Editorial Comment

Calcium Channel Blockers and Progression of Coronary Artery Disease

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During the past 10 years, evidence has accumulated that calcium channel blockers such as nifedipine, verapamil, and diltiazem retard the development of atheromatous lesions in animals on high-fat diets.\textsuperscript{1-5} In the vast majority of experiments, the drugs exerted no hypolipidemic effects.\textsuperscript{1} In addition, in animals without hyperlipidemia or hypertension, proliferative lesions developing at the site of mechanical arterial trauma (e.g., balloon catheterization\textsuperscript{6,7} or nonconstrictive periarterial cuffing\textsuperscript{8}) were substantially suppressed by treatment with Ca\textsuperscript{2+} blockers. Because Ca\textsuperscript{2+} blockers are effective antihypertensive agents and hypertension is a recognized risk factor of atherosclerosis, several authors have attempted to relate the antiatherogenic effects of Ca\textsuperscript{2+} blockers to a reduction in arterial pressure. In most animal studies, however, Ca\textsuperscript{2+} blockers produced modest or no demonstrable hypotensive effects, which suggests that antiatherogenic effects of the drugs were not determined predominantly by a reduction in arterial pressure.\textsuperscript{9-11} The possibility that Ca\textsuperscript{2+} blockers exert antiatherosclerotic effects without appreciably influencing major risk factors of atherosclerosis such as hypercholesterolemia and arterial pressure is of considerable theoretical and practical interest. If Ca\textsuperscript{2+} blockers act by mechanisms partly unrelated to those of dietary and pharmacological regimens in current clinical use, their beneficial effects might complement those of established therapeutic manipulations.

One important question is whether Ca\textsuperscript{2+} blockers exert their effects by influencing calcium-regulated reactions in cells participating in the formation of atheromatous lesions. Possible target cells are vascular smooth muscle cells, which are known to express voltage-dependent L-type calcium channels, sometimes held to represent the only site of action of Ca\textsuperscript{2+} blockers.\textsuperscript{12} Potentially antiatherogenic effects of Ca\textsuperscript{2+} blockers on cultured arterial smooth muscle cells include inhibition of chemotaxis,\textsuperscript{13} migration,\textsuperscript{13} proliferation,\textsuperscript{14,15} and net uptake of cholesterol.\textsuperscript{16} Ertingin and Hajjar\textsuperscript{17} obtained aortic biopsies from patients who had been treated or not treated with Ca\textsuperscript{2+} blockers (e.g., nifedipine, diltiazem, or verapamil) before open-heart surgery and showed that cholesterol ester hydrolase activity in aortic tissue was elevated threefold in treated compared with untreated patients. These apparent effects of Ca\textsuperscript{2+} blockers on cholesterol ester hydrolase, a key reaction of reverse cholesterol transport, will deserve further evaluation.

According to current concepts, nonmuscle cells such as endothelial cells, monocytes, macrophages, T lymphocytes, and platelets play an important role in the development of early atheromatous lesions.\textsuperscript{18} Cell culture experiments have shown that such cells, although not known to express L-type Ca\textsuperscript{2+} channels, may be sensitive to Ca\textsuperscript{2+} blockers. For instance, net lipid uptake by rabbit\textsuperscript{19} and mouse macrophages\textsuperscript{20} in culture may be inhibited by Ca\textsuperscript{2+} blockers. Possible target molecules mediating such effects include a variety of ion channels, receptors, and transporters located in plasmalemmal, sarcoplasmic reticular, and mitochondrial membranes.\textsuperscript{21,22} It is important to recognize that Ca\textsuperscript{2+} blockers, lipophilic drugs that may accumulate intracellularly by several orders of magnitude,\textsuperscript{23,24} may bind to low-affinity receptors and influence a variety of cell functions, including Ca\textsuperscript{2+} uptake. Some effects of Ca\textsuperscript{2+} blockers mediated by low-affinity receptors such as the multidrug resistance related P-glycoprotein may be of clinical importance.\textsuperscript{21,22,25} Finally, the possibility must be considered that calcium blockers act indirectly on endothelial cells, monocytes, or macrophages by modulating the release of cytokines from intimal smooth muscle-like cells. In summary, there is substantial evidence that Ca\textsuperscript{2+} blockers may suppress the formation of atherosclerotic lesions in animals with dietary hypercholesterolemia. Cell culture experiments have suggested several possible mechanisms of action, but antiatherogenic effects of Ca\textsuperscript{2+} blockers still require elucidation.

