The Heart Surgery Forum #2005-1113
8 (5), 2005 [Epub September 2005]
doi:10.1532/HSF98.20051113

Online address: http://cardenjennings.metapress.com/link.asp?id=112496

Influence of Angiotensin Converting Enzyme Insertion/Deletion Polymorphism on Long-term Total Graft Occlusion after Coronary Artery Bypass Surgery

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ABSTRACT

Background: The renin-angiotensin system has a very important role in coronary thrombosis and restenosis. Plasma angiotensin converting enzyme (ACE) activity is associated with an insertion/deletion polymorphism in the gene coding for ACE. It is known that there is a strong correlation between ACE DD and atherosclerosis. However, little has been documented about its role in venous graft failure. The objective of this study was to investigate the relationships among the ACE gen polymorphism and long-term vein graft occlusion.

Methods: The study population consisted of 87 consecutive white patients with symptomatic coronary artery disease in the previous month, who had had aorto-coronary bypass surgery (ACBS) more than 5 years back and who underwent coronary angiography for diagnostic purposes. On the same day as angiography, 10 mL whole blood was taken for ACE gene insertion/deletion (I/D) polymorphism.

Results: Mean age of the patients was 64.4 ± 8.6 years, and 71 (82%) of the patients were men. The average ACBS time was 7.9 ± 1.9 years. The ACE genotype was II in 15 patients (17.2%), ID in 47 patients (54.0%), and DD in 25 patients (28.7%). Thus, D allele frequency was .82. There was no significant difference between the cases with regard to age, body mass index, blood pressure status, plasma glucose level, plasma lipid profile, smoking status, average of ACBS time or family history of coronary heart disease. In ACE II group 5 patients had total venous graft occlusion, in ACE ID group 27 patients had total occlusion and in ACE DD group 20 patients had at least one graft total occlusion. The frequency of the venous graft occlusion about total venous grafts is 36% in the ACE II group, 49% in the ACE ID group, and 80% in the ACE DD group (P = .01).

Conclusion: The ACE I/D gene polymorphism is associated with long-term survival of venous conduit. The ACE DD genotype or D allele influences the angiographic outcome of patients post-ACBS. These data suggest that routine determination of the ACE genotype may help identify patients who are at higher risk of venous graft failure after ACBS.

Received April 12, 2005; received in revised form May 17, 2005; accepted May 30, 2005.

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INTRODUCTION

Evaluation of the saphenous vein graft used in aorto-coronary bypass surgery (ACBS) has taken a long time. The objective of the graft is to relieve symptoms, alleviate ischemia, and reduce the possibility of cardiac events. It is known that the saphenous vein graft is the standard conduit. Approximately 80% of vein grafts are open for 5 years after operation. After 5 to 7 years, the progression of atheromatous disease in coronary bypass vein graft appears [Fitzgibbon 1996]. The late occlusion of vein grafts is associated with thrombosis at the site of atherosclerotic lesions. It is known that vein graft occlusion is associated with dislipidemia and smoking [Campeau 1984]. It was demonstrated that the haptoglobin 2-2 genotype polymorphism influences graft survival time in patients who underwent ACBS [Delange 1997]. This point is important for a role of genetic factors of coronary artery bypass graft survival. The ACE gene polymorphism is created by the insertion (I allele) or deletion (D allele) of a 287 base-pair DNA sequence within intron 16. An insertion–deletion polymorphism of the angiotensin converting enzyme gene has been reported to be associated with an increased risk of atherosclerotic coronary artery disease [Ruiz 1994, Gardemann 1995, Mattu 1995]. The DD genotype shows higher plasma ACE and Ang II levels compared to individuals with the II or ID genotypes [Rigat 1990]. Agerholm-Larsen et al demonstrated that there was no evidence in the development of myocardial infarction or any other manifestations of ischemic heart disease between genotype classes of the ACE gene polymorphism [Agerholm-Larsen 1997]. Until now, the relationships among ACE genotype and graft occlusion after long-term ACBS have not been demonstrated in the literature. The present study has been designed to determine the influence of ACE gene polymorphism on long-term saphenous graft occlusion.

MATERIALS AND METHODS

Study Population

The study population consisted of 87 consecutive white patients with symptomatic coronary artery disease lasting for a month and who had undergone ACBS surgery before >5 years and who underwent coronary angiography for diagnostic purposes. All the subjects were evaluated with a detailed questionnaire and physical examination. The questionnaire provided information about risk factors such as smoking, diabetes mellitus, hypertension, family history, and presence of new angina pectoris. Laboratory data were obtained from medical records. Patients, who had current smoking history or smoking history after ACBS were not included in the study. Patients were classified into three groups according to their ACE I/D genotypes. The study protocol was approved by the ethics committee. Medications included ACE inhibitors, beta blockers, diuretics, angiotensin receptor blockers, isosorbid mononitrates, statins, and oral anti-diabetics.

