Effects of Calcium Channel Antagonists on Carotid Sinus Baroreflex Control of Arterial Pressure and Heart Rate in Anesthetized Dogs

Dean F. Rigel and Ronald W. Millard

Our study was designed to determine whether the calcium channel antagonists verapamil, diltiazem, and nifedipine and the nitrate vasodilator sodium nitroprusside modulate carotid sinus (CS) baroreflex control of mean arterial pressure (MAP) and heart rate (HR). Pentobarbital-anesthetized, vagotomized dogs were surgically prepared for reversible vascular isolation of the CS regions. Open-loop performance of the CS baroreflex was determined under control conditions and after intravenous infusion of each agent for 20 minutes at four rates (nitroprusside: 0.3-10 μg/kg/min; verapamil and diltiazem: 1-30 μg/kg/min; nifedipine: 0.1-3 μg/kg/min). With the CS baroreflex loop closed, each vasodilator decreased MAP from control (nitroprusside: 127±3 to 69±5 mm Hg; verapamil: 137±7 to 100±5 mm Hg; diltiazem: 137±9 to 100±5 mm Hg; nifedipine: 140±6 to 109±7 mm Hg). Each compound also caused a dose-dependent downward shift in the open-loop CSP-MAP relations. The higher doses of each vasodilator also depressed the total range of control of MAP (i.e., maximum MAP minus minimum MAP) by the baroreflex and significantly attenuated the peak open-loop MAP/CSP gains (nitroprusside: 1.21±0.19 to 0.56±0.12; verapamil: 1.36±0.16 to 0.64±0.10; diltiazem: 1.52±0.34 to 0.89±0.11; nifedipine: 1.35±0.20 to 0.83±0.14) but did not alter the CSP at which the peak gain was manifest. Only verapamil and diltiazem significantly shifted downward the CSP-HR relations, whereas none of the drugs affected the baroreflex control of HR (i.e., maximum HR minus minimum HR) or the peak open-loop HR/CSP gains. Our results suggest that 1) it is unlikely that calcium channel antagonists act directly on the baroreceptors or the neural components of the baroreflex loop (i.e., afferent, central and efferent nerves) because they impair CS baroreflex control of MAP but not HR and 2) the impairment of MAP control is predominantly due to a nonspecific blunting of adrenergic vasoconstriction. (Circulation Research 1989;64:276-286)

Calcium channel antagonists are used for the treatment of a variety of disorders including arrhythmias, angina, and hypertension. In therapeutic concentrations, these agents act primarily to inhibit transmembrane calcium influx, which results in vascular smooth muscle relaxation and vasodilation, inhibition of cardiac automaticity and conduction, and a reduction of myocardial contractility. In animals or patients with intact reflexes, the direct cardiodepressant and vasodilatory actions of these drugs may be offset or modulated by reflex changes in autonomic nervous activity. For example, acute administration of nifedipine and verapamil to patients is invariably accompanied by a tachycardia that is attributable to baroreceptor stimulation secondary to the drug-induced hypotension. After 4-6 days of treatment, the tachycardia usually subsides, probably due to a baroreflex resetting to the lower prevailing arterial pressure. However, these responses are variable depending on the responsiveness of the individual patient's reflex pathways and on the specific calcium channel antagonist administered. Although the degree of interaction between the calcium channel antagonists and the baroreceptor reflex is clearly an important determinant of the integrated cardiovascular response to these agents, meaningful information about this interaction is lacking.
Evaluation of baroreflex responsiveness in patients is limited by the inability to open the feedback loop, by the difficulty in applying a wide range of input pressures, and by the restrictions on measuring physiologically relevant output variables. Consequently, clinical investigators have resorted to less desirable means of characterizing baroreflex function, such as examining the reflex chronotropic response to an induced change in arterial pressure. Such studies in patients have led to unforced speculation regarding the effect of calcium channel antagonists on baroreflex control of arterial pressure. Thus, calcium channel antagonists have been reported to attenuate, to not alter, or to enhance baroreflex chronotropic sensitivity in patients.

The need is evident for a well-controlled systematic study to elucidate the possible calcium channel antagonist-baroreflex interactions. Proper characterization of arterial pressure control requires opening the baroreflex loop and applying input stimuli over the entire physiological range of pressures. Therefore, in the present study, we examined the effects of the calcium channel antagonists verapamil, diltiazem, and nifedipine and, for comparison, the nitrate vasodilator sodium nitroprusside on open-loop carotid sinus baroreflex control of arterial pressure and heart rate in anesthetized dogs.

