and in vivo\textsuperscript{6} of the clinically available drugs, in experimental or clinical heart failure. Furthermore, the comparative effects of afterload reduction by calcium-channel blockade and conventional vasodilators have not been assessed.

We therefore used an animal model for chronic volume overload (CVO) to assess the peripheral and myocardial effects of diltiazem before and after the onset of congestive heart failure. To study potential negative inotropic effects of this drug independent of the direct and reflex effects of peripheral arterial vasodilation, we chose to compare its effects with those of nitroprusside, a widely used vasodilator without direct myocardial actions.\textsuperscript{16} The potency, rapid onset of action, and short half-life of this drug permitted us to precisely match the reduction in mean arterial pressure induced by diltiazem in the same animal before and after aortocaval fistula.
Methods

Surgical instrumentation. Six mongrel dogs, weighing 18 to 30 kg, were surgically instrumented (figure 1) for long-term physiologic monitoring by methods previously described for this laboratory. Specifically, a left thoracotomy was performed under halothane (1.5%) anesthesia with xylazine and sodium pentobarbital induction (figure 1). We placed 16-gauge polyvinyl catheters in the descending aorta, apical left ventricle, and left atrium. A solid-state pressure transducer (P-18; Konigsberg Instruments, Inc., Pasadena), precalibrated with a mercury manometer, was placed in the apex of the left ventricle. Paired 5 MHz piezoelectric crystals with resin-focusing lenses were positioned for anteroposterior measurement of a left ventricular transverse diameter. The dogs were allowed to recover at least 2 weeks, and control studies were performed with the animals unsedated and lying quietly in a sling. An infrarenal 0.5 cm aortocaval fistula was constructed during a second operation via a midline abdominal incision. Shunt patency was confirmed in each animal by the presence of intraoperative and postoperative bruit/thrill, hemodynamic data, and postmortem examination. Animals were restudied in an identical fashion to the control animals 2 to 4 weeks after aortocaval fistula.

Measurements. Analog signals were recorded with a Beckman RM oscillograph. Analog-to-digital signal conversion with an on-line minicomputer (Minc 11; Digital Equipment Corp., Marlborough, MA) was performed at a rate of 100 Hz and data were stored on floppy discs for subsequent analyses. Transit time between the piezoelectric crystals was measured by a multichannel sonomicrometer (Scheulessler and Associates, Cardiff-by-the-Sea, CA) and was converted to distance by assuming a constant velocity of sound in blood of 1.55 m/sec. The resolution of this system has been reported to be 0.07 mm with 5 MHz signals. The percent of shortening of the anteroposterior diameter (%AD) was calculated as the difference between the left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD) divided by the LVEDD and multiplied by 100. End-diastolic length was defined as the diameter of the ultrasonic transverse dimension signal at the "Z" point of the high-fidelity left ventricular pressure signal. End-systolic length was measured as the transverse diameter at peak negative rate of change in left ventricular pressure (dp/dt), which occurs within 10 msec of aortic valve closure. External manometers (P23 Db; Statham Instruments, Oxnard, CA) measured aortic and ventricular pressures. Before each experiment, the solid-state transducer was calibrated to the left ventricular pressure tube signal.

High-fidelity left ventricular pressure was differentiated to determine the maximal rate of rise of left ventricular pressure (dP/dtmax) by an active resistance capacitance circuit with a linear frequency response to 75 Hz with a 3 dB variance at 100 Hz. Analog dP/dt was calibrated from the digitized data obtained from analog-to-digital conversion of the solid-state transducer with software developed in our laboratory and processed by a minicomputer.

Drug protocol (figure 2). Diltiazem HCl (Marion Laboratories, Kansas City, MO) was administered as a 200 μg/kg left atrial bolus and as a continuous infusion at 40 μg/kg/min, a dose we had noted previously to produce a decline in mean arterial pressure of approximately 10% from that in control in the absence of an arteriovenous (AV) fistula (unpublished observations). Recordings of heart rate, left ventricular pressure by solid-state transducer, left ventricular end-diastolic pressure (LVEDP) on an expanded scale, LVEDD, LVESD, and aortic pressure were made at paper speeds of 25 mm/sec at 30 sec, 3 min, and 10 min after the initial diltiazem bolus. Signals from 10 consecutive beats were averaged for each data point.