Cardiac Catheterization

Angiography is the most frequently used method for the determination of vein graft patency. It was performed by the Judkins technique with femoral approach. Selective coronary angiography, selective graft angiography, and left ventriculography were performed. Definitions for native artery stenosis are as follows: Single coronary artery disease is a narrowing of the coronary artery diameter of the lumen by 50% in one of the native coronary arteries, such as the left anterior descending artery, the circumflex artery, the right coronary artery, or their major branch. Double vessel disease is a narrowing of the diameter of the lumen by more than 50% in two native coronary arteries and three vessel disease is a narrowing of the diameter of the lumen by more than 50% in three native coronary arteries.

Definitions for graft failure are as follows: Single graft disease is a narrowing of the vein graft diameter of the lumen by 50% in one of the vein grafts, such as the left anterior descending artery–saphenous vein, the circumflex artery (optus marginalis)–saphenous vein , the right coronary artery (posterior descending artery–saphenous vein), or another major branch (such as the diagonal artery–saphenous vein). Double vessel disease is a narrowing of the diameter of the graft lumen by more than 50% in two grafts and three vessel disease is a narrowing of the diameter of the graft lumen by more than 50% in three grafts.

Genetic Analysis

On the same day as angiography, 10 mL whole blood was obtained. Deoxyribonucleic acid (DNA) was extracted from the whole blood by lysing the red blood cells and digesting the cell pellet with proteinase K. Extracted DNA was stored at –20°C until genotyping was performed. The genotype was then determined by the polymerase chain reaction (PCR) and subsequent gel electrophoresis of the PCR products. To eliminate mistyping subjects with ACE I/D genotype as D homozygous, DNA genotyped as homozygous for the D allele was reamplified with an insertion-specific primer pair, which recognizes only the insertion sequence. The laboratory responsible for genotyping was blinded for clinical values and angiographic data of the patients.

Statistics

Statistical analysis was performed with SPSS 12.0 program. All continuous variables were reported as mean ± SD. To compare variables between the three groups, ANOVA and Scheffe post-hoc test was used for continuous data, and Chi-square test used for categorical data. $P < .05$ was considered statistically significant.

RESULTS

Characteristics of the Study Population

Mean age of the patients was 64.4 ± 8.6 years, and 71 (82%) of the patients were men. Average of the ACBS time was 7.9 ± 1.9 years. The ACE genotype was II in 15 patients (17.2%), ID in 47 patients (54.0%), and DD in 25 patients (28.7%). Thus D allele frequency was .82. The baseline characteristics of the study population are shown in Table 1. There was no significant difference among the cases with regard to age, body mass index, blood pressure status, plasma glucose level, plasma lipid profile, smoking status, or family history of coronary heart disease or medical treatment.

Genotype-Stenosis Association

The native coronary artery's angiographic data of the subjects was determined: Three vessel disease in 20 patients, two vessel disease in 5 patients in ACE DD group; three vessel disease in 35 patients, two vessel disease in 12 patients in ACE ID group; three vessel disease in 9 patients, two ves-

Table 1. Patients Characteristics*

Groups	ACE II	ACE ID	ACE DD	P
Clinical	n = 15	n = 47	n = 25	
Age, y (SD)	64.2 ± 6.4	62.5 ± 9.4	67.3 ± 7.2	ns
Female/male	3/12	8/39	5/20	ns
BMI	28.3 ± 1.6	29.0 ± 2.2	28.9 ± 2.0	ns
EF, %	44.7 ± 9.3	44.0 ± 10.9	48.6 ± 11.9	ns
ACBS time, y	7.9 ± 1.6	7.8 ± 1.9	8 ± 2.3	ns
DM	3 (20%)	13 (27.6%)	3 (12%)	ns
Chol.	4 (26%)	11 (23.4%)	8 (32%)	ns
HT	4 (26.6%)	10 (21.2%)	7 (28%)	ns
Drug therapy				
Nitrates	10 (66%)	30 (63%)	15 (60%)	ns
ACE inhibitors	8 (53%)	26 (55%)	14 (56%)	ns
Digitalis	2 (13%)	8 (17%)	4 (16%)	ns
Diuretics	3 (20%)	10(22%)	5 (20%)	ns
B-blockers	12(80%)	36 (76%)	18(72%)	ns
Spironolacton	4 (26%)	10 (21%)	6 (24%)	ns
Statins	8(53%)	24(51%)	12 (48%)	ns

*BMI indicates body mass index; EF, ejection fraction; ACBS, aorto coronary bypass surgery; DM, diabetes mellitus; and ns, not significant.