Materials and Methods

Experimental Preparation

Thirty mongrel dogs of either sex (15–23 kg) were anesthetized with pentobarbital sodium (30 mg/kg i.v.). Supplemental doses of pentobarbital were administered throughout the experiment to maintain a stable plane of anesthesia. Rectal temperature was monitored and maintained within ±0.5°C of baseline temperature (approximately 38–39°C) with heat lamps. Systemic arterial blood pressure was measured with a Gould P23LD transducer (Gould Instruments, Cleveland, Ohio) and a polyvinylchloride catheter inserted into the aorta via a femoral artery. Mean arterial pressure (MAP) was derived by electronic integration of the pulsatile pressure signal. Drugs were administered through a femoral vein cannula. Beat-by-beat heart rate (HR) was obtained by triggering a Gould biotachometer coupler with a lead II electrocardiogram.

Carotid sinus (CS) regions were prepared bilaterally for later reversible isolation from the systemic vasculature. The internal carotid, laryngeal, ascending pharyngeal and anterior thyroid arteries were ligated. The occipital arteries were ligated at their origin from the external carotid arteries in order to preclude confounding interactions by the CS chemoreceptors. Dogs in which an occipital artery had a different origin were excluded from the study. Carotid sinus pressure (CSP) was measured bilaterally via lingual artery cannulae and Gould P231D transducers. After heparin administration (200 units/kg; 100 units/kg/hr boli i.v.), each common carotid artery was cannulated with a T tube. The free ends of each tube were joined at a common “Y,” which was connected to a pressure source. The vagosympathetic trunks were severed bilaterally to eliminate the buffering effects of vagally mediated pressure receptors. HR, pulsatile arterial pressure, MAP and left and right CSP signals were displayed on a Gould strip chart recorder (model 2800).

Generation of CSP Stimulus

Open-loop CS baroreflex performance was evaluated using slow ramp CSP stimuli. Both CS were reversibly isolated by clamping each common carotid artery proximal to the T cannulae and the external carotid arteries distal to the lingual artery origins. Pressure ramps were generated by a syringe pump that infused and withdrew saline at a constant rate into a compliance chamber connected in parallel to the input to the carotid sinus plumbing. The rate of rise and fall of the pressure ramp was adjusted for each dog to 0.8 mm Hg/sec by varying the chamber compliance.

CSP ramps were selected instead of the more conventional step changes in CSP because of the shorter time required to generate a single curve and thus to complete the experimental protocol. In five dogs, we compared CS stimulus-response curves derived by applying both CSP ramps and CSP steps. No statistically significant difference (two-way analysis of variance) was detected between the ramp and step data for either the CSP-MAP or the CSP-HR relations.

Experimental Protocol

Animals were divided randomly into one of five groups to evaluate the effects of 1) sodium nitroprusside, 2) verapamil, 3) diltiazem, 4) nifedipine, or 5) the drug vehicles (i.e., time control experiments) on CS baroreflex regulation of arterial pressure and HR. Protocols were initiated after completing the surgical preparation and allowing sufficient time (20–30 minutes) for hemodynamic stabilization.

Each individual experiment involved an assessment of CS performance after an initial control intravenous saline infusion and subsequently following intravenous infusion of either four logarithmically increasing doses of the preselected drug (nitroprusside: 0.3, 1, 3, and 10; verapamil: 1, 3, 10, and 30; diltiazem: 1, 3, 10, and 30; nifedipine: 0.1, 0.3, 1, and 3 μg/kg/min) or alternatively, after four infusions of drug vehicle (saline or ethanol/polyethylene glycol). Each dose of each drug, saline control or vehicle was infused at a constant volume flow rate of 0.01 ml/kg/min.

After 20 minutes of control saline infusion, baseline MAP and HR were evaluated, the CS were isolated as described above, and CSP was adjusted to 20 mm Hg. Systemic pressure and HR were allowed to stabilize for several minutes. CSP was increased linearly from the 20-mm Hg holding pres-
TABLE 1. Mean Arterial Pressure and Heart Rate Responses During Closed-Loop Baroreflex Conditions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean arterial pressure</th>
<th>Heart rate</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>C</td>
</tr>
<tr>
<td>Vehicle</td>
<td>5</td>
<td>127±8</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>5</td>
<td>127±3</td>
</tr>
<tr>
<td>Verapamil</td>
<td>5</td>
<td>137±7</td>
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<tr>
<td>Diltiazem</td>
<td>7</td>
<td>137±9</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>6</td>
<td>140±6</td>
</tr>
</tbody>
</table>

All values are mean±SEM.

