0022-3565/82/2213-0609$02.00/0
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Vol. 221, No. 3
Printed in U.S.A.

Inotropic and Chronotropic Effects of Vasodilators[1]

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Accepted for publication March 9, 1982

ABSTRACT

Pérez, Julio E., Leonor Borda, Rafael Schuchleib and Philip D. Henry: *Inotropic and chronotropic effects of vasodilators.* J. Pharmacol. Exp. Ther. **221:** 609–613, 1982.

Although vasodilators are used with increasing frequency for the treatment of heart failure and myocardial ischemia, their direct effects on cardiac muscle have not been completely characterized. To delineate the action of vasodilators on mammalian myocardium, the chronotropic and inotropic effects of vasodilators on isolated guinea-pig atria (n = 163) have been determined. The spontaneous frequency and the peak rate of isometric force development at a fixed frequency of 200/min were used as indexes of chronotropy and inotropy. The potency series for negative chronotropy was diltiazem > D600 > verapamil > lidoflazine > bepridil > prenylamine > perhexiline > nifedipine. The potency series for negative inotropy differed substantially, exhibiting the sequence nifedipine > D600 > verapamil > bepridil > lidoflazine > prenylamine > perhexiline > diltiazem. Therefore, nifedipine acted as an "ino-selective" and diltiazem as a "chrono-selective" depressant. Other vasodilators, including papaverine, nitroglycerin, nitroprusside, adenosine, dipyridamole, diazoxide and hydralazine exerted no or negligible negative chronotropic or inotropic effects even at high concentration (10^{-5} M). Therefore, only vasodilators classified among the calcium antagonists proved to have appreciable direct myocardial effects. This supports the view that these drugs constitute a category of agents distinct from classical vasodilators.

Recently, vasodilators have been used with increasing frequency for the treatment of heart failure, ischemic heart disease and hemodynamic disturbances associated with valvular regurgitation. *In vivo* vasodilators may have variable effects ranging from primary arteriolar to mixed to primary venodilator actions and therefore reduce cardiac preload and/or afterload altering cardiac performance in an indirect fashion (Miller *et al.*, 1976). However, there is relatively little information about the direct effects of these agents on the contractile and pacemaker activity of the heart. This type of evaluation is difficult to perform *in vivo* because vasodilators affect major determinants of myocardial performance including preload, afterload, heart rate and coronary flow. Moreover, cardiac performance during vasodilator-induced hypotension may be influenced by autonomic nervous system adjustments.

The present experiments were designed to delineate and compare direct cardiac effects of various vasodilators. Results demonstrate that agents with cardiac depressant effects may vary appreciably in their relative chronotropic and inotropic effects.

Materials and Methods

Guinea pigs weighing between 350 and 450 g were killed by a blow to the head. After rapid excision of the heart, the right atria (n = 163) were immediately dissected and mounted in a myograph as described by Levy (1971). Isometric force was measured with Statham model UC2 force transducers. The transducer signals were amplified and differentiated with Honeywell bridge amplifiers (model 143) and differentiators (model 132) and recorded with a Gould recorder (model 220). The preparation was equilibrated in a Krebs-Henseleit buffer of the following formulation (millimolar): NaCl, 118; KCl, 4.0; $CaCl_2$, 1.5; $NaHCO_3$, 25; NaH_2PO_4, 1.2; $MgSO_4$, 1.2; and glucose, 5. The buffer was equilibrated at 37°C with a 95% O_2-5% CO_2 gas mixture. The preparations were paced with a bipolar electrode and a model SK4 Grass stimulator. The stimuli had a duration of 2 msec and their voltage was 10% above threshold. The preload was increased stepwise during pacing at a frequency of 200/min until developed tension was maximum. Chronotropic effects were evaluated while the atria were beating spontaneously, whereas inotropic effects were assessed recording the maximum rate of isometric force development during electrical stimulation at a fixed frequency of 200/min (dF/dt_{max}). The frequency of 200/min is close to the resting heart rate of guinea pigs and consequently tests inotropy within the physiological range of the force-frequency relation (Henry, 1975). Control values (=100%) refer to the spontaneous frequency and dF/dt_{max} at 200/min before the addition of drug. Absolute values for frequency and dF/dt_{max} at the end of equilibration ranged between 182 and 244 beats/min and 11.6 and 19.3 g/sec, respectively, and mean values in the different groups did not differ significantly ($P > .5$) applying Bonferroni's modified t test for two variables (Wallenstein *et al.*, 1980).

