Effect of Diabetes Mellitus on Formation of Coronary Collateral Vessels

Adnan Abacı, MD; Abdurrahman Oğuzhan, MD; Sinan Kahraman, MD; Namık Kemal Eryol, MD; Şükrü Ünal, MD; Hüseyin Arınc, MD; Ali Ergin, MD

Background—Although myocardial ischemia is known to be significantly related to the development of coronary collateral vessels (CCVs), there is considerable variation between patients with ischemic heart disease in the presence of collateral development. The nature of this variability is not well known. Likewise, it remains unclear whether diabetes mellitus (DM) has any effect on CCVs. The aim of this study was to evaluate the effect of DM on CCVs.

Methods and Results—Of the patients who underwent coronary angiography during the interval between March 1, 1993, and June 20, 1998, in our institution, 306 were diabetic. Those patients in whom coronary angiography is normal or severity of coronary artery stenosis is thought not to be sufficient for the development of CCVs (<75%) were excluded from the study. A total of 205 patients (mean age, 59±8 years) met the criteria for the DM group. For case-control matching, 205 consecutive nondiabetic patients (mean age, 58±9 years) who had ≥1 diseased vessel with >75% stenosis were included in the control group. The CCVs were graded according to the Rentrop scoring system, and the collateral score was calculated by summing the Rentrop numbers of every patient. There was no statistical difference between patients with and without DM in clinical baseline characteristics. The mean number of diseased vessels in the DM group (1.58±0.68) was higher than that in the nondiabetic group (1.42±0.65, P=0.005). The mean collateral score was 2.41±2.20 in the DM group and 2.60±2.39 in the control group. After confounding variables were controlled for, the collateral score in the diabetic group was significantly different from that in the nondiabetic group (P=0.034).

Conclusions—Our findings suggest that CCV development is poorer in patients with than in patients without DM. Thus, we can speculate that DM is an important factor affecting CCV development. (Circulation. 1999;99:2239-2242.)

Key Words: collateral circulation • coronary disease • diabetes mellitus

Collaterals develop in the advanced stages of coronary atherosclerosis. Although all aspects of the mechanisms underlying the development of coronary collaterals are not well known, the pivotal role of myocardial ischemia is well established. However, there is considerable variation between patients with ischemic heart disease in the presence of collateral development. The factors responsible for this variation are not well known. Histological studies documented thin-walled capillarylike morphology of “mature” collaterals in the early stages of its development. In later stages of development, collaterals actively grow, as demonstrated by mitotic activity in the endothelial and smooth muscle cells. Endothelial cells are important in this collateral maturation process. Coronary artery disease patients with diabetes mellitus (DM) have a less favorable outcome compared with those without diabetes, including a 3- to 4-fold increase in mortality risk. Moreover, diabetic patients whose tests sustain a nonfatal myocardial infarction experience a more complicated course, including more frequent postinfarction angina, infarction extension, and congestive heart failure. The precise mechanism underlying this unfavorable effect is not clear. However, diffuse endothelial dysfunction is thought to be one of the important elements in this process. Endothelial cells are important in the development and maturation of coronary collaterals. Accordingly, we sought to evaluate the relationship between DM and coronary collaterals in patients with advanced coronary artery disease. We have reviewed the coronary angiograms of all diabetic patients that underwent coronary angiogram in our institution in a 5-year period and compared them with those of a control group.

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Methods

Patient Population
Between March 1, 1993, and June 20, 1998, 5223 patients underwent coronary angiography in our institution. Of these patients, 306 were diabetic, defined as patients who were treated with insulin or oral hypoglycemic agents. Of the 306 patients, those with <75% diameter stenosis, those who received nitrates or calcium channel blockers immediately before the procedure, and those with technically inadequate studies were excluded from this study. The remaining
205 patients constituted the DM group. The control group consisted of 205 consecutive patients with ≥1 coronary stenosis with >75% narrowing. Clinical information, including age, weight, sex, history of hypertension, serum cholesterol level, smoking, clinical presentation, and history of prior myocardial infarction, was obtained from a review of the patient’s chart.

Coronary Collateral Filling
Selective coronary angiography was performed in multiple orthogonal projections using the Judkins or Sones technique after administration of 5000-U intravenous heparin. Coronary artery stenosis was estimated visually by 2 independent observers who were blinded to the identities and clinical information of the patients. Single-vessel disease was defined as >75% diameter stenosis in only 1 coronary artery. Two- and 3-vessel diseases were defined according to the same criteria. Collateral vessels were graded according to the Rentrop classification: 0=no filling of any collateral vessels, 1=filling of 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. The reproducibility of this grading system has previously been validated.6 The collateral score was based on the injection that best opacified the collateralized vessel. The collateral score was calculated by summing the Rentrop numbers of every patient.