*Significantly different from control value (C) as determined by analysis of variance followed by Bonferroni multiple comparisons (overall p<0.05). Refer to text for actual infusion rates of each drug and vehicle.

Data Analysis

MAP and HR were evaluated at CSPs beginning at 25 mm Hg and at each subsequent 20 mm Hg up to 245 mm Hg for both the rising and falling CSP ramps. Because hysteresis in the input-output relation is generally exhibited when CSP is increased and decreased,7,8 the two sets of values were averaged to generate a single curve. The characteristics of each resulting curve were quantitated by fitting the sigmoidal data by nonlinear least-squares regression (with a standard Marquardt type algorithm) to a mathematical model relating CSP to MAP9

\[
\text{MAP} = \frac{\text{MAP}_{\text{max}} - \text{MAP}_{\text{min}}}{1 + e^{-k\text{CSP}-\text{CSP}_{\text{opt}}}} + \text{MAP}_{\text{min}}
\]

in which MAP_{max} and MAP_{min} are the maximum and minimum MAP reached at low and high CSP, respectively, and CSP_{opt} (i.e., optimum CSP) is the CSP at which the maximum MAP/CSP gain (G_{max}) occurs. G_{max} is estimated from the parameters as (-k(MAP_{max} - MAP_{min}))/4. Likewise, the saturation and threshold CSP (CSP_{sat} and CSP_{th}) are estimated as CSP_{opt}±1.317/k, respectively. An additional parameter, MAP_{max} - MAP_{min}, was calculated as an indicator of the maximum range over which MAP may be regulated by the CS baroreflex. Similar analyses were applied to the sigmoidal CSP-HR relations.

Baseline and parameter values derived after the four drug doses (or the four vehicle infusions) were compared with the corresponding control values using a repeated measures one-way analysis of variance followed by the Bonferroni method of multiple comparisons.10 Differences were considered significant when p<0.05 for the family of comparisons. Results are presented as mean±SEM.

Drugs

The following drugs were used: sodium nitroprusside (Sigma Chemical Co, St. Louis, Missouri), verapamil (Knoll Pharmaceutical Co, Whippany, New Jersey), diltiazem (Marion Laboratories, Kansas City, Missouri), and nifedipine (Pfizer, Inc, New York, New York). Nitroprusside, verapamil, and diltiazem were dissolved in 0.9% saline. A stock solution of nifedipine (1,000 μg/ml) was prepared in 25% ethanol/25% polyethylene glycol 400 by volume and then diluted to the appropriate concentration with saline. Nitroprusside was protected from light during preparation and experiments. Nifedipine preparation and experiments were performed under lighting from a sodium vapor lamp.

Results

Closed-Loop MAP and HR Responses

Baseline MAP and HR values measured after each infusion and before the CS baroreflex loop was opened are displayed in Table 1. The animals remained hemodynamically stable over the 3-hour course of an experiment as evidenced by the lack of change in the MAP during the vehicle experiments. However, there was a significant time-dependent elevation of HR from 163±5 to 183±8 beats/min throughout the vehicle experiments (Table 1). These trends were consistent whether the vehicle solution was saline (n=3) or ethanol/polyethylene glycol (n=2), and therefore the results with the two vehicles were lumped.
Each vasodilator exhibited a dose-related hypotensive effect indicating that the calcium channel antagonists and nitroprusside can perturb arterial pressure in the presence of the buffering capacity of the CS baroreceptor reflex. These changes were statistically significant following the highest two or three doses of each agent (Table 1). HR responses obtained with the CS baroreflex loop closed depended on which drug was infused. Nitroprusside exhibited an increase in HR similar to that observed during the vehicle experiments. HR also increased with the nifedipine infusions during closed-loop conditions but to a less degree than during the vehicle infusions. On the contrary, verapamil and diltiazem tended to decrease HR (Table 1). It is likely that the actual depression of pacemaker automaticity is much greater than what is readily apparent from the data since the direct HR decrease by these agents is being opposed by the time-dependent HR rise (Table 1).