We dissolved 2.5 mg of sodium nitroprusside (Roche Laboratories, Nutley, NJ) in 50 ml of 5% dextrose in water, which was administered by continuous infusion at least 30 min after diltiazem after hemodynamic parameters had returned to control levels. Nitroprusside dosage was then titrated to match the diltiazem-induced fall in blood pressure as recorded by the oscillograph in that animal (mean dose = 1.75 ± 0.2 μg/kg/min). Hemodynamic measurements were made 30 sec, 3 min, and 10 min after the diltiazem-matched blood pressure fall was attained.

Statistical analysis. Statistical analyses were performed by two-way analysis of variance (2-way ANOVA) for repeated measures of the same parameters for intergroup drug interactions. One-way analysis of variance (1-way ANOVA) was used for intragroup dose interactions. The Newman-Keuls test and Dunnet's t test were used to assess intergroup and intragroup differences.

![Stage 1: Thoracotomy](image1)

![Stage 2: Laparotomy](image2)

FIGURE 1. Schematic illustration of the two-stage surgical procedure used for instrumentation and construction of aortocaval fistula.
statistical significance between means, respectively. The level of significance was chosen as p <= .05. Results are expressed as the mean ± SE.

**Results**

**Control data.** Baseline hemodynamic parameters in animals before construction of aortocaval fistula during control runs before diltiazem and nitroprusside differed only in that the heart rate was slightly higher before nitroprusside (72 ± 7 vs 82 ± 7 beats/min; p < .05). In experiments performed after construction of aortocaval fistula, there was no significant difference in any parameter between the prediltiazem and prennitroprusside controls (table 1).

**Effects of aortocaval fistula.** Hemodynamic changes produced by the construction of aortocaval fistulae appear in table 2 and are evident in figures 2 through 5. Significant increases in heart rate (before aortocaval fistula = 77 ± 7 beats/min vs after aortocaval fistula = 131 ± 7 beats/min; p < .001), LVEDD (before aortocaval fistula = 42.4 ± 1.7 mm vs after aortocaval fistula = 45.1 ± 1.5 mm; p < .01), LVEDP (before aortocaval fistula = 8 ± 1 mm Hg vs after aortocaval fistula = 13 ± 2 mm Hg; p < .01), and %ΔD (before aortocaval fistula = 19 ± 1%; after aortocaval fistula = 23 ± 2%; p < .01), and a decline in aortic diastolic blood pressure (before aortocaval fistula = 68 ± 2 mm Hg, after aortocaval fistula = 49 ± 2 mm Hg; p < .01) were observed. The dP/dt_max also increased significantly after aortocaval fistula from 2590 ± 260 to 3519 ± 323 mm Hg/sec (p < .01).

**Drug effects before and after aortocaval fistula.** Figure 3 shows selected portions of analog recordings made of typical experiments during steady-state infusions of equihypotensive doses of diltiazem and nitroprusside in a single dog before and after aortocaval fistula. Diltiazem had no effect on dP/dt_max before aortocaval fistula but depressed dP/dt_max from 3650 to 2883 mm Hg/sec after AV fistula. In addition, the calcium-channel blocker had no effect on LVEDD or LVEDP before or after CVO. By contrast, nitroprusside before and after aortocaval fistula reduced preload but had no effect on dP/dt_max.

Effects of nitroprusside. Group hemodynamic effects observed after equihypotensive calcium-channel blockade and vasodilator infusion before and after shunting are recorded in table 1. Heart rate increased significantly for the group above control levels during nitroprusside infusion before aortocaval fistula (control = 82 ± 1 beats/min, nitroprusside = 113 ± 7 beats/min; p < .001), but no significant change from

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**DRUG PROTOCOLS**

**Pre and Post (range 2-3 weeks) Aortocaval Fistula**

**CONTROL I - Pre Diltiazem**

↓

Diltiazem bolus 200 μg/kg followed by 40 μg/kg/min infusion

↓

Measurements ½, 3, 10 minutes post drug initiation

↓

Return to baseline hemodynamic status (20-30 minutes)

↓

**CONTROL II - Pre Nitroprusside**

↓

Nitroprusside infusion (x = 1.5 μg/kg/min) titrated to match decline in MAP produced by diltiazem

↓

Measurements ½, 3, 10 minutes from onset of steady state matched decline in MAP

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**FIGURE 2.** Simplified illustration of the experimental drug protocol used before and after CVO by aortocaval fistula.
TABLE 1
Hemodynamic effects of diltiazem and nitroprusside infusions before and after aortocaval fistula (mean ± 1 SEM, n = 6)

