Effects of a Calcium Channel Blocker on Cardiac Output Distribution in Conscious Hypertensive Dogs

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SUMMARY  The effects of nitrendipine, 8 µg/kg/minute, were evaluated in six conscious dogs through measurements of arterial pressure and blood flow in the ascending aorta (cardiac output), mesenteric, renal, and iliac arteries before and after induction of chronic perinephritic hypertension. Before hypertension was induced, nitrendipine reduced mean arterial pressure 19 ± 2.3% (from 95 ± 3.2 mm Hg), decreased total peripheral resistance (60 ± 2.6%), and increased cardiac output (108 ± 10.5%). These values returned to baseline within 15 to 30 minutes. Nitrendipine caused the greatest increase in blood flow in the iliac bed (98 ± 9.9%), an intermediate increase in the mesenteric bed (37 ± 3.7%), and the least increase in the renal bed (7 ± 2.2%). Two to six weeks after induction of hypertension, administration of nitrendipine elicited significant (p < 0.01) decreases in mean arterial pressure (32 ± 2.5% from 151 ± 4.8 mm Hg) and total peripheral resistance (67 ± 1.3%) compared with its administration in normotensive dogs, while the increase in cardiac output was not significantly changed (111 ± 10.9%). These changes in arterial pressure and vascular resistances also were prolonged (i.e., hemodynamics returned to baseline after 75–90 minutes). The increase in iliac (99 ± 16.8%) and renal (9 ± 6.1%) blood flows after nitrendipine administration in hypertensive dogs was similar to that found in the normotensive dogs, but mesenteric blood flow doubled (84 ± 8.4%). Thus, in conscious, hypertensive dogs, nitrendipine administration appears to markedly decrease arterial pressure and total peripheral and regional resistances, which also require more time to return to baseline, but appears to increase blood flow by a greater amount only in the mesenteric bed.

(Hypertension 7: 380–385, 1985)

KEY WORDS  • perinephritic hypertension • regional blood flow • total peripheral resistance • nitrendipine

Because of their potent action to relax vascular smooth muscle, calcium channel blockers are useful for the treatment of systemic hypertension.1–3 Previous studies have demonstrated that calcium channel blockers elicit enhanced relaxation of vascular smooth muscle and reductions in arterial pressure in both experimental animal models4–6 and humans7,8,9,10 with hypertension. The extent to which calcium channel blockers affect peripheral blood flow distribution in hypertension, particularly in the conscious animal and human, has not been established. In fact, relatively little is known about the effects of calcium channel blockers on regional blood flow distribution even in normotensive animals and humans.

The goal of our study was to determine the extent to which nitrendipine alters the distribution of cardiac output to the major peripheral beds (i.e., mesenteric, renal, and iliac beds) in the conscious, hypertensive animal. To accomplish this goal, nitrendipine was studied in chronically instrumented dogs with normal arterial pressures and again in the same dogs after inducing chronic, perinephritic hypertension. Nitrendipine, a 1,4 dihydropyridine, was selected because it is relatively specific for vascular smooth muscle and has been shown to bind to vascular smooth muscle with high affinity.11 It is recognized that while nitrendipine may be representative of the dihydropyridine derivatives, it may not reflect the action of other calcium channel blockers.12

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Methods

Six mongrel dogs weighing 20 to 40 kg were anesthetized with sodium pentobarbital, 30 mg/kg i.v. Through a left thoracotomy at the fourth intercostal space, a heparin-filled Tygon catheter was implanted in the descending thoracic aorta and an electromagnetic flow transducer (Zepeda Instruments, Seattle, WA) was placed around the ascending aorta. Through a midline laparotomy, Doppler ultrasonic flow transducers were implanted around the superior mesenteric and renal arteries and an electromagnetic flow transducer was implanted on the right iliac artery. A hydraulic occluder was implanted distally on the iliac artery to establish zero blood flow.

Arterial pressure was measured by connecting the aortic catheter to a Statham P23ID strain gauge transducer (Statham Instruments, Oxnard, CA). Ascending aortic blood flow (i.e., cardiac output minus coronary blood flow) and iliac blood flow were measured with a square-wave electromagnetic flowmeter (Benton Instruments, Cupertino, CA). Mesenteric and renal blood flows were measured with the Doppler ultrasonic flowmeter. The Doppler flowmeter had been calibrated previously against the electromagnetic flowmeter and was found to be linear with a reliable zero flow reference.13

