Effects of Ramipril on Endothelial Function and the Expression of Proinflammatory Cytokines and Adhesion Molecules in Young Normotensive Subjects With Successfully Repaired Coarctation of Aorta

A Randomized Cross-Over Study

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Objectives
The purpose of this study was to evaluate the effect of ramipril on endothelial function and inflammatory process in a group of normotensive subjects with successfully repaired coarctation of the aorta (SCR).

Background
Subjects with SCR experience higher long-term cardiovascular risk as a result of the relapse of arterial hypertension or owing to nonreversible structural changes in the pre-coarctation arterial tree. These subjects experience endothelial dysfunction in the right forearm and appear to have elevated levels of proatherogenic inflammatory markers, even in the absence of arterial hypertension.

Methods
Twenty young individuals age 27.3 ± 2.4 years old with SCR 13.9 ± 2.2 years previously, received ramipril 5 mg/day for 4 weeks in a randomized, cross-over, controlled trial. Endothelial function was evaluated in the right forearm by gauge-strain plethysmography, and serum levels of interleukin (IL)-1β, IL-6, soluble CD40 ligand (sCD40L), and soluble vascular cell adhesion molecule (sVCAM)-1 were determined by enzyme-linked immunosorbent assay.

Results
Ramipril improved endothelial function (p < 0.001) and decreased the expression of proinflammatory cytokine IL-6 (p < 0.05) and sCD40L (p < 0.01). Furthermore, ramipril decreased serum levels of sVCAM-1 (p < 0.01) but failed to affect serum levels of C-reactive protein. These effects were independent of blood pressure lowering.

Conclusions
Ramipril reversed the impaired endothelial function and decreased the expression of proinflammatory cytokine IL-6, sCD40L, and adhesion molecules in normotensive subjects with SCR. These findings imply that ramipril treatment may have antiatherogenic effects in subjects with SCR, even in the absence of arterial hypertension. (J Am Coll Cardiol 2008;51:742–9) © 2008 by the American College of Cardiology Foundation.

It is now well documented that adults with successfully repaired coarctation of the aorta (SCR) experience higher risk for premature atherosclerosis than the general population (1,2). Despite the early and successful surgical repair of aortic coarctation, these subjects appear to have persisting vascular abnormalities such as impaired endothelial function (3,4) and abnormal elastic properties of large vessels (4–6), especially at the pre-coarctation arterial tree (3,4,7). In addition, these subjects appear to have higher levels of several proinflammatory molecules with a key role in atherogenesis, such as proinflammatory cytokines and adhesion molecules, as we have previously shown (4). Although the increased cardiovascular risk identified in these patients could be the result of the commonly relapsed hypertension (at rest or during exercise) (1,8), it seems that the observed proatherogenic abnormalities are also observed in the absence of arterial hypertension (4).

Recent studies have demonstrated that angiotensin-converting enzyme inhibitors (ACEI) have a number of beneficial effects on vascular function in patients with...
advanced atherosclerosis or arterial hypertension, and they decrease cardiovascular risk (9). In addition to their antihypertensive effect, ACEI have anti-inflammatory properties, improve nitric oxide (NO) bioavailability in human vasculature, and modify cardiovascular risk by interfering directly into the mechanisms of atherogenesis (10). Although the use of ACEI is recommended for hypertensive patients with SCR, their effects on endothelial function and inflammatory process in subjects with SCR and normal blood pressure are unknown.

In this randomized, cross-over, controlled study, we hypothesized that treatment with the ACEI ramipril may exert direct beneficial effects on vascular function in normotensive patients with SCR. We hypothesized that ramipril may improve endothelial function and decrease the expression of proinflammatory cytokines and adhesion molecules in a population of nonhypertensive low-risk subjects with SCR.

Methods

Study population. A total of 50 subjects with SCR (resection and end-to-end anastomosis in all) were initially screened for eligibility. Twenty-three of them fulfilled the inclusion criteria, and 20 agreed to participate. The patients were recruited from the registry of Hippokration Hospital in Athens. The successful repair of aortic coarctation was confirmed by continuous Doppler gradient at the distending aorta <25 mm Hg, the presence of palpable femoral pulses, and no radiofemoral delay.