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>MAP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>LVEDD (mm)</th>
<th>%ΔD</th>
<th>dP/dt\text{max} (mm Hg/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-AVF</td>
<td>Post-AVF</td>
<td>Nitroprusside</td>
<td>Diltiazem</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>Control</td>
<td>30 sec</td>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>82 ± 7^a</td>
<td>87 ± 2</td>
<td>8 ± 2</td>
<td>8 ± 2</td>
<td>18 ± 1</td>
<td>2584 ± 246</td>
</tr>
<tr>
<td>30 sec</td>
<td>106 ± 9^b</td>
<td>84 ± 1^c</td>
<td>5 ± 2^c</td>
<td>40 ± 2</td>
<td>19 ± 1</td>
<td>2818 ± 265</td>
</tr>
<tr>
<td>3 min</td>
<td>106 ± 7^b</td>
<td>79 ± 2^c</td>
<td>5 ± 2^c</td>
<td>39 ± 2^c</td>
<td>19 ± 1</td>
<td>2706 ± 207</td>
</tr>
<tr>
<td>10 min</td>
<td>113 ± 7^b</td>
<td>79 ± 2^b</td>
<td>1 ± 2^b</td>
<td>38 ± 2^c</td>
<td>17 ± 1</td>
<td>2730 ± 334</td>
</tr>
<tr>
<td>Diltiazem</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>72 ± 7</td>
<td>84 ± 2</td>
<td>8 ± 1</td>
<td>43 ± 2</td>
<td>19 ± 1</td>
<td>2602 ± 276</td>
</tr>
<tr>
<td>30 sec</td>
<td>99 ± 4^b</td>
<td>79 ± 3^c</td>
<td>8 ± 2</td>
<td>42 ± 2</td>
<td>21 ± 2</td>
<td>2795 ± 357</td>
</tr>
<tr>
<td>3 min</td>
<td>93 ± 4^b</td>
<td>79 ± 4^c</td>
<td>9 ± 2</td>
<td>42 ± 2</td>
<td>18 ± 1</td>
<td>2507 ± 260</td>
</tr>
<tr>
<td>10 min</td>
<td>94 ± 4^b</td>
<td>77 ± 3^b</td>
<td>7 ± 2</td>
<td>42 ± 2</td>
<td>19 ± 1</td>
<td>2431 ± 251</td>
</tr>
</tbody>
</table>

Pre-AVF = before aortocaval fistula; Post-AVF = after aortocaval fistula; HR = heart rate; MAP = mean arterial pressure; LVEDP = left ventricular end-diastolic pressure; LVEDD = left ventricular end-diastolic dimension; %ΔD = percent shortening of the minor diameter = (LVEDD - LVEDD/LVEDP) × 100; dP/dt\text{max} = maximal rate of left ventricular pressure increase.

^a p < .05 vs nitroprusside control.
^b p < .001 vs control by ANOVA.
^c p < .05 vs control by ANOVA.

comparison of hemodynamic data before and after aortocaval fistula (mean ± 1 SEM, n = 6)

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>MAP (mm Hg)</th>
<th>Diastolic BP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>LVEDD (mm)</th>
<th>%ΔD</th>
<th>dP/dt\text{max} (mm Hg/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-AVF</td>
<td>Post-AVF</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>77 ± 6.9</td>
<td>131 ± 6.9^a</td>
<td>86 ± 2.2</td>
<td>68 ± 2.0</td>
<td>8.3 ± 1.3</td>
<td>42.5 ± 1.7</td>
<td>18.7 ± 1.2</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>68 ± 2.0</td>
<td>75 ± 4.6</td>
<td>68 ± 2.0</td>
<td>49 ± 4.4^a</td>
<td>12.6 ± 1.8^a</td>
<td>45.1 ± 1.5^a</td>
<td>22.5 ± 2.0^a</td>
</tr>
</tbody>
</table>

BP = blood pressure; other abbreviations as in Table 1.