The initial experiments were conducted 2 to 4 weeks after instrumentation in normotensive, conscious dogs. These studies were performed in conscious, healthy animals to eliminate the effects of anesthesia and recent operation.14 Measurements of arterial pressure, cardiac output, heart rate, and mesenteric, renal, and iliac blood flows were continuously recorded during the control period and for 2 hours after the infusion of nitrendipine, 8 µg/kg/minute for 5 minutes (Miles Pharmaceuticals, New Haven, CT). Following the normotensive studies, hypertension was induced in the same six dogs with the method of Page.15 Through a flank incision, the renal capsule was stripped of fascia and the kidney wrapped first in raw silk followed by plastic sheeting to prevent adhesions. One week later, the contralateral kidney was removed. Three to six weeks after nephrectomy, when the pressure had stabilized at a hypertensive level, nitrendipine infusion was repeated. As the electromagnetic flow measurement on the iliac artery failed to operate properly in all dogs, two additional normotensive and two additional hypertensive animals were studied with measurements of iliac blood flow and arterial pressure. Total renal blood flow to one kidney was measured by implanting a transducer on either the right or left renal artery.

Nitrendipine was weighed and dissolved under a sodium vapor lamp in a solution of 50% polyethylene glycol and 50% sterile distilled water. The injections of the vehicle, administered before each experiment, elicited no detectable hemodynamic effects. All injections of the calcium channel blocker were protected from ultraviolet light during the experiments.

The data were recorded on a 14-channel magnetic tape recorder (Honeywell Test Instruments Division, Denver, CO) and monitored on two multichannel oscillographs (Gould Instruments, Cleveland, OH). Mean arterial pressure and mean mesenteric, renal, and iliac blood flows were derived using R-C filters with 2-second time constants. Mean aortic blood flow was derived with an R-C filter with an 8-second time constant. Heart rate was measured continuously with a cardiotachometer triggered by the signal from the pulsatile aortic blood flow. Total peripheral and regional resistances were calculated as the quotient of mean arterial pressure and cardiac output and mean arterial pressure and regional blood flows respectively. Stroke volume was calculated as the quotient of cardiac output and heart rate.

The means ± SEM were calculated for all variables. Paired responses to nitrendipine before and after systemic hypertension were analyzed in six dogs for all parameters except iliac blood flow. Thus, the t test for paired comparisons was used for all statistical analyses except in the iliac bed, where responses were analyzed using Student’s t test for group comparisons.16

Results

Typical responses to nitrendipine, 8 µg/kg/minute, are shown in the same dog before (Figure 1) and after hypertension was induced (Figure 2). Baseline values and absolute changes from baseline in response to nitrendipine, 8 µg/kg/minute, are shown in Tables 1 through 3. All data represent steady state conditions during the infusions and are expressed as means ± SEM.

Effects of Nitrendipine Infusion on Conscious Normotensive Dogs

Nitrendipine, 8 µg/kg/minute, reduced arterial pressure by 19 ± 2.3% and total peripheral resistance by 60 ± 2.6%, and increased cardiac output by 108 ± 10.5% and heart rate by 94 ± 12.3% without significantly increasing calculated stroke volume (8 ± 3.8%) (see Table 1). The largest increase in regional blood flows occurred in the iliac bed (98 ± 9.9%), where iliac resistance was decreased by 57 ± 3.0%. An intermediate vasodilation occurred in the mesenteric bed, where blood flow rose by 37 ± 3.7% and vascular resistance decreased by 42 ± 3.2%. Nitrendipine was least effective in the renal bed, where renal blood flow increased by 7 ± 2.2% and vascular resistance decreased by 26 ± 2.5% (see Tables 2 and 3). All values returned to baseline within 15 to 30 minutes following nitrendipine administration.

The percentage increases in iliac blood flow with nitrendipine were not significantly different from that of cardiac output. Nitrendipine induced significantly lower (p < 0.01) percentage increases in mesenteric blood flow than in either cardiac output or iliac blood flow; however, the increases in mesenteric blood flow with nitrendipine were significantly greater than the increases in renal blood flow (p < 0.01). Nitrendipine induced similar percentage decreases in iliac and total peripheral resistances, which were significantly greater (p < 0.01) than the percentage decreases in mesenteric resistance. The decreases in mesenteric resistance...
FIGURE 1. Typical response to an infusion of nitrendipine, 8 μg/kg/minute, as shown for a normotensive dog. Phasic arterial pressure, ascending aortic blood flow, mean aortic blood flow (cardiac output), phasic and mean mesenteric blood flow, phasic renal blood flow, and phasic and mean iliac blood flow were measured. Nitrendipine increased iliac blood flow more than mesenteric and renal blood flows. All values returned to baseline within 15 minutes.