Exclusion criteria were the presence of resting hypertension (>140/90 mm Hg as evaluated by 3 subsequent “office” blood pressure measurements and 24-h blood pressure monitoring) (11). Additional exclusion criteria were the presence of exercise-induced arterial hypertension, left ventricular hypertrophy, overt atherosclerotic peripheral vascular disease, presence of any acute or chronic inflammatory diseases (e.g., liver diseases), or any other cardiac disease (including coronary artery disease documented by medical history and exercise stress test). Subjects with any classic risk factor for atherosclerosis or receiving any systemic medication were also excluded from the study. In particular, we excluded patients with established risk factors such as diabetes mellitus, hypertension, dyslipidemias, smoking, homocysteinemia (fasting homocysteine >12 μmol/l), or obesity. Based on these criteria, 14 patients were excluded because of the presence of hypertension and 13 because of the presence of other classic risk factors for atherosclerosis, such as dyslipidemia (n = 6), smoking (n = 9), diabetes mellitus (n = 1), or a combination of more than 1 risk factor. During the treatment period, all patients were monitored for side effects of ramipril treatment (such as cough, allergic reactions, hypotension, or liver enzyme elevations), but none of the participants required reduction or termination of the drug use for any of these symptoms.

Study protocol. At baseline, gauge-strain plethysmography was performed in the right forearm and blood samples were obtained. By the end of the first visit, patients were randomized to receive ramipril 5 mg/day or no treatment (control) for 4 weeks in a randomized cross-over controlled trial, with 4 weeks’ wash-out period between the 2 intervention periods (Fig. 1). Gauge-strain plethysmography was performed and blood samples obtained at every visit. In a pilot study, we established that the 4 weeks’ wash-out period was adequate to allow for all the measured parameters to return to their baseline levels.

There were no drop-outs during the study period. The patients’ compliance to the treatment was monitored by counting the remaining treatment tablets at every visit. The protocol of the study was approved by the Institutional Ethics Committee of Hippokration Hospital, and informed consent was given by each subject.

Forearm blood flow (FBF) measurements. We evaluated post-ischemic hyperemia as an index of endothelial function in the right forearm. It was previously shown that NO is responsible for 50% of hyperemic flow, and reactive hyperemia (RH) is widely used as an index of endothelial function in human forearm circulation (12). Briefly, all measurements were performed in the morning in a dark quiet room under constant temperature of 22°C to 25°C. All subjects abstained from alcohol for 24 h and
from food, tobacco, and caffeine-containing drinks for at least 12 h before each vascular study. Before measurements were started, subjects were rested in a supine position for 30 min. Forearm blood flow was measured using venous occlusion gauge-strain plethysmography (EC-400, D. E. Hokanson, Bellevue, Washington) as previously described (12). The FBF was calculated as the percentage change of arm volume per 100 ml tissue per minute. Forearm vasodilatory response to RH was defined as the percentage change of FBF from baseline to the maximum FBF during reactive hyperemia after a 4.5-min ischemic occlusion of the forearm. Ischemia of the forearm was achieved by using an ischemic cuff at a pressure 50 mm Hg higher than the patient’s systolic blood pressure.

Forearm vasodilatory response to nitrate was defined as the percentage change of FBF from baseline to the maximum FBF achieved after sublingual administration of nitroglycerin (NTG) 0.4 mg (12). The RH is considered to be a marker of NO bioavailability (because infusion of endothelial NO synthase inhibitor N(G)-monomethyl-L-arginine inhibits RH by ~50%) (12). Mean intra- and interobserver variabilities of RH measurements in our laboratory in 20 healthy volunteers were 3.1 ± 1.7% and 4.1 ± 1.9%, respectively.

Biochemical determinations. Venous blood samples were taken at the beginning of each protocol. After centrifugation at 3,500 rpm at 4°C for 10 min, plasma or serum was collected and stored at −80°C until assayed. High-sensitivity C-reactive protein (CRP) was measured by particle-enhanced immunonephelometry (N Latex, Dade-Behring Marburg, Marburg, Germany). Serum levels of interleukin (IL)-1b, IL-6, and soluble vascular cell adhesion molecule (sVCAM)-1 were determined by enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Wiesbaden-Nordenstadt, Germany). Serum soluble CD40 ligand (sCD40L) was also determined by ELISA (Bender Medsystems, Vienna, Austria).