^a p < .01 vs pre-AV fistula value by ANOVA.
These declines in LVEDP before aortocaval fistula (control = 72 ± 7 beats/min, 10 min = 94 ± 4 beats/min; p < .001) but had no significant effect in the postaortocaval fistula state (control = 133 ± 6 beats/min, 10 min = 118 ± 13 beats/min; p = NS). Mean arterial pressure declined during diltiazem infusion before and after volume overload (before aortocaval fistula: control = 84 ± 2 mm Hg, diltiazem = 78 ± 3 mm Hg; p < .001; after aortocaval fistula: control = 75 ± 4 mm Hg, diltiazem = 66 ± 6 mm Hg; p < .001). The reductions in mean arterial pressure produced by diltiazem were equivalent to those observed with nitroprusside before and after volume overload by experimental design (table 1 and figure 4). However, in contrast to nitroprusside, diltiazem produced no significant change from control in LVEDD or LVEDP (figure 5) either before or after aortocaval fistula (before aortocaval fistula: control = 8 ± 1 mm Hg, diltiazem = 7 ± 2 mm Hg, p = NS; after aortocaval fistula: control = 14 ± 2 mm Hg, diltiazem = 15 ± 2 mm Hg, p = NS). Diltiazem had no significant effect on dP/dt\textsubscript{max} in the animals before aortocaval fistula (control = 2601 ± 276 mm Hg/sec, diltiazem = 2430 ± 251 mm Hg/sec; p = NS); however, after aortocaval fistula–induced CVO, the calcium-channel blocker produced a prompt sustained decline in dP/dt\textsubscript{max} (control = 3493 ± 274 mm Hg/sec, 10 min = 2773 ± 344 mm Hg/sec; p < .001) (figure 6). This 21% reduction in dP/dt\textsubscript{max} produced by diltiazem is in marked contrast to the slight increase in dP/dt\textsubscript{max} that had been observed with an equihypotensive dose of nitroprusside (control = 3546 ± 344 mm Hg, 10 min = 3759 ± 336 mm Hg; p = NS) in the same animals. Despite the substantial

![Figure 3](image_url)  
**FIGURE 3.** Analog recordings obtained at control and during steady-state equihypotensive infusions of diltiazem and nitroprusside in a single dog before and after aortocaval fistula. Diltiazem reduces left ventricular dP/dt only after CVO, and nitroprusside has no effect on dP/dt but decreases left ventricular end-diastolic minor diameter and pressure before and after AV fistula.

![Figure 4](image_url)  
**FIGURE 4.** The administered dosage of diltiazem produced significant declines in mean aortic pressure both before and after volume overload. These declines were matched with the nitroprusside infusion.
reduction in \( \frac{dP}{dt_{\text{max}}} \) produced by diltiazem after CVO, the percent shortening of the minor diameter signal was unchanged by the drug in both circulatory states (19 ± 1% before and after diltiazem before aortocaval fistula; 23 ± 2% before and after the drug after aortocaval fistula).

**Discussion**

The results of this investigation confirm the hypothesis that the net hemodynamic effect of calcium-channel blockade on left ventricular performance depends on the circulatory state in which it is used.

Our data indicate that diltiazem, the calcium blocker that has been shown in vivo and in vitro to possess the least negative inotropic effects of the available drugs, is capable of producing substantial reductions in \( \frac{dP}{dt_{\text{max}}} \) when given parenterally to the conscious preinstrumented dog during CVO effected by the creation of an aortocaval fistula. Despite significant depression of \( \frac{dP}{dt_{\text{max}}} \), the extent of myocardial fiber shortening as reflected by percent shortening of the ultrasonic left ventricular minor diameter crystals (%AD) was unaffected by the amount of diltiazem used in this study. The absence of a significant decline in percent of minor diameter shortening despite a substantial reduction in \( \frac{dP}{dt_{\text{max}}} \) in response to diltiazem after AV fistula may be explained by the increased sensitivity to changes in inotropic state and relative independence of loading conditions of isovolumetric \( \frac{dP}{dt} \) (dP/dt) as compared with ejection phase indices (%AD) previously observed in the conscious preinstrumented animal and in man. Specifically, the calcium blocker–induced reduction in systemic arterial pressure may have offset the direct effects of the drug on extent of shortening. By contrast, the same dose of diltiazem given to the same animals before the circulatory congestion imposed by volume overload was without discernible effect on either isovolumetric or ejection phase measures of left ventricular function. The diltiazem-induced reduction in \( \frac{dP}{dt_{\text{max}}} \) was not observed before or after CVO when nitroprusside, a vasodilator without direct myocardial effects, was used in the same animals to produce decreases in systemic arterial pressure equal to those obtained with the calcium blocker. In addition, the calcium-channel blocker produced no discernible effect upon left ventricular preload before or after AV fistula, whereas equihypotensive infusions of nitroprusside significantly reduced transverse LVEDD and LVEDP before and after CVO.
after CVO. These results suggest that relative to nitroprusside, diltiazem is primarily a systemic arteriolar vasodilator without important effects upon venous capacitance. Nitroprusside was given a minimum of 30 min after diltiazem by study design to precisely match the calcium entry blocker-mediated systemic arterial vasodilation. Although the elimination of half-life of diltiazem is 2.24 hr in the dog, it is unlikely that possible residual plasma or tissue levels of this drug affected the observed changes produced by nitroprusside since all hemodynamic parameters had returned to control levels before conventional vasodilation, and we are unaware of any pharmacodynamic interaction between the two drugs.