After a period of equilibration of 1 hr, each preparation was exposed to graded concentrations of a single drug. Cumulative dose-responses were studied by changing the bath fluid with Krebs' buffer containing increasing concentrations of drug. Drugs were dissolved in Krebs' buffer without addition of solvent and the solutions were warmed up to 37°C before use. To protect nifedipine from light inactivation, experiments with this drug were performed under yellow light (Westinghouse Gold Neon). Inasmuch as most of the calcium antagonists (calcium entry

Received for publication May 11, 1981.
[1] This work was supported in part by the National Institute of Health Grant HL-17646 (Specialized Center for Research in Ischemic Heart Disease), HL-21187 and a Grant-in-Aid from the American Heart Association, Missouri Affiliate, Inc.

blockers, slow channel blockers and calcium blockers) tested have a low solubility in Krebs' buffer, no attempt was made to test concentrations exceeding 10^{-6} M. Nitroprusside, adenosine, dipyridamole, diazoxide and hydralazine were tested up to 10^{-5} M and nitroglycerin up to 10^{-3} M.

Differences in sequential mean values in the same group were analyzed by the *t* test for paired observations. Comparisons between mean values from different groups were evaluated by Bonferroni's modified *t* analysis for two variables (Wallenstein *et al.*, 1980).

Drugs were gifts from pharmaceutical companies: nitroglycerin (Eli Lilly and Company, Indianapolis, IN); nitroprusside (Roche Diagnostic Div. Hoffmann La Roche Inc., Nutley, NJ); dipyridamole (Boehringer-Ingelheim Ltd., Ridgefield, CT); diazoxide (Schering Corporation, Kenilworth, NJ); prenylamine (Hoechst-Roussel Pharmaceuticals, Inc., Summerville, NJ); fendiline (Thiemann Pharmaceuticals, Lunen, West Germany); perhexiline (Merrell National Laboratories, Cincinnati, OH); nifedipine (Bayer, Wuppertal, West Germany); diltiazem (Marion Laboratories, Kansas City, MO); lidoflazine (Janssen Pharmaceutica, Beerse, Belgium); bepridil (Carter-Wallace, Inc., Cranbury, NJ); verapamil and D600 (Knoll Pharmaceutical Company, Whippany, NJ); prazosin (Pfizer Laboratories, New York, NY); and hydralazine (Ciba-Geigy Pharmaceutical Company, Summit, NJ). Adenosine, papaverine and theophylline were purchased from Sigma Chemical Company, St. Louis, MO.

Results

Chronotropic effects. Diltiazem and the verapamil derivative D600 exerted potent, dose-dependent negative chronotropic effects (figs. 1 and 2). Although other vasodilators with calcium antagonistic effects including lidoflazine, bepridil, prenylamine, perhexiline and nifedipine produced significant decreases in rate, they were appreciably less potent than diltiazem (fig. 3; table 1). Fendiline, a calcium antagonist structurally related to prenylamine, had little effect on frequency. Nitroglycerin had no influence on rate even at high concentration (fig. 4). Similarly, high concentrations of nitroprusside and diazoxide did not depress frequency (table 1). Theophylline, papaverine and prazosin, vasodilators possessing cyclic AMP phosphodiesterase inhibitory effects, exerted small positive chronotropic effects at high concentration (table 1). A small but

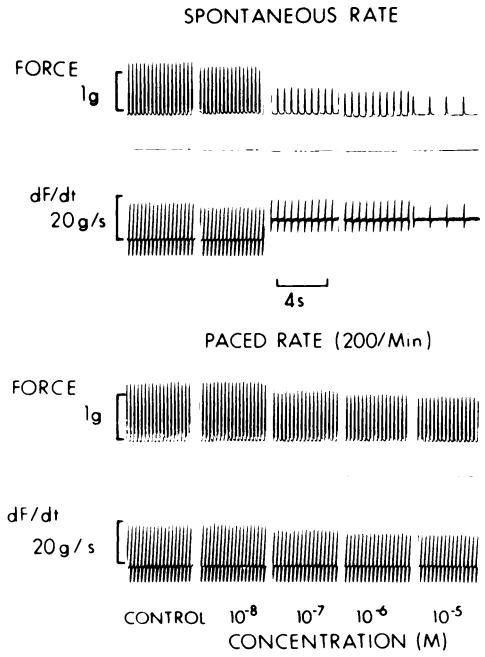

Fig. 1. Effects of diltiazem on guinea-pig atrium.