Table 2. Data on Angiographic Characteristics

Grafts	ACE II		ACE ID		ACE DD		
	Occ.	Patent	Occ.	Patent	Occ.	Patent	*P*
Lad-saph. (n = 11)	-	-	3	3	5	-	ns
Lad-lima (n = 76)	-	15	-	41	-	20	
Cx-saph (n = 75)	4	8	22	18	18	5	.03
Rca-saph (n = 56)	4	6	12	17	13	4	.05
Other (n = 4)	-	-	2	2	-	-	
Total (n = 222)	8	29	39	81	36	29	.01

*Occ indicates occluded; ns, not significant; Lad, left anterior descending artery; Saph, saphenous vein; Lima, left internal thoracic artery; Cx, circumflex artery; Rca: right coronary artery.

sel disease in 6 patients in ACE II group. In addition, 222 grafts (76 arterial grafts, 146 venous grafts) were investigated. In the ACE II group a total of 22, in the ACE ID group a total of 79, and in the ACE DD group a total of 45 saphenous venous conduits were investigated. All of the arterial conduits (implanted left anterior descending artery) were opened. Fifty-eight percent of the venous grafts had 100% occlusion. Data on angiographic characteristics of the grafts were demonstrated in Table 2. In ACE ID group, 5 patients had at least 1 total venous graft occlusion; in ACE ID group, 27 patients had total occlusion; and in ACE DD group, 20 patients had total occlusion. The frequency of the graft occlusion at least once is 33% in the ACE II group, 57% in the ACE ID group, and 80% in the ACE DD group. Our data demonstrated that the frequency of the venous graft failure about total venous grafts is 36% in ACE II group, 49% in ACE ID group, and 80% in DD groups. Also, there is a statistical significance between total graft occlusion and ACE genotype ($P = .01$). We could not find any significance between ACE gene polymorphism and the number of occluded grafts in the same patient ($P = .462$)

DISCUSSION

In the present study, we determined the impact of ACE I/D gene polymorphism on survival after coronary artery bypass venous grafting. The ACE genotype exhibits an insertion/deletion polymorphism resulting in three genotypes (DD, ID, II), which affect serum and tissue ACE activity. Coronary artery disease is a multifactorial disease and many environmental, genetic factors develop ischemic heart disease, exceptionally in coronary artery bypass grafting. Coronary artery bypass grafting using saphenous vein conduits, with or without arterial conduits, is standard treatment for intractable angina due to coronary artery disease, but it is possible to see the development of vein graft failure over many years. The graft failure rate has been estimated at 1-2% per year between 1 and 6 years, and at 4% per year between 6 and 10 years after surgery [Bourassa 1991, Fitzgibbon 1996]. It is known that vein graft occlusion is associated with dislipidemia and smoking [Campeau 1984]. Some investigators believe that 3-5 years after the ACBS, the histological appearance of occluded or obstructed coronary bypass grafts is consistent with atherosclerosis [Motwani 1998]. Also, Delange et al demonstrated that the haptoglobin 2-2 genotype had been shown to be associated with a shortened graft survival time in patients who underwent ACBS [Delange 1997]. This study is very important to show a role of genetic factors of coronary artery bypass graft survival.

It is known that the renin angiotensin aldosterone system (RAAS) is very important in the pathogenesis of atherosclerosis and in the remodeling of venous bypass grafts, because angiotensin II causes vasoconstruction, activates matrix synthesis, stimulates the proliferation of cultured vascular smooth-muscle cells, accelerates the synthesis of platelet-derived growth factor in vascular smooth-muscle cells, and causes hypertrophic changes of the vessel wall [Bonithon-Kopp 1994]. ACE is involved in coronary thrombosis, vasoconstruction, and smooth muscle cell proliferation. However, high levels of ACE may increase the risk of coronary thrombosis, among Ang II it facilitates oxidation of the LDL-C particle, and develops atherosclerosis. Also, it has a chemotaxis effect for neutrophilia, monocytes, and T lenfocytes [Farber 1990]. All of them are very important for atherosclerosis. Rigat et al first described I/D polymorphism in intron 16 of the angiotensin I-converting enzyme (ACE) gene [Rigat 1990]. The angiotensin I converting enzyme (ACE) I/D gene polymorphism has been used in the clinical manifestations of coronary atherosclerosis too [Cambien 1992, Oike 1995, Samani 1996]. Some studies have found that the level of plasma ACE is partly under genetic control [Cambien 1988]. Subjects who have the ACE D allele have a higher concentration of circulating ACE than those who have the I allele. It means that there is a strong correlation between ACE gene polymorphism and plasma ACE activity [Rigat 1990]. Increasing ACE activity increases Ang II level too. Ang II is a potent vasoconstrictor and inactivator of bradykinin resulting in decreased myocardial perfusion [Ehlers 1989]. Induced stimulation of plasminogen activator 1 may cause the formation of thrombus. Ang II at the same time decreases NO and vasodilatator prostaglandine levels [Finta 1993]. Some studies in the literature suggest that ACE D allele may have a higher risk of myocardial infarction [Cambien 1988], in-stent restenosis [Amant 1997, Ribichini 1998], and sudden death [Evans 1994]. But some studies show controversial results. Koch et al found that the ACE DD genotype or D allele does not influence the one year clinical and angiographic outcome of patients undergoing coronary stent placement [Koch 2000]. Agerholm-Larsen et al showed that there is no evidence in the development of myocardial infarction or any other manifestations of ischemic heart disease between genotype classes of the ACE gene polymorphism [Agerholm-Larsen 1997].