**Open-Loop MAP and HR Responses**

Open-loop baroreflex responses of MAP and HR are depicted in Figures 1 and 2, respectively, for the vehicle (n=5), nitroprusside (n=5), verapamil (n=5), diltiazem (n=7), and nifedipine (n=6) experiments. Each point represents the average MAP or HR measured at the corresponding CSP. Error bars have been omitted from the plots for the sake of clarity, but the average range of the SEMs is 6–12 mm Hg for the MAP points and 8–11 beats/min for the HR points.
Each individual CSP-MAP and CSP-HR relation was curve-fitted to the baroreflex model described in “Materials and Methods.” In each case, excellent fits were obtained as indicated by the small root-mean-square errors (i.e., the average deviation of the actual data points from the fitted curve). Root-mean-square errors ranged from 0.35 to 4.17 mm Hg (1.61 ± 0.06 mm Hg) for the CSP-MAP curves and from 0.28 to 3.25 beats/min (1.27 ± 0.5 beats/min) for the CSP-HR relations. Average parameters derived from the individual responses are displayed in Figures 3–5 for the MAP and HR data.

Opening the CS baroreflex loop and decreasing CSP to 20 mm Hg caused large (35–53 mm Hg) increases in MAP but only slight (0–13) increases in HR. In each animal, increasing CSP to 250 mm Hg decreased both MAP and HR in the characteristic sigmoidal fashion (Figures 1 and 2).

Combined results from saline or ethanol/polyethylene glycol vehicle infusions demonstrated that the CSP-MAP stimulus-response curves were quite reproducible over the 3-hour course of an experiment (Figure 1). Only the MAP_min parameter significantly decreased (81 ± 12 to 62 ± 5 mm Hg) from the control level during the fourth vehicle infusion (Figure 4C). Thus, there was also a concomitant time-dependent increase in MAP_max – MAP_min since the MAP_max remained unchanged (Figure 4E). No statistically significant time-related changes in the CSP_opt, CSP_th, CSP_min (Figures 3A, 3C, and 3E), or G_max (Figure 5A) were detected for the CSP-MAP relations although the magnitude of G_max tended to increase by 37% over the course of the vehicle infusions.

The three calcium channel antagonists and the nitrate vasodilator had remarkably similar effects.
on the CSP-MAP relations (Figure 1). Each agent caused a dose-related downward shift in the curves. The downward shift was greater when CSP was low (i.e., when sympathetic nerve activity was high) than when CSP was high (i.e., when sympathetic nerve activity was low) as reflected by the greater depression of MAP$_{max}$ than MAP$_{min}$ (Figures 4A and 4C). Thus, there was also an attendant significant depression of the total range of baroreflex control of MAP (i.e., MAP$_{max}$−MAP$_{min}$) with each drug (Figure 4E). None of the calcium channel antagonists shifted the curves laterally as indicated by the similar CSP$_{th}$, CSP$_{th}$, and CSP$_{opt}$ between control and the four doses of each agent (Figures 3A, 3C, and 3E). Nitroprusside also did not affect the CSP$_{th}$ or CSP$_{opt}$ (Figures 3A and 3E) but did cause a slight but statistically significant decrease in the MAP CSP$_{th}$ (from 91±7 mm Hg to 77±7 mm Hg) at the highest infusion level (Figure 3C). Each of the four vasodilators also attenuated the magnitude of the MAP G$_{max}$ (Figure 5A). Nitroprusside and verapamil exhibited the most pronounced effects, decreasing the peak gains by more than 50% at the highest doses (nitroprusside: 1.21±0.19 to 0.56±0.12; verapamil: 1.36±0.16 to 0.64±0.10).

CSP-HR relations for vehicle and drug experiments are displayed in Figure 2. A comparison of the CSP-HR curves with the CSP-MAP curves in Figure 1 indicates that the four vasodilators had dramatically different effects on CS baroreflex control of HR than of MAP. These differences are further illustrated by contrasting the MAP and HR parameters depicted in the left and right panels, respectively, of Figures 3–5. During the vehicle experiments the CSP-HR curves tended to shift upward in a time-dependent fashion (Figure 2). Only the increase in HR$_{max}$ was statistically significant (Figure 4B), and thus there was also a slight but significant augmentation in the total range of CS baroreflex control of HR (i.e., HR$_{max}$−HR$_{min}$) following the final vehicle infusion (Figure 4F). No lateral shift in the curves occurred since the CSP$_{opt}$, CSP$_{th}$, and CSP$_{sat}$ were not altered over the time course of the experiment (Figures 3B, 3D, and 3F). Likewise, the HR/CSP baroreflex sensitivity was unaltered by the vehicle infusions as evidenced by the lack of change of HR G$_{max}$ (Figure 5B).

