Distinct and Combined Vascular Effects of ACE Blockade and HMG-CoA Reductase Inhibition in Hypertensive Subjects

Pietro Nazzaro, Margherita Manzari, Massimo Merlo, Rita Triggiani, Annamaria Scarano, Luigi Ciancio, Anna Pirrelli

Abstract—Hypercholesterolemia and hypertension are frequently associated with elevated sympathetic activity. Both are independent cardiovascular risk factors and both affect endothelium-mediated vasodilation. To identify the effects of cholesterol-lowering and antihypertensive treatments on vascular reactivity and vasodilative capacity, we studied 30 hypercholesterolemic hypertensive subjects. They received placebo for 4 weeks, either enalapril or simvastatin for 14 weeks, and, finally, both medications for an additional 14 weeks. Postischemic forearm blood flow (MFBF) and minimal vascular resistance (mFVR) were used as indices of vasodilative capacity and structural vascular damage, respectively. Total (resting-stress-recovery phases) cardiovascular (blood pressure [BP] and heart rate [HR]) and regional hemodynamic (FBF and FVR) reactivity to stressful stimuli were calculated as area-under-the-curve (auc) (value×time). Compared with baseline levels, simvastatin reduced total (TOT-C) and LDL cholesterol (LDL-C) (1.27 mmol/L, P<0.001 and 1.33 mmol/L, P<0.001, respectively). Enalapril also reduced TOT-C and LDL-C (0.6 mmol/L, P<0.001 and 0.58 mmol/L, P<0.05, respectively). MFBF was increased substantially by both treatments (P<0.001). Enalapril had a greater effect (−1.7 arbitrary units [AU], P<0.001) than simvastatin (−0.6 AU, P<0.05) on mFVR. During stress, FBF increased more with enalapril (4.4 FBF×minutes, P<0.001) than with simvastatin (1.8 FBF×minutes, P<0.001). Conversely, FVR stress response was reduced more with enalapril (9.1 FVR×minutes, P<0.001) than with simvastatin (2.9 FVR×minutes, P<0.01). During combination treatment, a significant (0.001>P<0.05) additive effect on hypercholesterolemia, structural vascular damage, BP, and FVR was shown. The findings suggest that angiotensin-converting enzyme (ACE) inhibition induces a larger reduction than HMG-CoA reductase blockade in vascular reactivity and structural damage in hypercholesterolemic hypertensive subjects. (Hypertension. 1999;33:719-725.)

Key Words: hypertension ■ hypercholesterolemia ■ cardiovascular reactivity ■ plethysmography ■ vascular damage

Both hypertension and hypercholesterolemia, which frequently occur together,1,2 are independent risk factors for cardiovascular events,3 induce vascular damage,4 and affect coronary flow by impairing endothelium-mediated vasodilation.3 Moreover, borderline-to-mild hypertensive subjects, in whom sympathetic overdrive and exaggerated cardiovascular stress reactivity have been shown,6 tend frequently to have high total (TOT-C) and LDL cholesterol (LDL-C) levels.7,8 Several studies have shown also that patients characterized by emotional alertness often present dyslipidemia, exaggerated cardiovascular reactivity, and hypertension.9,10

In hemodynamic terms, borderline hypertension subjects in the resting state fail to accommodate to increased cardiac output with appropriate vasodilatation11 and, during laboratory mental stress, do not proportionally adjust forearm blood flow (FBF) while their blood pressure (BP) significantly increases.12 Sympathetic overactivity emanating from the central nervous system11 also enhances the effects of local factors that are conducive to vascular damage, including shear stress and turbulence, endothelial dysfunction, and atherosclerotic lesions.13 Therefore, hypertension and hypercholesterolemia, though independent cardiovascular risk factors, may share physiological features that can be related to vascular sympathetic overactivity.