Statistical Analysis
Continuous variables were expressed as mean±SD. The relation between the continuous variables was evaluated by use of the unpaired Student t test. The χ² test with Yates’ continuity correction was used to assess the significance of difference between dichotomous variables. Correlations between collateral score and other variables were analyzed by linear regression analysis. ANCOVA was used to assess the confounding effects of variables on comparisons of the groups according to DM status. Variables analyzed included age, sex, weight, previous myocardial infarction, hypertension, serum cholesterol level, number of diseased vessels, and smoking status. For all tests, P>0.05 was designated nonsignificant, and a value of P<0.05 was considered statistically significant. The SPSS statistical software package (version 5.0) was used to perform all statistical calculations.

Results
Patient Characteristics
Table 1 describes the clinical baseline characteristics of the study patients. The 2 groups were well matched in terms of baseline clinical characteristics. Mean age and distribution of risk factors for coronary disease did not differ significantly between groups. The proportion of patients with a history of myocardial infarction was similar in both groups. A similar proportion of patients in both groups had stable or unstable angina. Most patients were male in the 2 groups. The severity of coronary stenosis was similar in the 2 groups (Table 2), but the mean number of diseased vessels was significantly higher in the DM patients (P=0.005). One-vessel disease occurred more frequently in the nondiabetic group. In contrast, 2- and 3-vessel diseases were more common in the diabetic group. Therefore, the difference between diabetic and nondiabetic patients according to the angiographic variables was only in number of diseased vessels. By linear regression analysis, the collateral score was not related to age, smoking habits, hypertension, or total serum, LDL, or HDL cholesterol. Although sex was not significantly different between the 2 group, there was a weak relation between collateral score and sex (r=0.109, P=0.025). As expected, there was a significant relation between collateral score and number of diseased vessels (r=0.441, P<0.0001). The mean collateral score was 2.41±2.20 in the DM group and 2.60±2.39 in the control group.

Multivariate Analysis
The effect of these factors on collateral score was evaluated by performing an ANCOVA with DM as a factor and sex, age, weight, serum cholesterol level, smoking habits, previous myocardial infarction, and number of diseased vessels as covariates. Although the collateral score was related only to sex and the number of diseased vessels, other variables were also examined by multivariate analysis to exclude any possible interactions between these variables. After confounding variables were controlled for, the collateral score in the DM group (2.41±2.20) was significantly different from that in the nondiabetic group (2.60±2.39, P=0.034). The variables of sex and number of diseased vessels were the only important confounding variables of the collateral score after ANCOVA (r=0.115, P=0.015; r=0.467, P<0.001, respectively).

<table>
<thead>
<tr>
<th>Clinical Variables</th>
<th>Diabetic (n=205)</th>
<th>Nondiabetic (n=205)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59.08±8.49</td>
<td>58.89±9.11</td>
<td>NS</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>148 (72)</td>
<td>155 (75)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76.89±13.83</td>
<td>74.92±14.64</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>96 (46)</td>
<td>103 (50)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>112 (54)</td>
<td>101 (49)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum cholesterol level, mg/dL</td>
<td>210±23</td>
<td>206±24</td>
<td>NS</td>
</tr>
<tr>
<td>Serum LDL level, mg/dL</td>
<td>135±22</td>
<td>132±24</td>
<td>NS</td>
</tr>
<tr>
<td>Serum HDL level, mg/dL</td>
<td>35±5</td>
<td>34±6</td>
<td>NS</td>
</tr>
<tr>
<td>Stable angina pectoris, n (%)</td>
<td>82 (40)</td>
<td>80 (39)</td>
<td>NS</td>
</tr>
<tr>
<td>Unstable angina pectoris, n (%)</td>
<td>32 (16)</td>
<td>29 (14)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous myocardial infarction, n (%)</td>
<td>43 (21)</td>
<td>34 (17)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are mean±SD when appropriate.

<table>
<thead>
<tr>
<th>Angiographic Variables</th>
<th>Diabetic (n=205)</th>
<th>Nondiabetic (n=205)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of diseased vessels</td>
<td>1.58±0.68</td>
<td>1.42±0.65</td>
<td>0.015</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>108 (52)</td>
<td>136 (66)</td>
<td>0.017</td>
</tr>
<tr>
<td>1-Vessel disease</td>
<td>74 (36)</td>
<td>51 (25)</td>
<td>0.017</td>
</tr>
<tr>
<td>3-Vessel disease</td>
<td>23 (11)</td>
<td>18 (9)</td>
<td>0.017</td>
</tr>
<tr>
<td>Target lesion stenosis, %</td>
<td>86.32±18.04</td>
<td>86.66±19.21</td>
<td>NS</td>
</tr>
<tr>
<td>LAD</td>
<td>83.37±19.64</td>
<td>83.16±22.58</td>
<td>NS</td>
</tr>
<tr>
<td>Cx</td>
<td>83.05±20.63</td>
<td>80.20±24.75</td>
<td>NS</td>
</tr>
</tbody>
</table>

LAD indicates left anterior descending artery; Cx, circumflex artery; and RCA, right coronary artery.
Discussion
In the present study, the importance of DM in the development of coronary collateral vessels is documented by the finding that the prevalence of collateral circulation in DM patients is much lower than in those without DM.