Statistical analysis. All variables were tested for normal distribution using the Kolmokorov-Smirnov test. Normally distributed variables are expressed as mean ± SEM, and CRP (which was non-normally distributed) was log transformed for analysis and is presented in a nonlogarithmic format as median (25th to 75th percentile). At the beginning of the treatment, all variables were compared between the 2 groups by using an unpaired t test. The effect of treatment on each variable was examined by using 2-way analysis of variance (ANOVA). To test for order effects, we also used an additional between-groups factor (ramipril first vs. control first groups), and we used ANOVA with 3 factors (to determine the group order × treatment × time interactions). Correlations between variables were performed by univariate analysis, and the Pearson r coefficient was estimated. All analyses were carried out by using the SPSS version 12.0 statistical package (SPSS Inc., Chicago, Illinois).

Results

The demographic characteristics of the participants are presented in Table 1. All patients complied with therapy, and there were no drop-outs. There were no significant differences in any of the baseline/demographic characteristics between the 2 groups. Treatment with ramipril significantly improved maximum hyperemic FBF (p < 0.001) and RH (p < 0.001) and had no effect on resting FBF (p = NS) or NTG (Table 2, Fig. 2). Although ramipril slightly decreased systolic blood pressure (Table 2), this decrease was not associated with the changes in maximum hyperemic FBF (r = −0.107; p = 0.510) or RH (r = −0.276; p = 0.085). On the other hand, ramipril had no significant effect on diastolic blood pressure (Table 2), and there was no change in systolic or diastolic blood pressures during the control period (Table 2). The improvements of maximum hyperemic FBF and RH induced by ramipril were significantly higher compared with the variations observed during the control period (p < 0.01) (Table 2). In addition, when the change in systolic blood pressure was included as a covariate in the ANOVA analyses, there was no change in the effect of treatment on maximum hyperemic FBF or RH.

To test whether ramipril treatment has any effect on the expression of proatherogenic inflammatory molecules, we examined the effect of treatment on proinflammatory cytokines IL-1b and IL-6. Serum levels of IL-6 were significantly decreased after treatment with ramipril (p < 0.05), and the decrease of IL-1b did not reach statistical significance (p = 0.055) (Table 2, Fig. 3). Similarly, serum sCD40L levels were significantly decreased after ramipril treatment (p < 0.01) (Table 2, Fig. 3), suggesting that ramipril may exert a general anti-inflammatory effect in SCR subjects.

Because proinflammatory cytokines stimulate the expression of adhesion molecules in vascular endothelium and the synthesis of acute-phase proteins in the liver, we examined whether ramipril thus had any effect on serum levels of sVCAM-1 and CRP. Serum sVCAM-1 was significantly decreased after ramipril treatment (p < 0.01) (Table 2, Fig. 4). However, despite the trend toward a decrease of CRP levels after 4 weeks of treatment with

<table>
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<tr>
<th>Table 1 Population Characteristics</th>
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<tr>
<td>SCR Patients</td>
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<tr>
<td>Subjects screened, n</td>
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<tr>
<td>Subjects excluded, n</td>
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<tr>
<td>Subjects who agreed to participate in the study, n</td>
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<tr>
<td>Gender (male/female)</td>
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<td>Age (yrs)</td>
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<td>Years after operation</td>
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<tr>
<td>Body mass index (kg/m²)</td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
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<tr>
<td>Diastolic blood pressure (mm Hg)</td>
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Values expressed as mean ± SEM.

SCR = successful repair of coarctation of aorta.
ramipril, this change did not reach statistical significance (Table 2, Fig. 4). The decreases of IL-1β, IL-6, sCD40L, and sVCAM-1 induced by ramipril were significantly greater compared with the respective variations observed during the control period (Table 2). When the change in systolic blood pressure was included as a covariate in the ANOVA analyses, it had no impact on the detected effects of treatment on each one of the examined inflammatory markers. Finally, there was no order effect on the change of any of the variables examined.

**Discussion**

Impaired endothelial function and an increased inflammatory process are observed in subjects with SCR many years after repair of coarctation. Treatment with ramipril had no effect on resting forearm blood flow (FBF) (A), whereas it significantly improved maximum hyperemic FBF (B) and reactive hyperemia (C). Ramipril had no effect on nitrate-induced vasodilation in the forearm (D to F). *p < 0.01 versus before treatment. NTG = forearm vasodilator response to nitrate.