The changes in the CSP-HR relations during the nitroprusside experiments were essentially identical to those during the vehicle experiments (Figure 2). Thus, the curves tended to shift upward but not laterally as indicated by the significant increase in HR$_{max}$ (Figure 4B) but lack of change in CSP$_{opt}$, CSP$_{th}$, and CSP$_{sat}$ (Figures 3B, 3D, and 3F). HR$_{min}$
also tended to increase with the nitroprusside infusions (Figure 4D) but the changes did not reach statistical significance. However, the increases in HR_{max} balanced the increases in HR_{min} resulting in no significant change in HR_{max}−HR_{min} (Figure 4F). The similarity of nitroprusside results with those during vehicle infusions therefore suggests that this vasodilator has no inherent action on the CS baroreflex control of HR.

Effects of the three calcium channel antagonists on open-loop baroreflex control of HR (Figure 2) tended to reflect the changes observed with the respective agents during closed-loop conditions (Table 1). Thus, verapamil and diltiazem shifted the
CSP-HR curves downward as illustrated in Figure 2 and verified by the significant decreases in HRmax and HRmin (Figures 4B and 4D). The downward shifts were parallel since HRmax - HRmin (Figure 4F) and CSPmin, CSPmax, and CSPopt (Figures 3B, 3D, and 3F) were not significantly altered. Also, unlike the CSP-MAP responses, the HR Gm was not affected by either verapamil or diltiazem (Figure 5B). The CSP-HR data during the fourth infusion of verapamil are excluded from Figures 2-5 because in each of the five animals, second- or third-degree atrioventricular block developed. The blocked beats occurred only at higher CSPs when sympathetic tone to the atrioventricular node was presumably low. During nifedipine infusions there was no significant change in any of the parameters for the CSP-HR relations (Figures 3B, 3D, and 3F; Figures 4B, 4D, and 4F; Figure 5B).

Discussion

Our study is the first demonstration that systemic calcium channel antagonists impair open-loop baroreflex control of arterial blood pressure. This attenuation in blood pressure control became evident at drug infusion levels which also significantly lowered arterial pressure during closed-loop conditions and was manifest both as a decrease in the total range over which the CS baroreceptors may regulate arterial pressure and as a suppression of the peak gain of the baroreflex. These actions were common to verapamil, diltiazem and nifedipine, three structurally distinct calcium channel antagonists. The similar results with the nitrovasodilator sodium nitroprusside indicates that the depression of baroreflex function is not unique to the calcium channel antagonists.

Until now, only indirect indexes have been used to evaluate the effects of systemic calcium channel antagonists on baroreflex function in animals and patients.1-6,11-16 By and large, these prior studies examined the reflex chronotropic responses to an evoked arterial pressure increase or decrease. In general, evidence from these studies suggest an impaired baroreflex control of cardiac automaticity by verapamil14,15 and diltiazem,1,14,15 but a variable effect of the dihydropyridines. Thus, investigations with nifedipine and other dihydropyridines have indicated an attenuation,11,14,16 no change,2,4,15,16 or an enhancement5,6 of baroreflex chronotropic sensitivity. In our study, neither nitroprusside nor any of the three calcium channel antagonists altered open-loop carotid sinus baroreflex control of heart rate in spite of the pronounced compromise in arterial pressure control by these agents. These findings underscore the potential danger cited by Sagawa3 in interpreting closed-loop baroreflex chronotropic responses to indicate the overall baroreflex sensitivity.