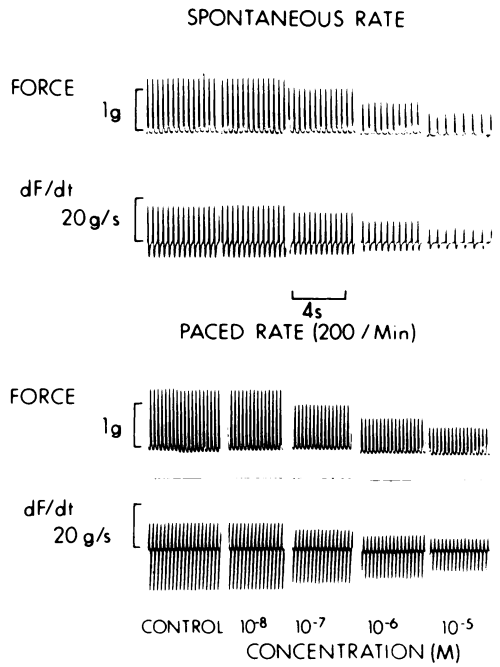

Fig. 2. Effect of D600 on guinea-pig atrium.

significant acceleration was also observed with hydralazine (table 1). These results demonstrate that only selected vasodilators with calcium antagonistic effects (Henry, 1980) were effective in slowing sinus node activity.

Inotropic effects. The maximum rate of rise of force development at a fixed paced rate of 200/min was used as an index of inotropy. D600 (fig. 2), verapamil and nifedipine acted as potent negative inotropic agents (table 2). Lidoflazine, an agent reported to exert only weak negative inotropic effects (Vanhoutte and Van Neuten, 1980), was unexpectedly potent (table 2). In contrast, other calcium antagonists including diltiazem (fig. 5) had modest depressant effects on contractility and the vasodilators nitroglycerin, nitroprusside, and diazoxide had no influence (table 2). The cyclic AMP phosphodiesterase inhibitors theophylline, papaverine and prazosin exerted no effects at low concentrations, but produced modest increases in contractility at high concentration. A similar phenomenon was observed with hydralazine (table 2).

To determine whether the positive chronotropic and inotropic effects of theophylline, papaverine, prazosin and hydralazine were partly mediated by the release of endogenous catecholamine, we performed experiments in which these agents were tested in the presence and absence of *beta* adrenergic blockade with 10^{-6} M propranolol. In six preparations, 10^{-6} M propranolol completely abolished the positive chronotropic and inotropic responses to 10^{-7} M isoproterenol, confirming the efficacy of the blockade. Propranolol slightly reduced the positive chronotropic and inotropic effects of theophylline, papaverine, prazosin and hydralazine, but the differences were not statistically significant ($P > .5$; paired *t* test). Therefore, the stimulatory effects of these agents did not appear to be mediated predominantly by a *beta* adrenergic mechanism.

Discussion

Agents that relax vascular smooth muscle may have a direct action on the heart. Direct myocardial effects may be difficult to evaluate in the intact organism because concomitant changes in vascular capacitance and resistance may influence important