**Table 2**

<table>
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<th>Control</th>
<th>Ramipril 5 mg/day</th>
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<tr>
<td></td>
<td>Baseline for Control Period*</td>
<td>After 4 Weeks of No Treatment</td>
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<tr>
<td>Systolic blood pressure (mm Hg)†</td>
<td>120.0 ± 3.7</td>
<td>121.7 ± 3.6</td>
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<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>74.0 ± 2.5</td>
<td>72.5 ± 3.9</td>
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<tr>
<td>Baseline FBF-1 (ml/100 ml tissue/min)†</td>
<td>5.5 ± 0.4</td>
<td>5.6 ± 0.4</td>
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<tr>
<td>Maximum hyperemic FBF (ml/100 ml tissue/min)†</td>
<td>7.7 ± 0.5</td>
<td>7.8 ± 0.7</td>
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<tr>
<td>RH (%)†</td>
<td>43.5 ± 5.4</td>
<td>41.4 ± 5.4</td>
</tr>
<tr>
<td>Baseline FBF-2 (ml/100 ml tissue/min)</td>
<td>6.2 ± 0.5</td>
<td>6.4 ± 0.6</td>
</tr>
<tr>
<td>Maximum FBF after nitroglycerine administration (ml/100 ml tissue/min)</td>
<td>11.1 ± 1.0</td>
<td>10.8 ± 0.9</td>
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<tr>
<td>NTG (%)</td>
<td>78.0 ± 5.8</td>
<td>70.4 ± 5.2</td>
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<tr>
<td>C-reactive protein (mg/l)†</td>
<td>1.03 (0.45–1.67)</td>
<td>1.02 (0.63–3.46)</td>
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<tr>
<td>Interleukin-6 (pg/ml)§</td>
<td>1.28 ± 0.18</td>
<td>1.34 ± 0.18</td>
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<tr>
<td>Interleukin-1β (pg/ml)§</td>
<td>0.89 ± 0.28</td>
<td>0.95 ± 0.27</td>
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<tr>
<td>sVCAM-1 (ng/ml)§</td>
<td>500.3 ± 43.3</td>
<td>504.6 ± 33.5</td>
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<tr>
<td>sCD40L (ng/ml)§</td>
<td>2.07 ± 0.35</td>
<td>2.47 ± 0.38</td>
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Values are expressed as mean ± SEM or median (25th to 75th percentile). *Baseline or after 4 weeks’ washout, according to the randomization order. †p < 0.1; ‡p < 0.05 versus baseline; §p < 0.05; ††p < 0.01 between the changes induced by the 2 interventions (control vs. placebo), as evaluated by 2-way analysis of variance.

FBF = forearm blood flow; NTG = forearm vasodilator response to sublingual nitroglycerin (0.4 mg); RH = forearm vasodilator response to reactive hyperemia; sCD40L = soluble CD40 ligand; sVCAM = soluble vascular cell adhesion molecule.
after the operation and may have a strong effect on cardiovascular risk in these subjects. We examined whether ramipril treatment affects endothelial function and inflammatory process in normotensive subjects with SCR. We demonstrated for the first time that 4 weeks of ramipril treatment improves endothelial function and decreases the expression of IL-6, sCD40L, and sVCAM-1 in these subjects. These findings suggest that inhibition of ACE may have direct antiatherogenic effects in subjects with SCR, even in the absence of arterial hypertension.

**Effects of ramipril on endothelial function in subjects with SCR.** It is widely believed that residual narrowing at the site of surgery (especially during exercise) after SCR is partly responsible for the relapse of hypertension in these subjects (13). However, the role of the aortic arc geometry (classified as normal, Gothic, and Crenel) does not seem to be related to the development of exercise-induced hypertension in these subjects (14). On the other hand, the very first reports about the impact of vasoreactivity on the development of post-SCR hypertension suggested that SCR patients with persisting post-operative hypertension had greater vasoreactivity in response to norepinephrine compared with those with normal blood pressure (15). It is now generally thought that endothelial dysfunction and decreased vascular NO bioavailability are key mechanisms affecting forearm vasoreactivity in SCR patients (2). In addition, evidence suggests that noninvasive evaluation of endothelial function has a prognostic value in hypertensive individuals (16) and, most importantly, in subjects with SCR (2).