One potential reason why our reflex chronotropic results are at variance with those of others may stem from the different states of autonomic cardiac control between the studies. Whereas our neurally mediated reflex alterations in heart rate were entirely sympathetic (cervical vagosympathetic trunks were cut), those in awake patients or dogs1-6,14,16 or anesthetized dogs with β-adrenergic blockade15 were predominantly or exclusively of parasympathetic origin. Verapamil has been reported to possess antimuscarinic properties17 and to inhibit bradycardic responses to vagal stimulation or injected acetylcholine.18 On the other hand, verapamil is devoid of β-adrenergic blocking actions17 and does not interfere with the tachycardic response to exogenous norepinephrine19,20 or stellate ganglion stimulation.21 Although we cannot exclude other possible mechanisms, our results are consistent with these findings since the sympathetically mediated baroreflex modulation of heart rate was unaltered despite a pronounced depression of intrinsic pacemaker automaticity by the calcium channel antagonists. Consistent with our previous findings,14,22 verapamil and diltiazem depressed heart rate to a greater degree than did nifedipine.

Although we did not directly measure atrioventricular conduction, following the highest dose of verapamil, second- or third-degree atrioventricular block became evident. Verapamil is known from in vitro electrophysiology studies and in vivo experiments to greatly depress atrioventricular conduction.1,14,19,20,22 In our study, atrioventricular block became evident only at high CSPs, when sympathetic tone to the atrioventricular node was presumably low. This finding indicates an important interactive role of the arterial baroreflex and autonomic nervous system in maintaining 1:1 atrioventricular conduction particularly in the presence of drugs like verapamil that have direct negative dromotropic actions.

The calcium channel antagonists and nitroprusside may act at a number of possible sites to depress baroreflex control of arterial pressure. For example, studies have demonstrated that these agents may interfere with function at the baroreceptors themselves, within the central or peripheral nervous system, or at the effector organs.23-27

It is unlikely that our findings may be explained by a direct effect of these agents on the sensory or afferent component of the baroreceptors for several reasons. First, in our study, all three calcium channel antagonists had an identical inhibitory effect on baroreflex control of arterial pressure. On the other hand, Heesch et al found that calcium channel antagonists applied locally to the carotid sinuses of dogs altered baroreceptor function in a drug-dependent fashion.25 Verapamil decreased, nifedipine increased, and diltiazem did not alter the slope and the maximum response of the relation between carotid sinus pressure and afferent nerve activity. Second, these direct baroreceptor actions occurred only at relatively high CS bathing concentrations of the drugs.25,27 Even at our highest infusion levels the plasma concentrations of verapamil and nifedipine would be expected to only slightly
exceed and to be two orders of magnitude lower, respectively, than the threshold CS concentrations in the dog. In a similar study in cats, local CS application of these agents altered the blood pressure in the dog. In our study, Kunze et al observed a suppression of the reflex hypotensive response following a CS pressure increase but no change in the maximum arterial pressure at subthreshold CS pressures. In contrast, systemic calcium channel antagonists in our study exhibited their greatest effect by depressing the maximum arterial pressure at low carotid sinus pressures. Thus, although we cannot specifically exclude the possibility of a direct CS baroreceptor action of the systemic calcium channel antagonists, it is clear that this action could not account for the observed depression of baroreflex control of blood pressure in our experiments.

Higuchi et al found that relatively high concentrations of verapamil, diltiazem, and nifedipine applied directly to the brainstem of rats decreased both heart rate and arterial pressure. These responses were prevented by pretreatment with 6-hydroxydopamine suggesting that they were mediated by a withdrawal of sympathetic activity to both the heart and the vasculature. The fact that we observed a pronounced attenuation in baroreflex sympathetic control to the vasculature but no parallel attenuation of sympathetic heart rate control suggests that this central mechanism of action is insignificant when calcium channel antagonists are applied systemically. However, we must consider the possibility that the calcium channel antagonists act differently on the brainstems of the rat and dog.

Verapamil has also been reported to inhibit norepinephrine release in response to electrical stimulation of postganglionic sympathetic nerves. This inhibitory action was evident only at verapamil concentrations two orders of magnitude greater than the highest plasma concentrations predicted from our infusions. Even if such an effect were evident at lower drug concentrations, verapamil would be expected to hinder norepinephrine release nonselectively from both cardiac and vascular sympathetic nerves. But in our study only sympathetic control of vascular tone was inhibited. It is therefore unlikely that interference with neurotransmitter release by the calcium channel antagonists may explain our results.

It is more likely that our observed depression of baroreflex function is due to a nonspecific blunting of sympathetic mediated vasoconstriction by the calcium channel antagonists and nitroprusside. This hypothesis is consistent with animal studies which show that in vivo vasoconstrictor responses to a-adrenergic agonists or sympathetic nerve stimulation are inhibited by verapamil, diltiazem, and dihydropyridines in doses comparable to those used in our study. Likewise, sodium nitroprusside, at infusion rates equivalent to those used in our study, also exhibits a similar depression of vascular responsiveness. Similar findings have been reported in human subjects in which calcium channel antagonists inhibit vasoconstrictor responses to exogenous a-adrenergic agonists or reflex stimuli such as cold pressor test or handgrip.