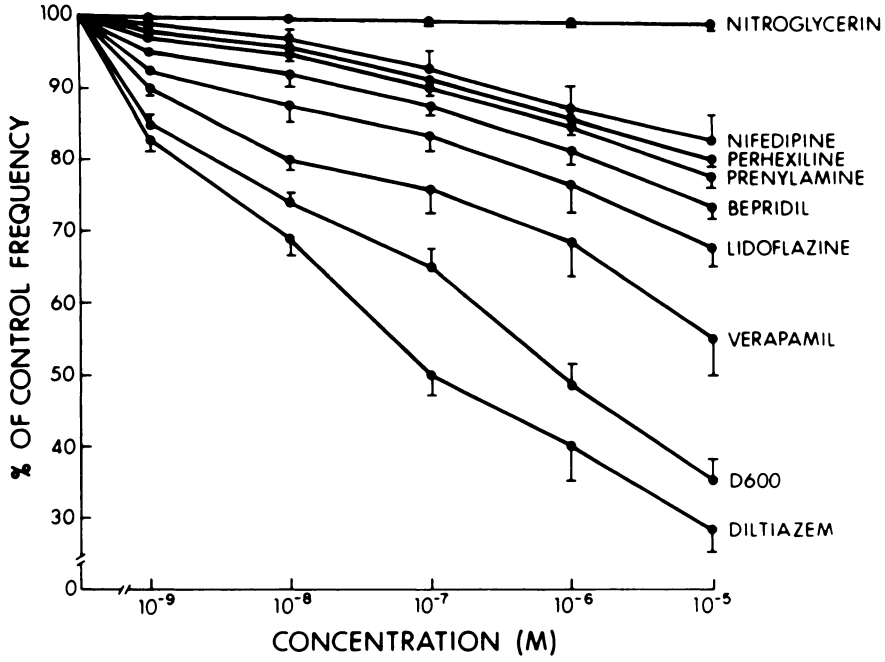

Fig. 3. Effects of selected vasodilators on spontaneous frequency of guinea-pig atria. Each data point represents mean values ± S.E. from six to eight experiments.

TABLE 1

Chronotropic effects of vasodilators

Drug (each 10^{-6} M)	Change in Frequency[a,b]
Prazosin	+4 ± 2%*
Papaverine	+3 ± 2%*
Theophylline	+2 ± 1%*
Hydralazine	+2 ± 1%*
Adenosine	−2 ± 1%*
Dipyridamole	−2 ± 1%*
Nitroprusside	−2 ± 1%*
Nitroglycerin	−3 ± 1%*
Diazoxide	−3 ± 1%*
Fendiline	−3 ± 1%*
Nifedipine	−14 ± 3%***[c]
Perhexiline	−15 ± 2%***
Prenylamine	−16 ± 3%***
Bepridil	−18 ± 3%***
Lidoflazine	−23 ± 4%***
Verapamil	−31 ± 5%***
D600	−51 ± 3%***
Diltiazem	−58 ± 5%***[c]

[a] Frequency refers to the frequency of contractions during spontaneous beating.

[b] Values express mean ± S.E. of six to eight experiments and represent percentage of changes from values before addition of drug.

[c] $P < .001$; comparison between nifedipine and diltiazem was performed by Bonferroni's procedure (see "Materials and Methods").

* $P < .05$ compared to values before addition of drug (paired t test); *** $P < .001$ compared to values before addition of drug (paired t test).

determinants of cardiac performance, such as preload, afterload and myocardial perfusion. In addition arterial hypotension resulting from vasodilation may trigger reflex adjustments and increase sympathetic outflow to the heart. Such adrenergic effects alter heart rate and cardiac contractility, changes that affect cardiac performance. Therefore, it is important to assess direct effects of vasodilators on the heart under controlled cardio-mechanical and neurohumoral conditions (Vater *et al.*, 1972; Jolly *et al.*, 1980). In the present study, we have used isometrically contracting guinea-pig atria to compare cardiac effects of vasodilators commonly used in cardiovascular therapeutics. Results demonstrate that potent vasodilators have a wide spectrum of cardiac activity.

One group of agents exerted no depressant effects even at

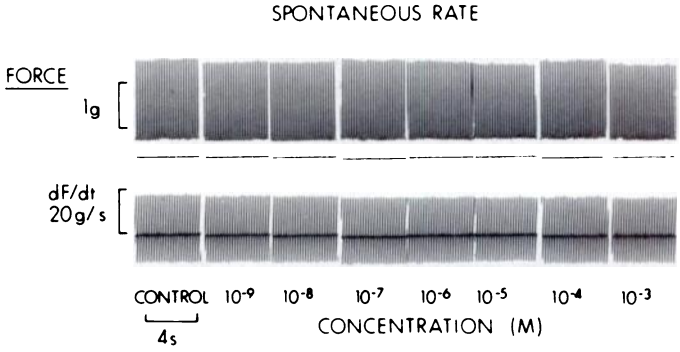

Fig. 4. Effect of nitroglycerin on guinea-pig atrium.

TABLE 2

Inotropic effects of vasodilators

Drug (each 10^{-6} M)	Change in dF/dt_{max}[a,b]
Prazosin	+10 ± 2%***
Papaverine	+5 ± 1%*
Theophylline	+3 ± 1%*
Hydralazine	+2 ± 1%*
Fendiline	−2 ± 1%*
Diazoxide	−2 ± 1%*
Dipyridamole	−2 ± 1%*
Nitroglycerin	−2 ± 1%*
Nitroprusside	−2 ± 1%*
Adenosine	−2 ± 1%*
Diltiazem	−8 ± 1%***[c]
Perhexiline	−12 ± 3%***
Prenylamine	−25 ± 4%***
Lidoflazine	−44 ± 4%***
Bepridil	−50 ± 4%***
Verapamil	−50 ± 4%***
D600	−58 ± 3%***
Nifedipine	−65 ± 8%***[c]

[a] dF/dt_{max} represents the maximum rate of rise of force development during pacing at a frequency of 200/min.

