The Relationship of Chronic Angiotensin Converting Enzyme Inhibitor Use and Coronary Collateral Vessel Development

Timucin ALTIN,[1] MD, Mustafa KILICKAP,[1] MD, Eralp TUTAR,[1] MD, Sibel TURHAN,[1] MD, Yusuf ATMACA,[1] MD, Sadi GULEC,[1] MD, Dervis ORAL,[1] MD, *and* Cetin EROL,[1] MD

SUMMARY

Background: Angiotensin II induces various growth factors such as vascular endothelial growth factor, platelet-derived growth factor, and fibroblast growth factor, and recent studies suggest that the expression of these growth factors promotes collateral growth. We hypothesized that the blockage of angiotensin II production by ACE inhibitors might interfere with collateral development in patients with coronary occlusion.

Methods: The study group consisted of 187 patients (114 males, mean ages, 62 ± 11 years) who had chronic (> 1 month) coronary occlusion (TIMI flow grade ≤ 1) in one of 3 epicardial coronary arteries. Collaterals were graded using the Rentrop classification, and the patients were divided into 2 groups according to having good (grade 2 and 3) or poor (grade 0 and 1) collaterals (n = 127 and 60, respectively). Clinical and angiographic characteristics were compared in the 2 groups.

Results: ACE inhibitor use (52% versus 35%, P = 0.04) and the prevalence of diabetes mellitus (DM) (43% versus 27%, P = 0.02) was higher in patients with poor collaterals. Patients with poor collaterals had a higher frequency of circumflex artery (Cx) occlusion, worse wall motion, and lower ejection fraction. In multivariate analysis, ACE inhibitor use (OR: 2.4; 95% CI = 1.23-4.68, P = 0.01) and the occlusion of Cx (OR: 3.3, 95% CI; 1.33-8.12, P = 0.01) were found to be independent predictors for poor collateral development, whereas there was a trend for DM as a predictor for poor collaterals (OR: 1.9, 95% CI = 0.97-3.8, P = 0.06).

Conclusion: The findings suggest that ACE inhibitor therapy may contribute to poor collateral development in patients with coronary occlusion. (Int Heart J 2007; 48: 435-442)

Key words: ACE inhibitors, Coronary occlusion, Coronary collateral vessels

CORONARY artery disease is the most frequent cause of death in developed countries. Well developed coronary collateral vessels protect the myocardium,

From the [1] Department of Cardiology, Ankara University School of Medicine, Ankara, Turkey.
Address for correspondence: Timucin Altin, MD, Department of Cardiology, Ankara Universitesi, Kalp Merkezi Kardiyoloji Anabilim Dalı, 06590, Dikimevi, Ankara, Turkey.
Received for publication February 19, 2007.
Revised and accepted May 18, 2007.

and thus lessen the development of heart failure and improve survival in patients with coronary artery occlusion.[1] However, there is limited information on the factors effecting the development of coronary collateral vessels despite their functional importance in ischemic heart diseases.[2]

Coronary collateral vessels may develop as a result of arteriogenesis and/or angiogenesis. Arteriogenesis refers to growth of anastomotic channels (preexisting arterioles) between coronary arteries to functional collateral arteries, in a manner resembling positive arterial remodeling. Angiogenesis refers to the sprouting of endothelial cells leading to new capillary networks. In both, growth factors play an important role in mediating collateral development.[3] Angiotensin II may enhance collateral formation by virtue of increasing various growth factors such as vascular endothelial growth factor (VEGF),[4,5] platelet-derived growth factor (PDGF),[6] and fibroblast growth factor (FGF).[7]

The efficacy of angiotensin converting enzyme (ACE) inhibitors in the treatment of various cardiac diseases has been proven.[8,9] ACE inhibitors have been reported to promote angiogenesis in a rabbit model of hindlimb ischemia[10] and to increase capillary density in coronary microvasculature.[11] However, they may interfere with collateral development by reducing the expression of growth factors by decreased production of angiotensin II, and may reduce collateral development. In this study, we investigated the relationship between chronic ACE inhibitor treatment and collateral vessel development in patients with chronic coronary artery occlusion.

METHODS

Patients who underwent diagnostic coronary angiography for suspected or known coronary atherosclerosis or other reasons, and who had chronic total or near-total coronary occlusion (Thrombolysis in Myocardial Infarction Trial (TIMI) flow grade ≤ 1) at proximal or mid segments in one of the 3 major epicardial coronary arteries (left anterior descending artery, circumflex artery, right coronary artery) with a duration of > 1 month (on the basis of a previous angiogram, the date of a prior MI, or the onset of symptoms) were enrolled in the study. Patients who had had an acute myocardial infarction within 1 month, and patients receiving angiotensin receptor blocker (ARB) therapy were excluded.