Our results also indicate that the hypotensive effectiveness of the calcium channel antagonists (and sodium nitroprusside) is proportional to the prevailing level of vasoconstrictor tone. Data in Figures 1 and 4 indicate that the four vasodilators caused a twofold to threefold greater attenuation in arterial pressure when sympathetic tone was high (i.e., at low CSP) than when sympathetic activity was low or absent (i.e., at high CSP). For example, the highest dose of nifedipine (3 \( \mu \)g/kg/min) reduced arterial pressure from a control of 192 ± 9 mm Hg to 119 ± 9 mm Hg when CSP was low and from 104 ± 12 mm Hg to 69 ± 10 mm Hg at high CSP (ratio, -73: -35 = 2.1). Similarly, sodium nitroprusside (10 \( \mu \)g/kg/min) attenuated arterial pressure by 89 and 34 mm Hg at low and high CSP, respectively (ratio, 2.6). Our results are consistent with the findings of Morita et al in which sustained increases in vascular smooth muscle tone were produced in anesthetized, spinal dogs by exogenous a-adrenergic agonists.

Diltiazem and nifedipine were three times more effective in reducing arterial pressure in the presence of vasoconstriction than at basal levels of myogenic tone. In addition, a number of studies in hypertensive patients have documented a strong correlation between pretreatment arterial pressure (or vascular resistance) and the change in these variables consequent to nifedipine.

Calcium channel antagonists have gained widespread use in the clinical treatment of a variety of disorders including cardiac arrhythmias, coronary vasospasm and hypertension. It is generally agreed that the direct cardiac and vascular actions of the calcium channel antagonists may be greatly modulated by the baroreceptor reflexes. Yet, a basic understanding of this drug-reflex interaction in humans is lacking. Clinical studies attempting to address this issue have yielded conflicting conclusions, probably because of the complexity and variability of the experimental conditions. Most of these patient studies have examined the effects of dihydropyridines on the chronotropic response to an induced arterial pressure change. Nifedipine chronically administered to hypertensive humans or acutely administered to normotensive subjects enhanced the chronotropic sensitivity. On the contrary, this baroreflex index was unchanged by nifedipine and other dihydropyridines acutely or chronically administered to hypertensive patients and was decreased with diltiazem acutely administered to normotensive humans. Moreover, these results provide limited insight into baroreflex control of arterial pressure since it is well known that the vascular and cardiac responses to baroreceptor
stimuli do not usually change in a parallel fashion.8 Two patient studies have evaluated vascular responses to baroreceptor stimuli. Ferguson and Dorsey found that nifedipine did not alter the forearm vasoconstrictor response to lower body negative pressure in normotensive patients.13 However, the forearm vasoconstriction due to exogenous norepinephrine and nonbaroreceptor reflex stimuli was attenuated suggesting that nifedipine selectively sensitizes the baroreceptors. This observation was not supported by a study in which nicardipine administered to hypertensive patients did not alter the chronotropic or arterial pressure responses to dynamic exercise or to carotid sinus baroreceptor stimulation by neck suction.12 Evaluation of baroreceptor function in human subjects is limited by the inability to open the feedback loop and to apply stimuli over a wide physiological range without the confounding effects of other reflexes. Our animal study was designed to overcome these limitations by examining the effects of systemic verapamil, diltiazem and nifedipine on open-loop carotid sinus baroreflex control of arterial pressure and heart rate. Although our results cannot rule out a potential direct baroreceptor inhibition or sensitization by the calcium channel antagonists, the predominant action of all three drugs appears to be a blunting of sympathetic vasoconstriction and a resultant impairment of baroreflex control of arterial pressure. A comparable action of the calcium channel antagonists in patients with intact baroreceptor reflexes may be an important determinant of the therapeutic effects of this class of drugs. However, we must stress that our study was conducted in healthy, anesthetized normotensive animals following acute exposure to the calcium channel antagonists. It is possible that the arterial baroreflexes interact differently with these drugs when they are administered chronically to ambulatory patients with diseased hearts or hypertension.

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