[b] Values express mean ± S.E. of six to eight experiments and represent percentage of changes from values before addition of drug.

[c] $P < 0.001$; comparison between nifedipine and diltiazem was performed by Bonferroni's procedure (see "Materials and Methods").

* $P < .05$ compared to values before addition of drug; *** $P < .001$ compared to values before addition of drug.

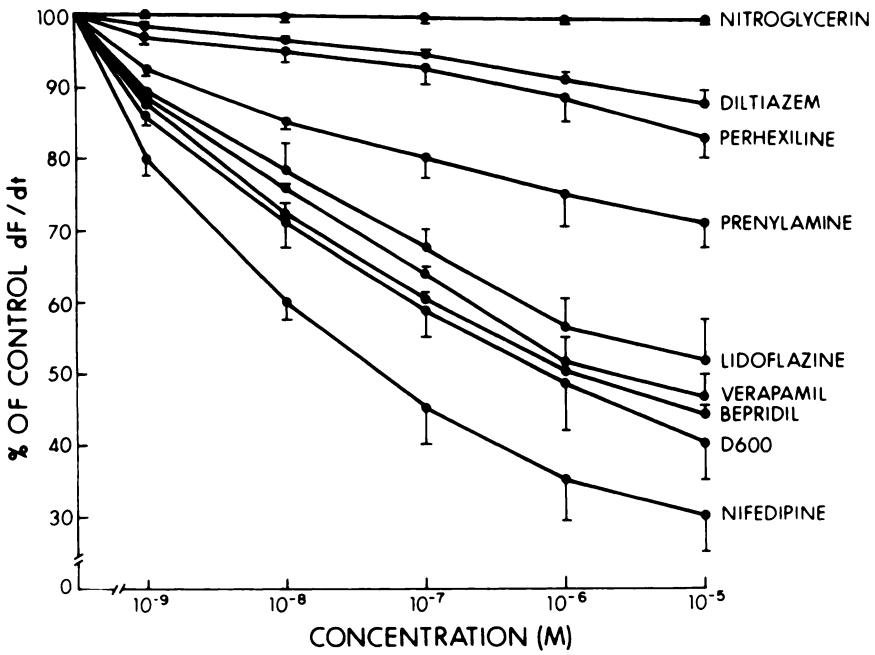

Fig. 5. Effects of selected vasodilators on contractile force at a fixed frequency of 200/min. Each data point represents mean values ± S.E. from six to eight experiments.

high concentration. Nitroglycerin and nitroprusside, both very potent vasodilators, had virtually no direct effect on the atria, in agreement with previous observations (Weder and Grün, 1973). Similarly, diazoxide, a drug recently described as a calcium antagonist (Bristow and Green, 1977; Godfraind, 1981), exerted only small effects on frequency and contractility. Adenosine was slightly more potent than nitroglycerin or nitroprusside, but required 10 μM concentrations to depress chronotropy and inotropy. Weak depressant effects of adenosine on canine trabecular myocardium have been reported by Urthaler *et al.* (1981). Whether myocardial receptor sites for adenosine are ever exposed to such concentrations *in vivo* is doubtful (Berne, 1980). Adenosine (1–10 μm) has been reported to produce no negative inotropic effects on rat atria at a paced rate of 120/min, but to antagonize the contractile response to 10^{-7} M isoproterenol (Rockoff and Dobson, 1980; Schrader *et al.*, 1977). Adenosine has been shown to block the slow action potential generated by isoproterenol in potassium-depolarized rat atria (Belardinelli *et al.*, 1979). This observation suggests that adenosine has slow channel blocking or calcium antagonistic effects at high concentrations. The physiological significance of the calcium antagonistic properties of adenosine remains to be determine, however. Another agent that exerted only weak effects on the atria was dipyridamole, a finding that agrees with previous observations (Kadatz, 1959; West *et al.*, 1962). Dipyridamole has been demonstrated to inhibit the disposal of endogenous adenosine (Berne, 1980) and to block cyclic AMP phosphodiesterase activity in platelets (Mills and Smith, 1971). Also, dipyridamole may promote the release of norepinephrine from sympathetic nerve endings and therefore increase cardiac contractility by acting on *beta* adrenergic receptors (Himori and Taira, 1976). In this study, however, dipyridamole failed to significantly enhance contractility, suggesting that release of norepinephrine was not an important factor in guinea-pig atria. Other agents with cyclic AMP phosphodiesterase inhibitor activity including prazosin, papaverine and theophylline (Hess, 1975) exerted weak positive inotropic effects, consistent with the hypothesis that cyclic AMP plays a role in regulating cardiac contractility.