FIGURE 2. Response to nitrendipine, 8 μg/kg/minute, after the induction of chronic perinephritic hypertension, in the same dog and on the same measurements as shown in Figure 1. The vasodilation induced by nitrendipine was augmented in magnitude as well as duration.
with nitrendipine were significantly greater \((p < 0.01)\) than the percentage decreases in renal resistance.

Effects of Nitrendipine Infusion on Conscious Hypertensive Dogs

With the development of hypertension in these dogs, mean arterial pressure rose from \(95 \pm 3.2\) to \(151 \pm 4.8\) mm Hg \((p < 0.01)\) without significantly changing any of the baseline values for aortic and regional blood flows or heart rate. Total peripheral resistance rose from \(0.037 \pm 0.002\) to \(0.43 \pm 0.04\) mm Hg/ml/minute \((p < 0.01)\), mesenteric resistance rose from \(0.24 \pm 0.02\) to \(0.43 \pm 0.04\) mm Hg/ml/minute \((p < 0.01)\), renal resistance rose from \(0.63 \pm 0.08\) to \(1.28 \pm 0.21\) mm Hg/ml/minute \((p < 0.01)\), and iliac resistance rose from \(0.86 \pm 0.08\) to \(1.27 \pm 0.19\) mm Hg/ml/minute \((p = 0.06)\).

Nitrendipine, \(8 \mu g/kg/minute\), in the presence of chronic hypertension, reduced mean arterial pressure by \(32 \pm 2.5\%\) and total peripheral resistance by \(67 \pm 1.3\%\) and increased cardiac output by \(111 \pm 10.9\%\) and heart rate by \(96 \pm 10.6\%\), again without significantly increasing calculated stroke volume \((9 \pm 6.0\%\); see Table 1). All values returned to baseline 75 to 90 minutes after nitrendipine administration (Figure 3).

The largest increases in regional blood flows occurred in the iliac bed \((99 \pm 16.8\%)\), where iliac resistance decreased by \(66 \pm 2.9\%\), and in the mesenteric bed, where blood flow rose by \(84 \pm 8.4\%\) and vascular resistance decreased by \(64 \pm 1.2\%\). Nitrendipine administration remained least effective in the renal bed, where renal blood flow increased by \(9 \pm 6.1\%\) and vascular resistance decreased by \(39 \pm 4.6\%\) (see Tables 2 and 3).

Following the development of hypertension, nitrendipine administration induced greater reductions in arterial pressure and total peripheral and regional resistances, which required a significantly longer time \((p < 0.05)\) to recover when compared with those responses in the normotensive state (see Figure 3). After hypertension was induced, however, administration of nitrendipine caused only slightly but not significantly greater changes in cardiac output, while the increase in mesenteric blood flow doubled compared with responses in the normotensive state (Figure 4).

The percentage increases in iliac blood flow were again not significantly different from that of cardiac output; however, the percentage increases in mesenteric blood flow with nitrendipine were no longer less than the percentage increases in cardiac output and iliac blood flows and remained significantly greater \((p < 0.01)\) than the percentage increases in renal blood flow. The percentage decreases in total peripheral resistance, iliac resistance, and mesenteric resistance with nitrendipine administration were similar to those

### Table 1. Effects of Nitrendipine on Central Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Change with nitrendipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>(95 \pm 3.2)</td>
<td>(-18 \pm 2.1^*)</td>
</tr>
<tr>
<td>Normotensive ((n = 6))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive ((n = 6))</td>
<td>(151 \pm 4.8^\dagger)</td>
<td>(-49 \pm 4.9^\dagger^*)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>(82 \pm 5.7)</td>
<td>(76 \pm 9.6^*)</td>
</tr>
<tr>
<td>Normotensive ((n = 6))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive ((n = 6))</td>
<td>(86 \pm 6.7)</td>
<td>(80 \pm 8.4^*)</td>
</tr>
<tr>
<td>Cardiac output (ml/min)</td>
<td>(2595 \pm 179)</td>
<td>(2715 \pm 142^*)</td>
</tr>
<tr>
<td>Normotensive ((n = 6))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive ((n = 6))</td>
<td>(2700 \pm 198)</td>
<td>(3043 \pm 438^*)</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>(32.1 \pm 2.7)</td>
<td>(2.5 \pm 1.3)</td>
</tr>
<tr>
<td>Normotensive ((n = 6))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive ((n = 6))</td>
<td>(33.0 \pm 4.6)</td>
<td>(3.0 \pm 2.2)</td>
</tr>
<tr>
<td>Total peripheral resistance (mm Hg/ml/min)</td>
<td>(0.037 \pm 0.002)</td>
<td>(-0.023 \pm 0.002^*)</td>
</tr>
<tr>
<td>Normotensive ((n = 6))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive ((n = 6))</td>
<td>(0.058 \pm 0.006^\dagger)</td>
<td>(-0.039 \pm 0.004^\dagger^*)</td>
</tr>
</tbody>
</table>

*Response significantly different from baseline \((p < 0.01)\).
†Hypertension significantly different from normotensive \((p < 0.01)\).
Values are means ± SEM.