Evidence suggests that endothelial function in the pre-coarctation arterial tree remains impaired many years after SCR (4). This could be the result of the relapsed arterial hypertension often observed after SCR (1,8,17). Indeed, increased post-operative levels of renin (18), reflecting the activation of the renin-angiotensin system, have been observed in these patients even before the development of arterial hypertension (19). This could be one of the mechanisms leading to the relapse of hypertension years after SCR, and may be directly implicated in the development of endothelial dysfunction in these subjects, because angiotensin II suppresses NO production, generates toxic vascular pro-oxidants, and enhances the production of endothelin-1 (a potent systemic vasoconstrictor) (20). Moreover, endothelial dysfunction is not strictly dependent

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**Figure 3** Effects of Ramipril on sCD40L, IL-1b, and IL-6

Treatment with ramipril induced a borderline (p = 0.055) decrease of interleukin (IL)-1b (A) and a significant decrease of IL-6 (B) and soluble CD40 ligand (sCD40L) (C) in normotensive subjects with successfully repaired coarctation of the aorta. *p < 0.05; **p < 0.01 versus before treatment.

**Figure 4** Effect of Ramipril on sVCAM-1 and CRP Levels

Treatment with ramipril induced a significant decrease of circulating soluble vascular cell adhesion molecule (sVCAM)-1 (A). However, serum levels of C-reactive protein (CRP) remained unchanged after 4 weeks’ treatment with ramipril (B). *p < 0.01 versus before treatment.
on the existence of hypertension (4,5), because it persists after successful surgical repair even when blood pressure is normalized (21). On the other hand, structural changes on the vascular wall, such as intimal and medial thickening, disruption of the internal elastic lamina, and an increase in the number of smooth muscle cells in the media (22), may contribute to the increased cardiovascular risk observed in subjects with SCR. The hypothesis that hypertension is not the main cause (or may even be a result) of these vascular abnormalities was also supported by our previous observations indicating that increased arterial stiffness is observed only in the pre-coarctation arterial tree (but not in the post-coarctation vasculature) many years after SCR in normotensive subjects (4).

In addition to the effect of angiotensin II on endothelial function, there is evidence suggesting that it acts via angiotensin type 1 receptors to alter sympathovagal balance during the establishment of coarctation hypertension, facilitating the sympathetic outflow to heart and peripheral circulation during baroreceptor unloading (23). The role of the sympathetic system in the development of post-SCR hyperdynamic circulation and increase in systolic blood pressure has been documented by demonstrating a favorable effect of nonselective beta-blockade by propranolol on the development of these complications (24). However, at a clinical level, beta-blockers may even induce a short-term increase of diastolic blood pressure after SCR (25), and their usefulness is not widely accepted, because their effect on long-term outcome of these patients has not been documented.

In the present study, we hypothesized that suppression of the renin-angiotensin system by using the ACEI ramipril may improve endothelial function in SCR subjects. We found that ramipril leads to a significant improvement of endothelial function in the right forearm of subjects with SCR. This improvement of NO bioavailability may be through both the direct induction of endothelial NO production and the decreased breakdown of bradykinin, which indirectly induces the B2-receptor-mediated release of endothelial NO (26).

**Effects of ramipril on the inflammatory process.** It is widely accepted that inflammation is a key component of atherogenesis (27). Proinflammatory cytokines such as IL-1b and IL-6 trigger the synthesis of acute-phase proteins (such as CRP) in the liver and stimulate the expression of adhesion molecules (such as VCAM-1), all with a major predictive role in atherogenesis (27). Proinflammatory cytokines are produced by a variety of tissues, including the vascular wall (27), and serum levels of inflammatory mediators are elevated in subjects with SCR in the absence of hypertension or overt atherosclerosis (4). It is therefore likely that increased inflammatory molecules produced by the dysfunctional arterial wall in the pre-coarctation arterial tree, could lead to the development of premature atherosclerosis (27), and it could also participate in the late development of arterial hypertension in subjects with SCR (28).

The observed activation of the renin-angiotensin system in SCR seems to promote the expression of inflammatory cytokines, leading to further leukocyte activation in the systemic circulation (29), which results in the direct elevation of proatherogenic inflammatory load in these subjects (4). There is strong evidence suggesting that inhibition of the renin-angiotensin system by ACEI (such as ramipril) depresses the expression of these proatherogenic inflammatory molecules in this population, as observed with patients with coronary artery disease (30), hypertension (31) or other risk factors for atherosclerosis (32). This is thought to be via the reduction of circulating angiotensin II levels. Angiotensin II up-regulates the expression of inflammatory mediators controlled by redox-sensitive pathways such as the nuclear factor kappa B pathway and others (26). This effect is thought to be via the activation of angiotensin type 1 receptor, as was recently shown in experimental models (33). The second alternative pathway by which ACEI could reduce inflammatory stimulation is believed to be the reduction of blood pressure per se (34).