In clinical studies, antihypertensive treatment with angiotensin-converting enzyme inhibitors (ACEIs)14,15 as well as cholesterol-lowering therapy with statins16,17 were found to improve vasodilating properties and to reduce vascular damage. Nevertheless, to the best of our acknowledge, no study has investigated their effect on regional vascular stress response and vascular structure in hypercholesterolemic hypertensive subjects. The current study analyzed forearm vascular response to psychophysiological tasks in hypercho-
Reactivity in Hypercholesterolemic Hypertensive Subjects

TABLE 1. Characteristics of Subjects at Enrollment in Enalapril and Simvastatin Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EP (n=15)</th>
<th>SP (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>44±2</td>
<td>42±2</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.1±0.3</td>
<td>26.7±0.4</td>
</tr>
<tr>
<td>Office SBP, mm Hg</td>
<td>164±3</td>
<td>162±2</td>
</tr>
<tr>
<td>Office DBP, mm Hg</td>
<td>100±2</td>
<td>97±1</td>
</tr>
<tr>
<td>History of hypertension, mo</td>
<td>19±3</td>
<td>18±2</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.69±0.14</td>
<td>6.73±0.2</td>
</tr>
</tbody>
</table>

Values are mean±SEM. EP indicates placebo-treated patients assigned to the enalapril group; SP, placebo-treated patients assigned to the simvastatin group. P=NS for all values.

Methods

Study Population

Men with hypercholesterolemia (total cholesterol ≥5.95 mmol/L) and borderline-to-mild hypertension (systolic BP [SBP] ≥150 mm Hg/ diastolic BP [DBP] ≥90 mm Hg) who had not been previously treated with cholesterol-lowering drugs were enrolled through the Hypertension Clinic, Medical School of Bari. They received physical examinations, ECG, chest x-ray films, and fasting blood chemistry to confirm dyslipidemia and to exclude secondary hypertension, hepatic or renal impairments, diabetes, coagulation and fibrinolytic abnormalities, or other metabolic disorders. Patients with a positive history for cerebral, coronary, and peripheral vascular diseases were also excluded from the study. Because dietary habits influence several metabolic variables, the food intake of the subjects was investigated. Patients accustomed to a healthy Mediterranean diet16 received comprehensive dietary recommendations to decrease saturated fat. In patients taking antihypertensive drugs, medication was discontinued for the 4-week placebo phase preceding the cardiovascular reactivity study. During the placebo period, the patients remained under strict medical supervision. The study was approved by the Ethical Committee of the University of Bari Medical School, and patients gave their informed consent.

Study Design

The present study had an open 3-phase design. (1) During a 4-week run-in period, 30 untreated hypercholesterolemic hypertensive subjects received placebo. Subjects were then divided into 2 equal groups, matched by age, body mass index (BMI), BP, history of hypertension, and TOT-C, and assigned to enalapril (EP) or simvastatin (SP) therapy (Table 1). (2) During a 14-week monotherapy period, the patients were treated for hypertension with enalapril (E), 20 mg QD, or for hypercholesterolemia with simvastatin (S), 10 mg QD. (3) During a final 14-week period, patients received both treatments simultaneously, simvastatin added to enalapril treatment (E+S) or enalapril to simvastatin therapy (S+E). Laboratory measurements were performed at the end of each study period.

Laboratory Methods

To prevent anxiety from a new medical examination, patients were invited to visit the laboratory and to become familiar with the equipment. Patients arrived in the laboratory after a 12-hour fasting period. After the patients rested in supine position for 10 minutes, their heart rate (HR) and BP were taken in triplicate at both arms to exclude any difference, and measurements were averaged. Samples for routine blood chemistry and lipids were taken. TOT-C and triglycerides were determined enzymatically. HDL cholesterol (HDL-C) was assayed by precipitation of the non-HDLs, and LDL-C was calculated by the Friedewald equation.

Cardiovascular reactivity was induced through a frustrating cognitive task, the Stroop color test, and through a physical stress, the cold pressor forehead test. The Stroop color test, 5 minutes long and based on incongruent visual input, demanded that the patients recognize, within a time limit, in which color of ink the name of an incongruous color word was printed. The cold pressor forehead test consisted of the application of ice cubes and water (4°C) contained in a plastic bag to the subject’s forehead for 90 seconds. Each task was preceded and followed by 10-minute baseline recovery phases. The study was performed between 9 and 10 AM, after 20 minutes of acclimatization, in a quiet, temperature-controlled room (22°C) with the patient in the supine position.