The previous hemodynamic characterizations of this animal model of CVO suggests several potential explanations for the discrepant effects of diltiazem on left ventricular function observed before and after creation of the aortocaval fistula. During the first few weeks after AV fistula formation, circulatory congestion is shown by pulmonary rales, ascites, and peripheral edema. The hemodynamic basis for these changes observed in this study included significant increases in heart rate and in left ventricular diameter and pressure (table 2). Previous investigators have noted reduced systemic vascular resistance due to a threefold increase in cardiac output of which 55% is shunted from left to right at the level of the aortocaval fistula. Thus, this preparation constitutes a model of high-output congestive heart failure. Myocardial performance is known to be normal to enhanced in these dogs as indicated by the 22% increase in percent of left ventricular minor diameter shortening that we observed (table 2). Others have noted augmented ejection fractions, contractile element velocities, and mean velocities of circumferential fiber shortening for at least 6 weeks after aortocaval fistula. Le Winter et al. have demonstrated that part of this increased myocardial function is related to increased sympathetic activity. More recently Crozatier et al. noted a nonadrenergically mediated increase in inotropic state within 48 hr of volume overload produced by aortic insufficiency in the awake unrestrained dog. This phenomenon may have been produced by an increase in calcium availability for excitation contraction coupling.

Several potential mechanisms may be evoked to explain the myocardial depression produced by diltiazem after CVO given the aforementioned direct and reflex circulatory adjustments that occur in this model.

First, the high resting level of sympathetic tone and low peripheral vascular resistance after AV fistula may have prevented short-term reflex adaptation to calcium-channel blockade and hence unmasked the direct myocardial depressant effect shared by these compounds. Similarly, the absence of a significant reflex increase in heart rate after systemic vasodilation by diltiazem and nitroprusside after AV fistula in contrast to the reflex tachycardia evoked by both drugs before AV fistula, may be a consequence of the elevated basal sympathetic tone produced by CVO. Indeed, heart rate actually declined (133 ± 6 beats/min to 118 ± 13 beats/min; p = NS) with diltiazem after AV fistula. It is possible that the direct negative chronotropic effect of calcium-entry blockade predominated in this setting.

Second, if increased availability of calcium to the contractile apparatus is partially responsible for the normal to enhanced left ventricular function observed in CVO, the myocardium may be more sensitive to calcium blockade in this condition. Finally, hepatic congestion may have increased bioavailability by reduced hepatic drug deacetylation, the major route for elimination of diltiazem, and resulted in higher plasma levels in the post-AV fistula state.

Clinical implications. In this study, vasodilation with nitroprusside infusion failed to increase the extent of left ventricular shortening before or after CVO, and vasodilation with equilhypotensive calcium blockade produced significant myocardial depression (table 1). Caution must be exercised with the extrapolation of these data to the management of patients with congestive heart failure of diverse causes. Most forms of low-output heart failure are associated with variably elevated systolic impedance and wall stress and diminished left ventricular function. In this setting, arterial vasodilation by calcium-channel blockade or other direct or receptor-dependent afterload-reducing drugs may permit more effective shortening during ventricular systole. For example, we have recently demonstrated improved left ventricular performance in response to intravenous and oral diltiazem in a group of patients with severe congestive heart failure due to myocardial depression. By contrast, patients with heart failure characterized by normal or enhanced left ventricular performance may have reached the limit at which systolic ejection can increase in response to peripheral arterial vasodilation. Such conditions might occur in heart failure due to left-sided valvular regurgitation, central left-to-right shunts, arteriovenous fistulae, or any high cardiac output state. Further arteriolar vasodilation may merely lower systemic arterial pressure without improvement in cardiac performance. Calcium-channel blockade has the additional potential risk of producing frank myocardial depression due to
unmasking of direct negative inotropic effects, a property not shared by conventional pure vasodilators.

We appreciate the technical assistance of Danny Escobedo, Richard Miller, and Don Watkins, and the secretarial assistance of Julia E. Wells.

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Differential effects of diltiazem and nitroprusside on left ventricular function in experimental chronic volume overload.

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Circulation. 1983;68:685-692
doi: 10.1161/01.CIR.68.3.685

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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