In the present study, we have shown that 4 weeks of treatment with ramipril induced a significant decrease of IL-6 and a borderline reduction of IL-1b levels in normotensive SCR patients, independently of blood pressure lowering, suggesting that inhibition of the renin-angiotensin system may have a significant direct anti-inflammatory effect in these subjects.

We have also shown that ramipril treatment decreases serum sCD40L, an important proinflammatory molecule involved in atherogenesis (35), which is secreted by both activated platelets and the immune system (35). Evidence suggests that sCD40L release in severe inflammatory conditions may be regulated by proinflammatory stimuli and especially by cytokines such as IL-6, whereas ligation of CD40 mediates an array of proinflammatory effects in subjects with risk factors for atherosclerosis, including the expression of cytokines, chemokines, and adhesion molecules (35). There is evidence that the sCD40L level is a strong predictor of cardiovascular risk (36), but its role in subjects with SCR has not been evaluated until now. We have demonstrated that ramipril decreases sCD40L levels in SCR patients, suggesting that it may have a beneficial effect in atherogenesis in this population.

A key mechanism by which proinflammatory cytokines affect atherogenesis is the up-regulation of the expression of adhesion molecules on the endothelial surface, molecules with a critical role in platelet adhesion and migration to the subendothelial space (27). The soluble forms of adhesion molecules such as sVCAM-1 seem to have a predictive value in cardiovascular risk assessment (35). As we have previously shown (4), subjects with SCR appear to have elevated sVCAM-1, suggesting that this inflammatory marker may be a rational target for treatment at the level of primary prevention in these subjects. We have demonstrated in the
present study that 4 weeks’ treatment with ramipril decreases circulating sVCAM-1 levels independently of blood pressure lowering, implying that treatment with ACEI may have antiatherogenic effects even in normotensive subjects with SCR.

Acute-phase proteins such as CRP have a major predictive value in cardiovascular risk assessment (27,35). Although proinflammatory cytokines are the main stimuli for the expression of CRP in the liver, 4 weeks’ treatment with ramipril failed to induce any change in CRP levels, despite the lowering of IL-6 and sVCAM-1. This finding could be a result of the relatively short treatment period, and it requires further evaluation by longer-term clinical trials.

**Study limitations.** A limitation of this study is the absence of angiographic evaluation of the degree of anatomic obstruction in the subjects. Although our patients had echocardiographic estimation of the transcoarctation site <25 mm Hg, we cannot preclude the presence of recoarctation, because the echocardiographic estimation is not as accurate as magnetic or invasive angiography. In addition, the present study uses a short-term treatment period (only 4 weeks) and it has “soft” end points, such as endothelial function and the levels of inflammatory markers. Although endothelial function and inflammatory markers have a predictive value for cardiovascular risk in the general population, their true role in the outcome of patients with SCR is still unknown. Therefore, the results of the present study can only be used as the basis for the design of other large-scale clinical trials using long-term ACEI treatment of normotensive patients with SCR to demonstrate a possible effect on cardiovascular risk. Only when the outcomes of such studies are available could we address the question of whether all SCR patients should routinely receive ramipril. Finally, it is unclear whether the levels of the examined inflammatory markers are abnormally elevated in SCR subjects. Despite our previous observation that SCR subjects have significantly greater levels of inflammatory markers compared with age- and gender-matched controls (4), the “normal range” for most of these markers remains unclear (37).

**Conclusions**

We demonstrated that 4 weeks’ treatment with ramipril leads to an improvement of endothelial function in normotensive patients with SCR, independently of blood pressure lowering. Furthermore, ramipril reduces the expression of proatherogenic inflammatory cytokines (such as IL-6), adhesion molecules (sVCAM-1), and sCD40L in this population. Taken together, these findings suggest that the blockade of the renin–angiotensin system may be a rational therapeutic target even in normotensive subjects with SCR, and it may lead to a reduction of overall cardiovascular risk.

**REFERENCES**