Results with hydralazine confirm previous observations indicating that this vasodilator exerts only weak direct myocardial effects (Koch-Weser, 1976). The small positive inotropic and chronotropic effects elicited by a micromolar concentration of hydralazine was not significantly suppressed by *beta* adrenergic blockade with propranolol. However, in feline papillary muscle, very high concentrations of hydralazine (10^{-3} M) have been reported to produce increases in contractility which are blocked by propranolol (Koch-Weser, 1974).

At the other end of the spectrum were agents with potent cardio-active effects compared with the agents discussed above. Of interest was that these agents differed in their relative potency on chronotropy and inotropy. Nifedipine depressed predominantly inotropy and diltiazem depressed predominantly chronotropy, whereas other agents such as verapamil and D600 were more or less equally potent in depressing heart rate and contractility (Bayer *et al.*, 1975; Fleckenstein, 1980). The finding that some agents appear to have some "chrono-selectivity" or "ino-selectivity" is important because it suggests that calcium channels (slow channels) in pacemaker and contractile cells have different drug affinities, a fact that might ultimately permit the development of more selective drugs. One drug that proved unexpectedly potent was lidoflazine, an agent previously described as a calcium antagonist with selectivity for smooth muscle (Vanhoutte and Van Neuten, 1980). This is difficult to reconcile with recent studies indicating that lidoflazine may be as effective as nifedipine (Clark *et al.*, 1981) and diltiazem (Vouhé *et al.*, 1980) in protecting the globally ischemic heart during cardiopulmonary bypass (Flameng *et al.*, 1980). Previous studies in our laboratory have shown that pure vasodilators such as nitroprusside exert in general no protective effects on the bypassed dog heart (Clark *et al.*, 1981). Inasmuch as lidoflazine acts promptly on smooth muscle and myocardium *in vitro* (Vanhoutte and Van Neuten, 1980) and because it is effective after i.v. administration *in vivo*, it is possible that the slow onset of action of lidoflazine as an oral antianginal agent may be due to low oral dosage and/or bioavailability. Among the newer compounds exhibiting potent depressant effects was bepridil. This drug appears to be a promising antianginal agent because it tends to reduce heart rate *in vivo* (Vogel *et al.*, 1979; Cosnier *et al.*, 1977).

It is important to recognize that some agents with potent cardiodepressant effects *in vitro* may be even more potent as smooth muscle relaxants and that therapeutic doses of these drugs may cause profound vasodilation before directly depressing the heart. For example, nifedipine has been generally found to have little or no negative chronotropic and inotropic effects when given in usual oral or i.v. dosage (Henry, 1980). However, intracoronary injection of nifedipine exerts depressant effects corresponding to those observed *in vitro* (Narimatsu and Taira, 1976; Serruys *et al.*, 1981). These observations may simply reflect the fact that vascular smooth muscle is approximately 10 times more sensitive to the dihydropyrydine than myocardium (Narimatsu and Taira, 1976). Another important consideration is that some agents may act by multiple mechanisms when used in high concentrations. There is an abundance of experimental studies in which vasodilators with calcium antagonistic effects were tested only at micromolar or higher concentrations. In such experiments, one may not conclude that observed inhibitory effects necessarily reflect calcium antagonism. This is particularly true for drugs with appreciable local anesthetic effects such as verapamil or diltiazem (Henry, 1980). In the case of verapamil, evaluation of the effects of high concentrations should also consider nonselective (*alpha* or *beta*) antiadrenergic effects (Melville and Benfey, 1965; Blackmore *et al.*, 1979; Atlas and Adler, 1981) or muscarinic effects (Carey *et al.*, 1977).

In the recent past, the term "calcium antagonist" has been applied to numerous drugs, the electrophysiological effects of which are complex and incompletely understood. The notion that calcium antagonists represent a uniform group of drugs has led to unfortunate over-simplifications. Knowledge of the relative potencies of vasodilators on heart rare, cardiac contractility and vascular smooth muscle is important for the rational use of these agents in cardiovascular therapeutics.

Acknowledgments

The authors appreciate the technical assistance of Cynthia Lucas and the preparation of the manuscript by Joyce Kalayeh.

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