### Table 2. Effects of Nitrendipine on Regional Blood Flows (ml/min)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Change with nitrendipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesenteric blood flow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive ((n = 6))</td>
<td>(408 \pm 40.9)</td>
<td>(150 \pm 16.7^*)</td>
</tr>
<tr>
<td>Hypertensive ((n = 6))</td>
<td>(369 \pm 28.3)</td>
<td>(303 \pm 23.9^\dagger)</td>
</tr>
<tr>
<td>Renal blood flow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive ((n = 6))</td>
<td>(157 \pm 17.6)</td>
<td>(10 \pm 3.0^*)</td>
</tr>
<tr>
<td>Hypertensive ((n = 6))</td>
<td>(134 \pm 19.7)</td>
<td>(11 \pm 6.3^*)</td>
</tr>
<tr>
<td>Iliac blood flow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive ((n = 6))</td>
<td>(114 \pm 14.2)</td>
<td>(108 \pm 10.9^*)</td>
</tr>
<tr>
<td>Hypertensive ((n = 6))</td>
<td>(132 \pm 19.2)</td>
<td>(134 \pm 31.1^*)</td>
</tr>
</tbody>
</table>

*Response significantly different from baseline \((p < 0.01)\).
†Hypertension significantly different from normotensive \((p < 0.01)\).
Values are means ± SEM.

### Table 3. Effects of Nitrendipine on Regional Resistances (mm Hg/ml/min)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Change with nitrendipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesenteric resistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive ((n = 6))</td>
<td>(0.24 \pm 0.02)</td>
<td>(-0.10 \pm 0.01^*)</td>
</tr>
<tr>
<td>Hypertensive ((n = 6))</td>
<td>(0.43 \pm 0.04^\dagger)</td>
<td>(-0.28 \pm 0.03^\dagger^*)</td>
</tr>
<tr>
<td>Renal resistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive ((n = 6))</td>
<td>(0.63 \pm 0.08)</td>
<td>(-0.17 \pm 0.03^*)</td>
</tr>
<tr>
<td>Hypertensive ((n = 6))</td>
<td>(1.28 \pm 0.21^\dagger)</td>
<td>(-0.50 \pm 0.11^\dagger^*)</td>
</tr>
<tr>
<td>Iliac resistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive ((n = 6))</td>
<td>(0.86 \pm 0.08)</td>
<td>(-0.49 \pm 0.04^*)</td>
</tr>
<tr>
<td>Hypertensive ((n = 5))</td>
<td>(1.27 \pm 0.19)</td>
<td>(-0.83 \pm 0.11^*)</td>
</tr>
</tbody>
</table>

*Response significantly different from baseline \((p < 0.01)\).
†Hypertension significantly different from normotensive \((p < 0.01)\).
FIGURE 3. The percent decreases in arterial pressure (AP) and total peripheral resistance (TPR) in response to nitrendipine, 8 μg/kg/minute, are compared in the same dogs studied before and following induction of hypertension. After induction of hypertension, nitrendipine caused significantly greater (p < 0.05) decreases in AP and TPR, which required significantly more time to return to baseline.

FIGURE 4. Average ± SEM percent increases in cardiac output (CO), mesenteric (MBF), renal (RBF), and iliac (IBF) blood flows are shown in response to nitrendipine, 8 μg/kg/minute, before (open bars) and after (shaded bars) inducing perinephritic hypertension. After hypertension was induced, nitrendipine administration caused a significantly greater percentage increase in blood flow only to the mesenteric bed (p < 0.01).

obtained in the normotensive dogs, and all were significantly greater (p < 0.01) than the percentage decrease in renal resistance.

Discussion

Nitrendipine, a dihydropyridine calcium channel blocker, elicited a differential pattern of vasodilation in the normotensive, conscious dog. It decreased arterial pressure and total peripheral resistance and induced the greatest dilation in the limb, the least dilation in the kidney, and an intermediate dilation in the mesenteric bed. Other studies have examined the effects of calcium channel blockers in normotensive animals.4, 8, 15-20 These studies, using different calcium channel blockers, have observed vasodilation in the gastrointestinal tract, renal and iliac vascular beds12, 18-21 that varied depending on the animal model and the classification of the calcium channel blockers used. We and other investigators13, 18, 19, 31 found only slight vasodilation induced by calcium channel blockers in the renal bed compared with other regional circulations. This finding might suggest that renal vessels are less sensitive to these agents.