Patients having a stenosis of ≥ 50% in more than one major epicardial coronary artery were termed to have multivessel disease. Collateral vessels were graded according to the Rentrop classification: 0 = no filling of any collateral vessels, 1 = filling of the side branches of the artery to be perfused by collateral vessels without visualization of the epicardial segment, 2 = partial filling of the epicardial artery by collateral vessels, and 3 = complete filling of the epicardial

artery by collateral vessels.[12] Patients were classified as having good (grade 2 and 3) or poor (grade 0 and 1) collaterals. Angiographical and clinical characteristics and the frequency of ACE inhibitor (other than captopril) use were compared between the 2 groups. In terms of ACE inhibitor use, there were also 2 groups; one with chronic users (more than 3 months), and the other with patients who had never used ACE inhibitors. The duration of ACE inhibitor treatment was 25 ± 11 months. Patients with total cholesterol levels greater than 190 mg/dL were considered to have hyperlipidemia. Patients with systolic or diastolic blood pressure > 140 mmHg or 90 mmHg or who were under antihypertensive treatment were considered to be hypertensive. Patients who were being treated for diabetes mellitus (DM) or who had a fasting glucose concentration ≥ 126 mg/dL were considered to have DM. Wall motion in the territory of the occluded coronary artery was classified as poor (akinetic or aneurysmatic) or good (normal or hypokinetic), on the basis of echocardiography or ventriculography. The investi-

Table. Clinical and Angiographical Characteristics in the Two Groups

	Good Collateral (n = 127)	Poor Collateral (n = 60)	P
Age, years	62 ± 11	61 ± 11	0.5
Male, %	61	62	0.9
Diabetes mellitus, %	27	43	0.02
Hypertension, %	55	47	0.3
Hyperlipidemia, %	53	63	0.3
Family history of CAD, %	35	33	0.9
Old myocardial infarction, %	65	75	0.2
Multivessel disease, %	76	75	0.8
Occluded coronary artery,			
LAD, %	43	35	0.03
Cx, %	10	25	
RCA, %	47	40	
Lesion localization,			
Proximal, %	39	45	0.5
Mid, %	61	55	
Smoking, %	48	45	0.7
LV wall motion,			
Akinesia-aneurysm, %	34	57	0.005
Normokinesia-hypokinesia, %	66	43	
EF, %	53 ± 14	49 ± 13	0.04
Angina, %	74	75	0.9
Beta blocker, %	34	39	0.5
Nitrate, %	50	45	0.6

Continuous variables are shown as mean ± standard deviation. CAD indicates coronary artery disease; Cx, left circumflex artery; EF, ejection fraction; LAD, left anterior descending artery; LV, left ventricle; and RCA, right coronary artery.

gator who interpreted the angiograms was blinded as to whether the patient had received ACE inhibitor therapy.

Statistical analysis: Statistical analysis was performed using SPSS version 11.5 software (SPSS Inc., Chicago, Illinois). Categorical variables are presented as percentages and continuous variables as the mean ± SD. The chi-square test was used to compare the frequencies of the categorical variables of gender, diabetes mellitus, hypertension, hyperlipidemia, family history of coronary artery disease, old myocardial infarction, multivessel disease, smoking, angina, medication, the distribution of the occluded coronary arteries, proximal or mid localization of the occlusion, and wall motion (akinesia-aneurysm or normokinesia-hypokinesia). Student's *t*-test was used to compare continuous variables of age and ejection fraction. Multivariate logistic regression analysis was used to determine the independent variables affecting the collateral development. A probability value of < 0.05 was considered significant.