Völzke et al found that the ACE DD genotype is associated with increased midterm mortality (after 2 years) and cardiac morbidity after coronary bypass surgery [Völzke 2002]. O'Donohoe et al demonstrated that elevated ACE in the endothelial layer causes the intimal hyperplasia of experimental vein grafts [O'Donohoe 1994]. For this reason we investigated the importance of the ACE I/D gene polymorphism on long-term graft occlusion after ACBS. There is little data about the correlation with ACE gene polymorphism and

graft occlusion. Our data has demonstrated that there is a high risk of graft failure for a long time in subjects who had the ACE DD genotype. It was probably increasing ACE activity and Ang II levels that caused this high risk.

Late period occurrence of the vein graft occlusions can cause some suspect for the study group. All of the cases have been operated according to standard ACBS procedure in our institution by different surgeons. Vein graft failure is related to multiple factors, such as technical points that include the individual surgeon's skill, the method to protect the venous endothelium during harvesting, the match of the vein and targeting coronary arteries. It is known that technical procedure that may cause thrombotic closure at the anastomoses can be seen within the early period (in the first month) after surgery. The accelerated process of intimal hyperplasia and thickening in the early stage of atherosclerotic plaque formation is seen in the venous graft after coronary bypass surgery too. If the proliferation of atherosclerotic plaque is severe, it may occur at the site of anastomosis between grafts and the recipient artery, total occlusion can occur within one year [Morrow 2005]. However, the study group had normal quality of life after the operation and had begun to have anginal complaint in the last month. Consequently, it is thought that graft occlusion improvement in the late period can be the result of present complaints.

The genotype, theoretically, should be also related to the occlusion of arterial grafts, not only the vein graft. In the present study, we did not determine the impact of ACE I/D gene polymorphism in survival arterial conduits such as internal mammary artery (IMA). Comparative morphological and angiographic studies of IMA and saphenous vein bypass grafts that have been implanted for long-term show that accelerated atherosclerosis occurs commonly in saphenous vein grafts but is extremely rare in IMA grafts [Morrow 2005]. The high patency rate of arterial conduit probably relates to the presence of endothelial vasodilatory factors, which is very important for atherosclerosis. The endothelium of the IMA produces significantly more prostacyclin than that of the saphenous vein and may explain the more endothelium-dependent relaxation and may allow flow-dependent autoregulation. Fibrointimal proliferation develops in IMA graft too, and may be a factor in late graft occlusion. In this study if the late term angiography was performed or a more long-term follow-up was obtained it would have been possible to find a correlation between ACE gene polymorphism and arterial conduit occlusion.

LIMITATIONS OF THE STUDY

This present study is not a prospective and controlled trial. A small number of patients is a limitation of this study. It is known that the genotype is also related to the progressive disease of the native coronary artery. However, the aim of the study was to investigate the role of the ACE gene polymorphism and vein graft occlusion rather than to investigate the native coronary disease progression. Preoperative coronary angiography films were not present for all of the study group. Therefore, it is not possible to give the comparison between preoperative native coronary disease and present coronary artery disease. As a result, the relation between the ACE genotype and progression of the native coronary artery disease was not able to be investigated. In this study the occlusion rate at the long term is among the worst results. Patients included in this study were all symptomatic in the last month prior to angiography and asymptomatic patients were not present. Some of them are in unstable angina. High occlusion rate might be due to the characteristics of the study group. In conclusion, prospective studies with larger patient populations are needed to clarify the long-term efficacy of the ACE gene polymorphism in vein and arterial graft failure.

CONCLUSION

The ACE I/D gene polymorphism is associated with long-term survival of venous conduit. The ACE DD genotype or D allele influences venous graft failure of patients post-ACBS. These data suggest that routine determination of the ACE genotype may help identify patients who are at higher risk of venous graft failure after ACBS.

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