During the entire stress session, SBP, mean BP (MBP), DBP, HR, FBF (ml·min⁻¹·100 g⁻¹), and forearm vascular resistance (FVR) (MBP/FBF, AU) were measured. SBP, MBP, DBP (mm Hg), and HR (bpm) were obtained continuously via Finapres (Ohmeda Monitoring System) with the digital cuff wrapped up the middle finger midphalanx of the left hand. Myocardial oxygen demands were evaluated through the rate pressure product (RPP) (HR×SBP×10⁻²). FBF was measured by venous occlusion plethysmography (EC-5R+E-10, D.E. Hokanson Inc).10,12 A mercury-in-Silastic strain gauge was placed 5 cm below the antecubital crease of the right forearm, which was supported above the level of the heart at 30° to horizontal. To arrest hand circulation, a pediatric arterial occlusion cuff was placed around the wrist and inflated at 200 mm Hg for 1 minute before any measurements. The forearm vascular measurements were started at the first, fifth, and ninth minute of each of the resting recovery phases, at the second and fourth minute during the Stroop color test, and at the 30th second during the cold pressor forehead test. Values were averaged every minute. To consider total stress reactivity, including mental and physical tasks and resting recovery phases, the area-under-the-curve (auc) (value×time×10⁻²) was adopted in the present study.

Because hemodynamic reactivity may be influenced by hypertrophy of forearm arterioles,19 we measured postischemic forearm blood flow (MFBF) after 10 minutes of rest. Postischemic hyperemia, which elicits endothelium-dependent vasodilation, served as the index of vasodilating capacity, and the residual (minimal) FVR (mFVR) (MBP/MFBF, AU) was used as an index of vascular hypertrophy.20,21 MFBF and mFVR were determined from measurements obtained during the 60 to 90 seconds after the 10-minute ischemic period induced by inflating the upper cuff at 200 mm Hg.21,22 Subjects attended laboratory sessions to have all the above measurements repeated after 14 weeks of monotherapy and again after 14 weeks of combined drug treatment.

Data Analysis

To analyze the impact of treatments on blood lipids, cardiovascular reactivity, forearm stress response, and structural hemodynamic index changes, the results at each time were compared with repeated measures ANOVA and post hoc analysis by Student–Newman-Keuls test. Values are shown as mean±SEM in the text and tables and as mean±SD in the figures.

Results

Three subjects, 2 receiving enalapril and 1 receiving simvastatin, did not complete the protocol. One patient had persistent cough related to the ACEI, 1 considered the session too stressful, and 1 required more aggressive antihypertensive treatment. These subjects were replaced with new enrollments. During the entire study, BMI, smoking habit, serum creatinine, glucose, urea, uric acid, and bilirubin remained unchanged. Serum potassium slightly increased (+0.4 mmol/L) with enalapril treatment. Creatinine phosphokinase, aspartate aminotransferase, alanine aminotransfer-
ase, and coagulation-fibrinolytic indices were not affected by the treatments.

TOT-C and LDL-C (Table 2) were, as expected, significantly reduced in monotherapy (S), S+E, and E+S groups. Interestingly, patients receiving the only antihypertensive treatment also had a decline in cholesterol levels. Cholesterol reduction was greater during combination therapy. Simvastatin caused a further decrease of TOT-C and LDL-C in the enalapril group, whereas enalapril induced smaller but significant TOT-C and LDL-C reductions in the simvastatin group. HDL-C (Table 2) increased with both monotherapies.

The efficacy of treatments on resting values in the laboratory is reported in Table 2. SBP and DBP were substantially reduced during monotherapy in the enalapril group. A small DBP reduction also occurred in simvastatin-treated patients, but only enalapril lowered myocardial oxygen demands significantly. FBF was increased and FVR was reduced during both monotherapies but more so when enalapril was added to simvastatin-treated patients. MFBF was enhanced and mFVR was lowered by simvastatin but to a greater extent when subjects received enalapril (Table 2).

SBP total response (SBP auc) was lowered by both monotherapies but more extensively when patients were treated for hypertension (Figure 1) (SBP auc=EP, 67.9±0.9 mm Hg×minutes versus E, 51.2±1.1 mm Hg×minutes, P<0.001; versus E+S, 48.4±0.8 mm Hg×minutes, P<0.001;
counted for the differences in myocardial oxygen demand during

change in the different conditions (HR auc (Figure 1). HR total response (HR auc) did not significantly