Previous studies have examined the effects of calcium channel blockers in hypertensive animal models and humans.2-10 These studies showed enhanced reductions in arterial pressure and total peripheral resistance to calcium channel blockers in hypertension.8, 10 In the present investigation, conscious animals were studied before and after chronic, perinephritic hypertension was induced. We also observed enhanced vasodilation and reductions in arterial pressure and total peripheral resistance. Even more prominent was the prolonged recovery time for a single infusion of nitrendipine. Whereas arterial pressure and total peripheral resistance returned to baseline values within 15 to 30 minutes after nitrendipine administration in the normotensive dogs, 75 to 90 minutes was required for these values to return to baseline in the presence of hypertension.

There are even less data on the effects of calcium channel blockers on blood flow distribution to the peripheral beds in hypertension. We utilized the model of chronic, perinephritic hypertension so that nitrendipine could be studied in the same dogs before and after establishment of hypertension. In the presence of hypertension, neither baseline levels of cardiac output nor any of the regional blood flows were different from the normotensive state, but baseline levels of total peripheral and regional vascular resistances were significantly elevated. Under these conditions, nitrendipine enhanced vasodilation of all three peripheral beds studied. This greater vasodilation was most likely due to the altered baseline resistances induced by the hypertensive processes and the enhanced reduction in arterial pressure. The possibility that autoregulation is involved in the enhanced systemic and regional vascular responses to nitrendipine cannot be ruled out, as autoregulatory mechanisms may have been responsible for the elevated levels of total peripheral and regional vascular resistances in the hypertensive state.

The major difference in response to nitrendipine in the presence of hypertension occurred in the mesenteric bed. Nitrendipine induced an intermediate vasodilation in the mesenteric bed in the normotensive state, where it increased mesenteric blood flow significantly less than either iliac blood flow or cardiac output. In the presence of hypertension, nitrendipine induced a twofold greater vasodilation in the mesenteric bed that was no longer significantly less than in the limb or the systemic circulation. Although this finding has not been demonstrated previously, Aoki et al.5 have shown that nitrendipine induced enhanced relaxation of mesenteric vascular strips from hypertensive rats. This greater effect in the mesenteric strips was not compared with strips from other vascular beds.5
The increased blood flow response to nitrendipine in the mesenteric bed following hypertension in the present investigation could have been the result of either greater cardiac output or redistribution of blood flow from other beds. As we did not observe a reduced blood flow response in the renal or iliac bed, it is most likely that the greater response in the mesenteric bed was due to increased cardiac output. In the hypertensive state, nitrendipine induced a slightly greater cardiac output response that was not statistically significant. Although the greater increase in cardiac output (300 ml) was not sufficient to attain statistical significance, it could be sufficient to double the mesenteric blood flow response to nitrendipine. This suggestion further points out the importance of studying regional blood flow responses in addition to cardiac output, as selective blood flow changes in only one bed would be difficult to detect from the measurement of cardiac output alone; however, redistribution of blood flow from other beds not studied in these experiments (e.g., coronary and cerebral beds), cannot be discounted.

Even though autoregulation of the regional vascular beds may be responsible for the elevated vascular resistances in the hypertensive state, the possibility that autoregulation is responsible for the difference in the mesenteric blood flow response to nitrendipine following hypertension is unlikely. It is important to note that autoregulatory theory indicates that blood flow is maintained in the face of altered driving pressure. When nitrendipine was administered to the dogs following induction of hypertension, a significantly greater increase in blood flow to the mesenteric bed was observed that cannot be explained entirely by autoregulatory theory.

The enhanced vasodilation of the mesenteric bed could be of therapeutic interest because, in the presence of hypertension, increased vasodilation in the gastrointestinal tract would be preferred to greater vasodilation of muscular beds. This finding might be potentially important in patients with mesenteric vascular insufficiency, in whom enhanced perfusion of the mesenteric bed would be salutary in the face of hypertensive therapy, which reduces perfusion pressure.

In summary, administration of nitrendipine to hypertensive dogs produced a greater reduction in arterial pressure and total peripheral and regional resistances, which required a significantly longer time to recover when compared with those responses in the normotensive state. In addition, the response of the mesenteric bed to nitrendipine was unique when compared with the responses of other peripheral beds studied, in that this calcium channel blocker induced a greater increase in blood flow only in the mesenteric bed.

Acknowledgments

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