RESULTS

The patient population consisted of 114 males (61%) and 73 females (39%) (mean age, 62 ± 11 years). The clinical and angiographic characteristics of the patients are summarized in the Table. The prevalence of DM was higher in the poor collateral group compared to the good collateral group in univariate analysis ($P = 0.02$). Left ventricular wall motion in the territory of the occluded artery was better ($P = 0.005$) and ejection fraction was higher ($P = 0.04$) in patients with good collaterals than in those with poor collaterals. The distribution of the

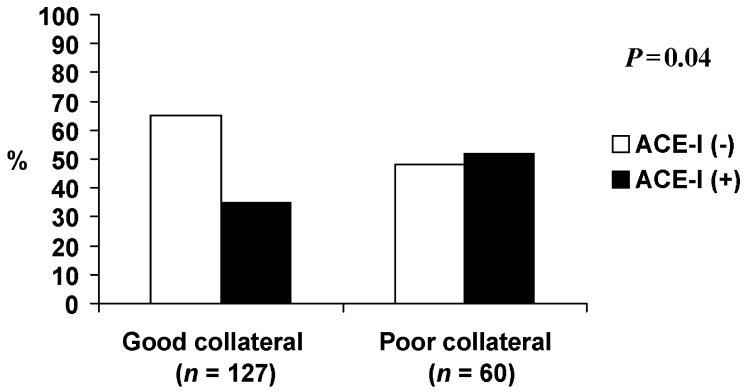


Figure. Relationship of collateral development and chronic angiotensin-converting enzyme inhibitor (ACE-I) use.

occluded epicardial major coronary artery was significantly different between the groups ($P = 0.03$). The use of ACE inhibitors was higher in the poor collateral group ($P = 0.04$) (Figure). The factors affecting coronary collateral development (ACE inhibitor use, presence of DM, and the occluded coronary artery) were evaluated by multivariate analysis. ACE inhibitor use (OR: 2.4; 95% CI = 1.23-4.68, $P = 0.01$) and occlusion of the circumflex artery (OR: 3.3, 95% CI = 1.33-8.12, $P = 0.01$) were found to be independent predictors for poor collateral development, and DM appeared to be a slight independent predictor for poor collaterals (OR: 1.9, 95% CI = 0.97-3.8, $P = 0.06$).

DISCUSSION

In the present study, chronic use of ACE inhibitors was found to be an independent predictor of poor collateral development in patients with chronic total coronary occlusion.

Angiotensin II has been previously reported to increase the production of growth factors that participate in collateral development.[4-7] Our finding might be attributed to decreased angiotensin II formation, and hence blunted growth factor secretion as a result of ACE inhibition. Contrary to our result, some previous experimental studies have proposed that ACE inhibitors enhance collateral development.[10,11] The possible mechanism for enhanced angiogenesis has been suggested to be the bradykinin-mediated angiogenic action of ACE inhibitors. Accumulation of bradykinin, a potent activator of the L-arginine-nitric oxide pathway, has been shown to promote angiogenesis by potentiating the effects of various growth factors.[13,14] Another mechanism by which bradykinin exerts its angiogenic effect is postulated to be a long-term increase in coronary flow and thus by increasing shear stress-induced release of growth factors involved in the angiogenic process.[15]

These earlier studies evaluated mostly angiogenesis, not arteriogenesis. Angiogenesis includes new capillary formation, which cannot be seen by conventional coronary angiography. On the other hand, vessels formed by arteriogenesis might more readily be visualized by coronary angiography by their large diameters, and may be superior to the newly formed capillaries because they are able to sustain proper circulation and to adapt to changes in physiological demands of blood supply with their 3 layered configuration.[16] Moreover, even visibility of the collaterals alone is not sufficient for myocardial protection. A study showed that a grade 1 collateral does not differ from a grade 0 collateral (absent collateral), and grade 2-3 collaterals have been found to be protective.[17] For this reason, we evaluated the effect of chronic ACE inhibitor use on the development of beneficial collaterals.

Shear stress, which is the initiating stimulus for arteriogenesis, increases dramatically in the preexisting arteriolar shunts after occlusion of the main supplying vessel, and it has profound effects on the functional expression of many endothelial and smooth muscle cell proteins, including enzymes such as ACE and NOS, growth factors including PDGF-A and B and TGF-B, an array of complex interactions that results in arteriogenesis.[16] Gosgnach, *et al* demonstrated that shear stress increased ACE expression in vascular smooth muscle cells that is important in vascular wall remodeling.[18] ACE inhibition may reduce the collateral development by interfering with this pathway.