0.5 mm Hg

mm Hg

SP, 18.0 ± 2.0 FBF × minutes, P < 0.001; versus S + E + SP, 13.1 ± 1.2 FBF × minutes versus S, 14.9 ± 1.3 FBF × minutes, P < 0.01; versus S + E + SP, 18.8 ± 1.2 FBF × minutes, P < 0.001) and lowered vasoconstriction (FVR auc = EP, 19.1 ± 1.2 FVR × minutes versus E, 9.9 ± 0.5 FVR × minutes, P < 0.001; versus S + E, 8.1 ± 0.3 FVR × minutes, P < 0.001; SP, 15.8 ± 1.4 FVR × minutes versus S, 12.9 ± 0.9 FVR × minutes, P < 0.01; versus S + E, 7.9 ± 0.4 FVR × minutes, P < 0.001), although enalapril showed larger effects (Figure 2). Reduced BP induced a larger cumulative efficacy, increasing vasodilatory response (S versus S + E, P < 0.001; E versus E + S, P < 0.01) and reducing vasoconstrictive reactivity (S versus S + E, P < 0.001; E versus E + S, P < 0.05) in the patients previously treated with the monotherapies.

The findings suggest that ACEI and statin treatments possess a distinct and additive vascular effect that may critically modify the structural characteristics and functional responses of peripheral arteries during stressful stimuli in hypercholesterolemic hypertensive subjects.

Discussion

Exaggerated hemodynamic responses to behavioral tasks may contribute to coronary heart disease and, similarly, hypercholesterolemia may affect coronary vasodilation. Both cardiovascular reactivity and dyslipidemia have been associated with sympathetic overdrive. In addition, ACEIs were found to reduce vascular damage within 3 months, and
low statin dosages resulted in lower cholesterolemia and enhanced vasodilative capacity within 12 weeks of treatment. Consequently, not only BP and cholesterol reductions could be ascribed, as expected, to enalapril and simvastatin, respectively, but also both medications, separately and combined, induced significant changes in hemodynamic reactivity, vascular damage, and cholesterolemia. The tendency toward BP reduction in statin-treated hypertensive subjects and the further decrease of BP when the antihypertensive treatment was associated with cholesterol-lowering therapy suggest that both medications have vasodilating properties, conceivably secondary to distinct effects on the arterial wall.

As expected, TOT-C and LDL-C were significantly reduced when the patients were treated with simvastatin. Unexpectedly, a smaller but significant TOT-C and LDL-C reduction has also been shown in patients treated only with enalapril. These results confirm previous findings that enalapril can ameliorate dyslipidemia in hypertensive subjects and in hypertensive cigarette smokers. Nevertheless, more studies, including placebo control groups, are necessary to corroborate this outcome. Some of these effects may relate to reduction of cardiovascular sympathetic nerve activity by enalapril. In fact, catecholamines contribute to elevation of plasma lipids, and the explanation for this finding may be related to the property of angiotensin II (Ang II) that increases sympathetic drive to the arteries. It is conceivable, therefore, to ascribe this effect to properties of enalapril that reduce Ang II, restrain sympathetic activity, and, thus, increase peripheral muscular flow. Interestingly, pharmacological and laboratory studies have shown that muscular blood flow influences glucose and cholesterol metabolisms. In fact, impaired peripheral blood flow was found to be associated with reduced insulin sensitivity and to facilitate the onset of dyslipidemia. Results are also consistent with evidence that hypercholesterolemia amplifies vasoconstrictive neurogenic response and that antidysslipidemic agents contribute to prevention of the development of hypertension.

Several investigations have shown that posts ischemic hyperperemia, which causes vasodilatation via release of the endothelium-derived relaxing factor, is impaired in hypertensive subjects and in hypercholesterolemic patients. Additionally, residual vascular resistance can also be reduced by cholesterol-lowering therapy. In our patients, posts ischemic FBF and the structural vascular damage index were significantly improved by both treatments, and the effect was enhanced when they were associated. These findings are consistent with other evidence that highlighted the capability of ACEI and statins to interfere with vascular properties. Ang II may promote collagen production and influence the morphology of the arterial wall in hypertensive subjects. Statins constrain the synthesis of mevalonate that is also the precursor of isoprenoids that modulate the low-molecular-weight GTP-binding proteins, which are fundamental in the growth signal transduction pathways. When, in the present study, the antiproliferative and metabolic effects of the 2 medications were combined, the vascular properties markedly improved. In fact, a further increase of the vasodilating capacity and an additional reduction of the vascular damage index occurred. However, enalapril induced a larger decrease of mFVR as monotherapy and when associated with the cholesterol-lowering treatment. Then, the BP decrease was critical to reduce extensively the vascular damage in young adults who had a brief history of hypertension and hypercholesterolemia.