In recent years, several prospective clinical trials aimed at determining effects of Ca\textsuperscript{2+} blockers on the progression of atherosclerosis have been initiated, and some of these trials have been completed. In the
present issue of *Circulation*, Waters et al.\textsuperscript{26} report on the result of a prospective, placebo-controlled, double-blind one-center trial in which hypercholesterolemic patients with symptomatic coronary disease were randomized to a 2-year treatment period with nicardipine (90 mg/day; 192 patients) or placebo (191 patients). Among 8,915 patients who had undergone arteriography at the Montreal Heart Institute between 1984 and 1986, 5% of the patients (n=449) satisfied entry criteria, and 85% of them (n=383) were entered into the trial. Randomization produced satisfactorily matched groups, although there were more smokers (51% versus 39%) and fewer patients with three-vessel disease (15% versus 23%) in the control group than in the treated group. Clinical events, drop-out rates, plasma total cholesterol (=260 mg/dl), and high density lipoprotein cholesterol did not differ between groups. However, patients receiving nicardipine exhibited slightly lower systolic and diastolic arterial pressures. Arteriography after 2 years of treatment was repeated in 87% of the patients. Frames from the two cine angiograms were analyzed quantitatively using the video technique of Reiber et al.\textsuperscript{27} A total of 2,323 lesions, or 6.9 lesions per patient, was assessed in single optimal views. Using stenosis diameter changes of more than 0.4 mm as a criterion for a change in lesion severity, progression occurred in 10% and regression in 3.5% of the patients in both groups. A subgroup analysis was subsequently performed to determine whether a potentially important difference on “early lesions” could be defined as lesions producing less than 20% stenosis in the initial arteriogram. Four hundred eleven such lesions were detected in 217 angiograms—178 lesions in 99 treated (1.80 lesions per patient) and 233 lesions in 118 untreated patients (1.96 lesions per patient). It is unclear whether the 217 patients with small lesions had on average significantly fewer or less-severe lesions overall compared with the remaining 166 patients. Using again a 0.4-mm-diameter change as a criterion, lesion progression occurred in 7.3% treated and 14.2% untreated patients (p<0.039 by two-sided test). In a stepwise logistic analysis, there appeared to be a marginally significant association between nicardipine effects on the progression of small lesions and arterial pressure measured 6 months after onset of therapy. No data are provided regarding possible associations at other time points (12, 18, and 24 months). The authors are appropriately cautious in interpreting the statistical analysis. As a result of the composite analysis focusing first on severe and then on minor stenoses (more than 50% and less than 20%), we are provided little information about lesions with occlusions between 20% and 50%, a range that accounted for 40% of all lesions in another recent angiographic trial (CLAS).\textsuperscript{28} The authors conclude that nicardipine had no effect on advanced coronary atherosclerosis but may retard the progression of small lesions. The validity of the conclusion rests on the objectivity of the subgroup analysis. The authors assure us that “the choice of a <20% occlusion as the definition for minimal lesions was made before reviewing the data” and that “the cutpoint of 20% was not chosen to maximize differences post hoc.”

The study of Waters et al.\textsuperscript{26} is similar in many respects to the International Nifedipine Trial on Antiatherosclerotic Therapy (INTACT).\textsuperscript{29} The IN-\textsuperscript{TACT} study was a prospective, double-blind, placebo-controlled multicenter (n=9) trial in which patients with mild coronary disease were randomized to treatment with nifedipine (80 mg/day) or placebo. Standardized arteriography performed in 425 patients was repeated in 82% of the patients after a 3-year period. Blinded computer-assisted evaluation of the arteriograms was performed by the same technique (CAAS)\textsuperscript{27} as that used by Waters et al. The European researchers selected patients with mild coronary disease (lesions per patient =3.5 compared with =7 in the Montreal study or =11 in the CLAS study)\textsuperscript{28} to assess the appearance of small lesions in coronary segments initially showing no lesions. Taking into consideration the inaccuracy of quantitative arteriography in the detection of small lesions, they accepted as “lesions” stenoses producing more than 20% luminal narrowing. Two-sided statistical tests indicated that treatment had significantly reduced the number of new lesions (p<0.034 by two-sided test). As in the Montreal study, an effect on the progression or regression of preestablished severe lesions was not demonstrable. In contrast to the Montreal study, arterial pressures in the treated and placebo groups were virtually identical. An interesting feature of the INTACT study was the frequency of total occlusions in initially normal-appearing segments.\textsuperscript{29} In a small-scale prospective coronary angiographic study, Loaldi and collaborators\textsuperscript{30} compared the effects of treatment with nifedipine (39 patients), propranolol (36 patients), or isosorbide dinitrate (36 patients) on the progression of coronary disease. Angiograms obtained at the beginning and end of a 2-year treatment period were evaluated blindly by a computer-assisted quantitative method. The authors concluded that nifedipine-treated patients had developed significantly fewer new stenoses compared with the other two groups, but they underscored the desirability of a large-scale study. Based on encouraging retrospective data with verapamil, another prospective coronary arteriographic study in 444 patients with coronary artery bypass grafts has been initiated (Frankfurt Isoptin Progression Study, or FIPS).\textsuperscript{31} Another ongoing trial evaluates effects of isradipine on the progression of carotid disease in 800 hypertensive men monitored for 3 years by standardized ultrasound imaging (MIDAS).\textsuperscript{32} In an ongoing trial evaluating effects of nifedipine (60 mg/day) on the patency of coronary bypass grafts, Gottlieb et al.\textsuperscript{13} reported that repeat arteriography 1 year after surgery had visualized more disease-free grafts in the nifedipine compared with the placebo group (62 of 93 [67%] versus 71 of 136 [52%], p<0.04).
In summary, the study of Waters et al\textsuperscript{26} combined with the results of the studies of Lichtlen et al (INTACT),\textsuperscript{29} Loaldi et al,\textsuperscript{30} and Gottlieb et al\textsuperscript{33} suggest that Ca\textsuperscript{2+} blockers might have a beneficial effect on the progression of arterial disease in humans. Recent large-scale controlled trials have shown that hypolipidemic interventions influence the rates of coronary complications (death and infarction) only after several years of treatment.\textsuperscript{34} Accordingly, for Ca\textsuperscript{2+} blockers to establish themselves as an effective treatment of coronary atherosclerosis, long-term, large-scale trials must be performed.

References
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