Studies investigating the effects of ACE inhibitors on coronary collateral development in humans are limited. In a retrospective observational study, Miura, *et al*, in contrast to our finding, demonstrated that ACE inhibitors increased coronary collaterals.[19] Although it is difficult to explain the exact pathophysiological mechanisms based on a retrospective study, we may speculate about some mechanisms for the contradictory findings. First, they compared the groups with respect to absence (Rentrop grade 0) or presence (Rentrop ≥ 1) of collaterals. On the other hand, we assigned a patient to the good collateral group if the patient had grade 2 or 3 collaterals based on the previous studies suggesting grade 1 collateral is almost equal to grade 0 collaterals in terms of functional aspects.[17] Therefore, the difference between the frequencies of the collaterals may be caused by the difference in the groups. Secondly, they demonstrated that an ACE inhibitor-dependent increase in collateral development is relatively and significantly higher in patients with one-vessel disease, not in multivessel disease. Compared to their study, the higher frequency of multivessel disease in our study (76% versus 56%) may be one of the causes of the different results. Finally, our study group consisted of only patients who had a totally occluded coronary artery. Like multivessel disease, a totally occluded coronary artery may be considered a more advanced disease, and may be one of the factors responsible for the difference.

Previously, it was reported that stimulation of B2 receptors by bradykinin led to transactivation of VEGF receptors and eNOS activation, which induced angiogenesis.[14] Previous studies suggested that the effects of ACE inhibitors on collaterals were due to increased bradykinin levels.[10,11,19] If it is true for angiogenesis as well as arteriogenesis, ARBs might be related with poorer collateral development. Consistent with this hypothesis, Imaizumi, *et al* found that ARBs did not enhance collateral development and they were related with poorer collateral development than ACE inhibitors.[20] On the other hand, in an ischemic hindlimb model, Emanueli, *et al* showed that both ACE inhibitors and ARBs impaired reparative angiogenesis, and this effect remained unaltered during bradykinin receptor blockade.[21] There are contradictory results with respect to the effects of

ARBs on angiogenesis in experimental studies.[21-23] These contradictory results might be attributed to different levels of expression of the angiotensin receptor subtypes AT_1 and AT_2 in healthy and disease states, that have counterregulatory actions in terms of vascular growth.[24] In the present study, we did not investigate the effects of ARBs on collateral development.

We observed a slightly higher prevalence of DM in patients with poor collaterals. Consistent with our results, Abaci, *et al* also found that diabetics had poor collaterals compared to nondiabetics.[25] However, the effect of medication on collateral development was not taken into consideration in their analysis. It is well known that ACE inhibitors are widely used in diabetic populations.[26] In our study, multivariate analysis revealed that the use of ACE inhibitors was an independent predictor of poor collateral development.

Another finding of our study is that the circumflex artery received less collateral supply than the LAD and RCA, and that occlusion of the circumflex artery was an independent predictor for poor collateral development. Although the mechanism is unclear, our finding is concordant with previous studies indicating that the circumflex artery received the poorest collateral supply among 3 coronary arteries.[27-29]

In conclusion, the results of our study have shown that collateral vessel development may be hampered by ACE inhibitor treatment in patients with totally occluded coronary arteries. In future, larger prospective, randomized studies are warranted.

REFERENCES

1. Hansen JF. Coronary collateral circulation: clinical significance and influence on survival in patients with coronary artery occlusion. Am Heart J 1989; 117: 290-5.
2. Piek JJ, van Liebergen RA, Koch KT, Peters RJ, David GK. Clinical, angiographic and hemodynamic predictors of recruitable collateral flow assessed during balloon angioplasty coronary occlusion. J Am Coll Cardiol 1997; 29: 275-82.
3. van Royen N, Piek JJ, Buschmann I, Hoefer I, Voskuil M, Schaper W. Stimulation of arteriogenesis; a new concept for the treatment of arterial occlusive disease. Cardiovasc Res 2001; 49: 543-53. (Review)
4. Chua CC, Hamdy RC, Chua BH. Upregulation of vascular endothelial growth factor by angiotensin II in rat heart endothelial cells. Biochem Biophys Acta 1998; 1401: 187-94.
5. Otani A, Tagaki H, Suzuma K, Honda Y. Angiotensin II potentiates vascular endothelial growth factor-induced angiogenic activity in retinal microcapillary endothelial cells. Circ Res 1998; 82: 619-28.
6. Naftilan AJ, Pratt RE, Dzau VJ. Induction of platelet-derived growth factor A-chain and c-myc gene expressions by angiotensin II in cultured rat vascular smooth muscle cells. J Clin Invest 1989; 83: 1419-24.
7. Itoh H, Mukoyama M, Pratt RE, Gibbons GH, Dzau VJ. Multiple autocrine growth factors modulate vascular smooth muscle cell growth in response to angiotensin II. J Clin Invest 1993; 91: 2268-74.
8. Cleland JG, Erhardt L, Murray G, Hall AS, Ball SG. Effect of ramipril on morbidity and mode of death among survivors of acute myocardial infarction with clinical evidence of heart failure. A report from the AIRE Study Investigators. Eur Heart J 1997; 18: 41-51.