Hemodynamic reactivity in hypertensive subjects is altered and is frequently characterized by prolonged responses and incomplete recoveries. Measurement of the auc is an improvement on the 1-dimensional ‘time-to-recovery’ measurement, as it does control for the steepness of the decline in the level of the physiological parameter. Although it is likely to be influenced by the initial level of reactivity, the problem can be resolved by looking at the recovery phase as part of the same baseline task protocol and by calculating a single auc index that covers the entire time span from baseline to the last measurement point. The method has been previously proposed for the analysis of serial measurements in biomedical and psychophysiological studies. When enalapril was given alone, BP reactivity was reduced most, vasodilating response was increased, and, thus, vasoconstrictive reactivity was markedly decreased. Patients treated with simvastatin had a smaller BP reactivity reduction and myocardial oxygen demands were not as much reduced as in patients receiving enalapril. Vasoconstrictive response was less remarkably reduced by simvastatin alone, and when simvastatin was prescribed in enalapril-treated patients, it induced a decrease lower than that which occurred in simvastatin-treated patients who received the ACEI. Again, reduction of BP was critical to reduce vasoconstrictive reactivity. Interestingly, an impaired functional stress flow/resistance response, characterized by reduced forearm vasodilation, was shown in young hypertensive subjects from the early stages of the disease. Neurogenic stimuli can increase BP and HR and, thereby, dangerously increase cardiac oxygen demands. Further, sympathetic drive does restrain, tonically and phasically, arterial distensibility. In aggregate, these functional hemodynamic changes may increase oxygen demands while reducing coronary and peripheral blood supplies during recurrent stressful events. Laboratory, epidemiological, and behavioral studies have amply shown that stressful conditions are significantly associated with hypercholesterolemia and hypertension. Thus, hypercholesterolemic hypertensive patients, whose cardiovascular risk is increased by vascular damage and impaired arterial vasodilation during psychophysiological stimuli, require prompt and appropriate antihypertensive therapy.

We are aware, as possible limitations of the present study, that structural and functional changes may have been influenced by the progressive familiarity of the patients with the experimental apparatus (ie, habituation) and by the effects initiated during the monotherapy. However, hemodynamic reactivity to laboratory stimuli in borderline hypertensive subjects was previously shown to be stable over substantial periods of time. Moreover, the unique hemodynamic and metabolic properties of enalapril and simvastatin are also evident in the different changes induced during combination therapy in patients previously treated for hypercholesterolemia or hypertension alone. These effects were manifested during combination therapy when the results of the initial medication should be maximal and stable, and, interest-
ingly, they were associated with a further increase of functional blood flow. The results are also consistent with the notion that metabolic alterations may be related to impaired peripheral blood flow and sympathetic overdrive. In fact, endothelium-dependent vasodilation is significantly affected in patients with a high normal range of blood cholesterol. Moreover, hypercholesterolemia upregulates Ang II–mediated vasoconstriction, whereas sympathetic overdrive can induce endothelial leisure and accelerate arterial structural and functional impairments. Vascular damage lessens the flow and increases sympathetic vasoconstrictive response, which can impair flow-dependent metabolic pathways. Hypertension and hypercholesterolemia per se can stimulate the atherosclerotic process and accelerate vascular complications through a vicious circle.

At present, this is the first study that highlights the possible independent and additive effects of hypertension and hypercholesterolemia on systemic and regional hemodynamic reactivity. In the present study, simvastatin was shown to reduce damage to the arteries and to moderate vascular reactivity, improving the hemodynamic pattern and the efficacy of the antihypertensive treatment. Likewise, enalapril effectively reduced high BP and vascular reactivity, improving the hemodynamic pattern and the efficacy of the antihypertensive treatment. Presence of cardiovascular structural changes in essential hypertensive patients with coronary microvascular disease and effects of long-term therapy.

In conclusion, the findings suggest that the structural and functional vascular impairments in hypercholesteremic hypertensive subjects may be primarily attributed to high BP. Hypertension, then, should be treated with more concern from the early stages, especially when the patient is, in addition, affected by a metabolic cardiovascular risk factor.

References


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