DM and Coronary Collateralization
Development of collateral vessels is triggered by the pressure gradient between the coronary bed of arteries caused by an obstruction and myocardial ischemia.1,2 However, a lack of collateral vessels in some patients despite the presence of coronary obstruction and evidence of myocardial ischemia suggests that additional factors may contribute to collateral development. Limited data are available on the effect of DM on collateral development. The present study includes the largest patient population reported thus far. DM has been found to be an inhibiting factor on coronary collateral development in a small clinic13 and a postmortem study.14 In an another study, the effect of carbohydrate intolerance with or without DM on collateral development was examined.15 Those investigators have claimed that although DM is known to affect the vascular tree, these underlying abnormalities do not inhibit the formation of collateral vessels, and DM affects small arteries, but the collateral channels usually represent large epicardial vessels that do not appear to be influenced by DM. However, it must be kept in mind that collaterals are also small vessels at the beginning of their formation. Therefore, it seems it is not possible to explain their findings with that assumption. Also, in the study of Heinle et al.,16 data from a large group of patients with collaterals (80 patients) were compared with the findings of a much smaller group without such vessels (16 patients). It is conceivable that the statistical power of such a comparison is low.

The most interesting aspect of coronary anastomosis is their ability to respond with growth when the large epicardial arteries become stenosed or occluded and the tissue becomes potentially ischemic.9 It is now widely accepted that myocardial ischemia somehow triggers collateral growth.20–21 A biochemical signal produced by ischemic myocardium may trigger the events leading to DNA synthesis and to mitosis in both endothelial and smooth muscle cells.7 The endothelium leads the process of growth adaptation; smooth muscle follows.9 Over the past decade, numerous angiogenic factors have been purified, and their amino acid sequences have been determined with subsequent gene cloning.22 In a canine model of myocardial ischemia, intracoronary infusion of vascular endothelial growth factor into the ischemic territory has been shown to accelerate native collateral development.24 Basic fibroblast growth factor has also been shown to enhance collateral development in a canine model of gradual coronary occlusion.25

There has been increasing interest in the literature in the functional impact of DM on coronary vascular function. It has been shown that a high concentration of glucose causes endothelial cell dysfunction.26–28 Because the function of the endothelium is important in collateral development and there is dysfunction of endothelium in DM, our finding that the prevalence of collateral circulation in patients with DM is much lower than those without DM may be explained by the effect of DM on endothelial function. It should also be noted that nitric oxide production is impaired in DM,29 and nitric oxide seems to be involved in vascular endothelial growth factor–induced angiogenesis.30

Study Limitations
In the interpretation of our findings, several limitations must be considered. First, angiographically visible collaterals represent only a fraction of the total collateral vessels because collaterals are angiographically demonstrable only when they reach 100 μm. Moreover, angiography may not detect most collaterals situated intramurally. Therefore, the collaterals visualized by angiography may not accurately quantify collateral circulation. But the effect of this problem on collateral score must be same in the 2 groups and thus should not change the interpretation of our results. Second, although the effects of clinical variables on collateral score were evaluated by multivariate analysis, because the effects of all potential confounding patients characteristics cannot be retrospectively controlled, there may be factors that were not taken into account that may have influenced our results. The most important of these uncontrolled variables was the physical activity of study patients. Improvement in coronary collateral circulation after exercise training has been shown.31,32 However, exercise is part of DM therapy; physicians recommend that DM patients perform regular physical activity. Therefore, there is no reason for the DM patients to be less physically active than those without DM. Moreover, it is possible that the DM patients tended to exercise more than the nondiabetics. Finally, and most importantly, the present study is a retrospective, observational one. However, the angiographic and clinical data belong to the same period and come from the same laboratory without substantial changes in management strategy.

Clinical Implications
This investigation is the first study with a large number of patients to show the relationship between DM and collateral vessel development. It demonstrates that collateral vessel development is poorer in DM than in nondiabetic patients. We can speculate that DM is an important factor among the factors affecting the development of coronary collaterals.

We believe that in the future, a complete understanding of the exact mechanisms of collateral growth and regression will help to establish a new therapeutic strategy for patients with coronary artery disease. Although this is not a biochemical study investigating the relation between DM and growth factors, it may stimulate such a study in this interesting field.

References
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_Circulation_. 1999;99:2239-2242
doi: 10.1161/01.CIR.99.17.2239

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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