9. Greenberg B, Quinones MA, Koilpillai C, *et al*. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction. Results of the SOLVD echocardiography substudy. Circulation 1995; 91: 2573-81.
10. Fabre JE, Rivard A, Magner M, Silver M, Isner JM. Tissue inhibition of angiotensin converting enzyme activity stimulates angiogenesis *in vivo*. Circulation 1999; 99: 3043-9.
11. Gohlke P, Kuwer I, Schnell A, Amann K, Mall G, Unger T. Blockade of bradykinin B2 receptors prevents the increase in capillary density induced by chronic angiotensin-converting enzyme inhibitor treatment in stroke-prone spontaneously hypertensive rats. Hypertension 1997; 29: 478-82.
12. Rentrop KP, Cohen M Blanke H, Phillips RA. Changes in collateral filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. J Am Coll Cardiol 1985; 5: 587-92.
13. Morbidelli L, Parenti A, Giovanelli L, Granger HJ, Ledda F, Ziche M. B1 receptor involvement in the effect of bradykinin on venular endothelial cell proliferation and potentiation of FGF-2 effects. Br J Pharmacol 1998; 124: 1286-92.
14. Miura S, Matsuo Y, Saku K. Transactivation of KDR/Flk-1 by the B2 receptor induces tube formation in human coronary endothelial cells. Hypertension 2003; 41: 1118-23.
15. Adair TH, Gay WJ, Montani JP. Growth regulation of the vascular system: evidence for a metabolic hypothesis. Am J Physiol 1990; 259: R393-404. (Review)
16. Conway EM, Collen D, Carmeliet P. Molecular mechanisms of blood vessel growth. Cardiovasc Res 2001; 49: 507-21. (Review)
17. Cohen M, Rentrop KP. Limitation of myocardial ischemia by collateral circulation during sudden controlled coronary artery occlusion in human subjects: a prospective study. Circulation 1986; 74: 469-76.
18. Gosgnach W, Challah M, Coulet F, Michel JB, Battle T. Shear stress induces angiotensin converting enzyme expression in cultured smooth muscle cells: possible involvement of bFGF. Cardiovasc Res 2000; 45: 486-92.
19. Miura S, Nishikawa H, Zhang B, *et al*. Angiotensin-converting enzyme inhibitor promotes coronary collateral circulation in patients with coronary artery disease. Circ J 2003; 67: 535-8.
20. Imaizumi S, Miura S, Nishikawa H, *et al*. Angiotensin II type 1 receptor blockers do not promote coronary collateral circulation in patients with coronary artery disease. Hypertens Res 2006; 29: 135-41.
21. Emanueli C, Salis MB, Stacca T, Pinna A, Gaspa L, Madeddu P. Angiotensin AT_1 receptor signaling modulates reparative angiogenesis induced by limb ischaemia. Br J Pharmacol 2002; 135: 87-92.
22. Sasaki K, Murohara T, Ikeda H, *et al*. Evidence for the importance of angiotensin II type 1 receptor in ischemia-induced angiogenesis. J Clin Invest 2002; 109: 603-11.
23. Schieffer B, Wirger A, Meybrunn M, *et al*. Comparative effects of chronic angiotensin-converting enzyme inhibition and angiotensin II type 1 receptor blockade on cardiac remodeling after myocardial infarction in the rat. Circulation 1994; 89: 2273-82.
24. Horuichi M, Akishita M, Dzau VJ. Recent progress in angiotensin II type 2 receptor research in the cardiovascular system. Hypertension 1999; 33: 613-21.
25. Abaci A, Oguzhan A, Kahraman S, *et al*. Effect of diabetes mellitus on formation of coronary collateral vessels. Circulation 1999; 99: 2239-42.
26. Johansen OE, Birkeland KI. Preventing macrovascular disease in patients with type 2 diabetes mellitus. Am J Cardiovasc Drugs 2003; 3: 283-97. (Review)
27. Pellinen TJ, Virtanen KS, Toivonen L, Heikkila J, Hekali P, Frick MH. Coronary collateral circulation. Clin Cardiol 1991; 14: 111-8.
28. Ilia R, Carmel S, Cafri C, Gueron M. Coronary collaterals in patients with normal and impaired left ventricular systolic function. Int J Cardiol 1998; 63: 151-3.
29. Levin DC. Pathways and functional significance of the coronary collateral circulation. Circulation 1974; 50: 831-7.