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Letter to the Editor

Effect of Blood Pressure Lowering on Coronary Vasodilator Reserve in Arterial Hypertension

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Dear Sir,

Coronary vasodilator reserve is often reduced in patients with arterial hypertension despite angiographically normal coronary arteries [1,2]. Aortic diastolic pressure is a major determinant of coronary blood flow. An abrupt reduction of systemic blood pressure from hypertensive to low-normal values has been demonstrated to induce ischemiclike electrocardiographic (ECG) changes in hypertensives without detectable coronary artery disease [3]. However, chronic reduction of arterial blood pressure by antihypertensive therapy has been shown to result in both normalization of coronary resistance vessel wall hypertrophy and coronary vasodilator reserve in hypertensive patients [4]. However, the effects of blood pressure reduction on coronary vasodilator reserve in the intermediate term, before regression of vascular smooth muscle hypertrophy, are not known. Therefore, we assessed the effect of blood pressure lowering on coronary vasodilator reserve in eight patients (mean age 51 ± 10 years), with mild to moderate essential hypertension, after 6 weeks of treatment with the calcium antagonist lacidipine.

Coronary vasodilator reserve was calculated by measuring myocardial blood flow (MBF), by means of ^{13}N-ammonia and positron emission tomography (PET), at baseline and during pharmacologically induced coronary vasodilatation. This was a single-blind, placebo-controlled study, whereby, following 3 weeks of placebo therapy, the patients were started on lacidipine treatment at a dose of 4 mg (p.o.) once daily for 3 weeks and titrated up to 6 mg once daily for 3 more weeks in patients who did not respond to the 4 mg dosage. Treatment was considered effective when a diastolic blood pressure <91 mmHg or a reduction of at least 15 mmHg compared to the placebo period were attained. Of the eight hypertensives, six had never received previous hypotensive treatment and two had been off treatment for at least 3 months before the study. Blood pressure measurements were obtained after 5 minutes of quiet sitting by an automatic oscillometric device [5], calculating the average of three consecutive readings. The presence of ischemic or valvular heart disease and cardiomyopathy were ruled out by history, physical examination, baseline ECG, two-dimensional Doppler echocardiography, exercise test, and high-dose dipyridamole echocardiography [6]. Seven of the eight patients had evidence of left ventricular hypertrophy according to the criteria proposed by Levy et al. [7]. The evaluation of MBF by PET was performed during treatment with placebo and during effective treatment in all patients. Simultaneously we studied a group of normotensive subjects with PET, without treatment, to compare their coronary vasodilator reserve with that of our patients. Regional myocardial blood flow was measured by means of ^{13}N-ammonia and dynamic PET at baseline and following an intravenous infusion of dipyridamole (0.56 mg/kg over 4 minutes) as previously described [8,9]. For each flow measurement, 0.25 mCi/kg of body weight of ^{13}N ammonia, prepared as reported elsewhere [10], was given by slow intravenous injection over a period of 15–20 seconds. Dynamic acquisition was started simultaneously with the beginning of the injection of the tracer and a total of 28 frames (16 × 3, 11 × 12, and 1 × 300 seconds) were acquired over 8 minutes. Blood flow during hyperemic conditions was assessed by injecting ^{13}N ammonia 4 minutes after the end of dipyridamole infusion. PET data were analyzed as previously described [8]. Regional coronary resistance was calculated as mean [(diastolic × 2) + systolic/3] arterial blood pressure (calculated from cuff method measurements made during PET study) divided by MBF. Coronary vasodilator reserve was calculated from the ratio dipyridamole/baseline MBF. The results are expressed

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as mean ± SD. Paired and unpaired Student's t tests were used to compare data within and between groups, respectively. A p value of <0.05 was considered significant.

MBF was regionally homogeneous in all subjects, both at baseline and after dipyridamole infusion. Off active treatment, average left ventricular MBF was lower and coronary resistance was greater in hypertensives than in normotensives, both at baseline and after dipyridamole (baseline MBF: 0.73 ± 0.10 vs. 0.97 ± 0.18 ml/min/g, $p < 0.01$; dipyridamole MBF: 1.26 ± 0.25 vs. 2.94 ± 0.93 ml/min/g, $p < 0.001$; coronary resistance at baseline: 175.1 ± 23.7 vs. 101.7 ± 20.2 mmHg × min × ml^{-1} × g^{-1}, $p < 0.0001$; coronary resistance following dipyridamole: 97.5 ± 23.4 vs. 34.7 ± 12.8 mmHg × min × ml^{-1} × g^{-1}, $p < 0.0001$, in patients and normals, respectively). Coronary vasodilator reserve was significantly reduced in the patients compared with normals (1.76 ± 0.49 vs. 3.05 ± 0.92, $p < 0.005$). After treatment with lacidipine, a significant reduction of both systolic (from 161.9 ± 16.5 to 148.1 ± 18.5 mmHg, $p < 0.05$) and diastolic blood pressure (from 108.1 ± 8.0 to 93.8 ± 5.8 mmHg, $p < 0.01$) was observed in the patients. Four patients responded to lacidipine 4 mg/day while the remaining four required 6 mg/day. During treatment, MBF distribution remained regionally homogeneous in all patients, both at baseline and after dipyridamole. Baseline MBF increased (1.00 ± 0.33 ml/min/g, $p < 0.05$ vs. corresponding value on placebo) and coronary resistance decreased significantly (122 ± 35 mmHg × min × ml^{-1} × g^{-1}, $p < 0.01$) compared to placebo (Figure 1).

Following treatment with lacidipine, MBF after dipyridamole infusion was not significantly different from the one on placebo (1.51 ± 0.34 ml/min/g, p = ns). Coronary resistance after dipyridamole was reduced compared to that on placebo (76 ± 23 mmHg × min × ml^{-1} × g^{-1}), although this difference fell short of statistical significance. Coronary vasodilator reserve tended to fall in four patients and to increase in the other four (Figure 1). However, the mean coronary vasodilator reserve following treatment was not significantly different from that on placebo (1.18 ± 2.78, vs. 1.76 ± 0.49 p = ns), respectively.

The results of the present study demonstrate, in agreement with previous reports [1,2,4], a significant impairment of coronary vasodilator reserve in patients with hypertension in the absence of symptoms and signs of myocardial ischemia. Lowering of arterial blood pressure with lacidipine therapy up to 6 weeks results in a significant increase of baseline MBF with a concomitant reduction of coronary resistance. This, combined with the fact that drug treatment did not substantially affect myocardial blood flow following dipyridamole infusion, explains the fall in coronary vasodilator reserve in some patients. Conversely, a small rise in baseline MBF compared to a greater rise in MBF post dipyridamole would explain the slightly

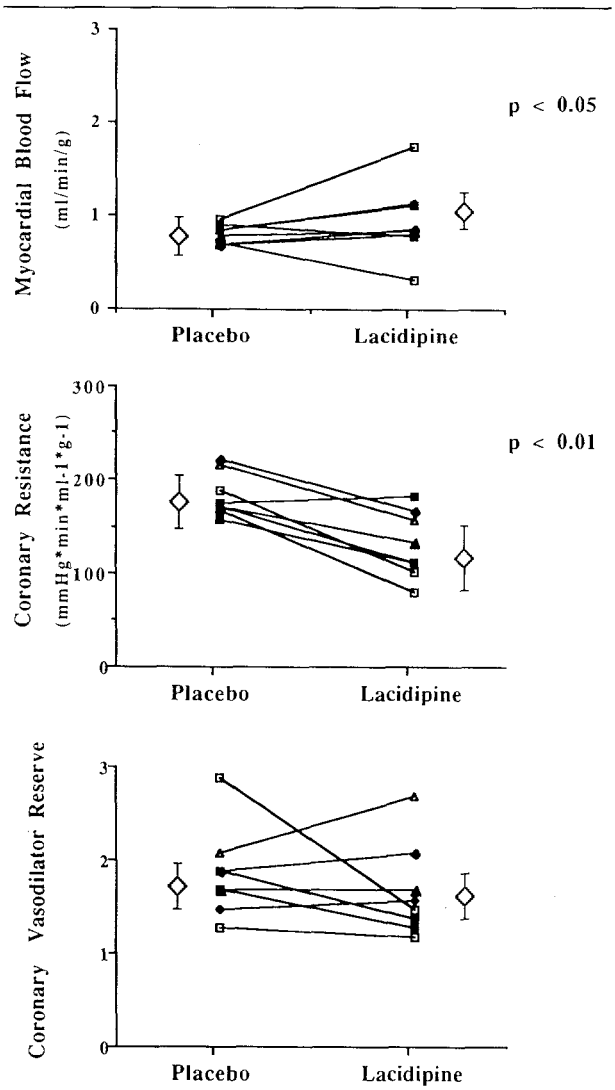

Fig. 1. Individual values of baseline myocardial blood flow (top panel), baseline coronary resistance (middle panel), and coronary vasodilator reserve (bottom panel) in hypertensive patients during placebo and lacidipine treatment.

increased coronary vasodilator reserve in the remaining patients. These effects can probably be ascribed to the different degrees of structural remodeling of the vascular wall in the different subjects, the effect of which will be mainly evident on maximal MBF [4]. The significant reduction of coronary vasodilator reserve observed in one patient during treatment may be explained by the fact that this subject had a nearly normal coronary reserve to start with, while treatment caused the baseline MBF to increase significantly, thus reducing the dipyridamole/baseline flow ratio. The number of patients studied is too small to conclude that blood pressure lowering with the calcium blocker lacidipine does not induce any further impairment of coronary vasodilator reserve. Further studies are needed to resolve this issue.

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