Effect of Diabetes Mellitus on Coronary Collateral Vessels

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DİABETES MELLİTÜS'ÜN KORONER KOLLETERAL DAMARLAR ÜZERİNE ETKİSİ

ÖZET

Normal ile stenotik vasküler bölgeler arası basınç gradienti kollateral gelişiminde en önemli faktördür. İskemik kalp hastalarındaki bireysel farklılıklardan sorumlu olan faktörler net olarak bilinmemektedir. Aynı şekilde diabetes mellitusun (DM) kollateral gelişimi üzerine olan etkiside net değildir. Koroner anjiyografi kollateral sirkülasyonu değerlendirmede en sık kullanılan metod olmakla birlikte kollaterallerin çoğunluğunun intramural olması ve anjiyografik olarak görülemeyecek derecede olabilmeleri sebebiyle yetersiz kalabilir. İntrakoroner basınç ölçümleri kollateral sirkulasyonun kantitatif ve kesin tayininde kullanılan bir tetkik yöntemidir. Biz bu çalışmada iskemik kalp hastalarında DM'un koroner kollateral gelişimi üzerine olan etkisini intrakoroner basınç ölçümleri yoluyla araştırdık.

Çalışmaya iskemik kalp hastalığı olan ve iskemik semptomları enaz bir noninvazif tetkik ile ispat edilerek kateter laboratuarına refere edilen, anjiyografisinde tek damar hastalığı olan ve bu damarına PTCA ve/veya stent implantasyonu yapılan 40 hasta dahil edildi (20 diabetik). Koroner anjiyografiyi takiben fiberoptik basınç ölçer tel dilate edilecek olan darlığın distaline yerleştirildi. Aynı tel anjiyoplasti kateteri için de kılavuz olarak kullanıldı. Balon ile tam oklüzyon sağlandığı anda distalden alınan basınç koroner tıkalı basıncı (KTB) olarak kaydedildi. Daha değerli bir parametre olarak kollateral akım indeksi (KAI) simultane olarak kaydedilen KTB'nin ortalama aortik basınca (AB) oranlanması ile belirlendi (KAI= KTB/AB).

Basınç ölçümleri 20 diabetik ve 20 nondiabetik hastada yapıldı. Ortalama KTB diabetik grupta 18.1 ± 8.6 mmHg ve nondiyabetik grupta 26.8 ± 9.6 mmHg olarak tespit edildi ve bu farklılık istatistiki olarak anlamlıydı ($p<0.05$). Aynı şekilde ortalama KAI değeri diyabetik grupta anlamlı ölçüde düşük bulundu (diyabetik grupta KAI : 0.17 ± 0.08, nondiyabetik grupta KAI : 0.25 ± 0.09, $P<0.05$)

Bu çalışma diyabetik hastalarda koroner kollateral gelişimin nondiyabetiklere göre anlamlı derecede az olduğunu göstermiştir.

Anahtar kelimeler: *Diabetes Mellitüs, koroner kolleteral dolaşım, koroner kalp hastalığı*

Collaterals are vessels structured as a connecting network between different coronary arteries. They are probably remnants of the embriyonal arterial network and may develop under influence of various stimuli. The pressure gradient between the normal and the stenotic vascular regions appears to be the most important factor for collateral development [1]. However, there is considerable variation between patients with ischemic heart disease with respect to collateral development. The factors responsible for this variations are not clearly known [2]. Predominant localization of the collaterals in the human heart is the subendocardium where a dense plexus develops. The proliferation of collateral arteries is not a process of passive dilatation but of active proliferation and remodelling. The histological structure of these vessels is that of abnormally thin-walled arteries. Macroscopically identifiable interconnecting larger vessels have a normal arterial wall structure but show extensive subintimal and endothelial proliferation [3]. Endothelial cells are also important in this collateral growth and maturation process [4,5]. Diffuse endothelial dysfunction appears to be responsible for more complicated course and less favorable outcome of coronary artery disease (CAD) in patients with diabetes mellitus (DM) [6-9]. DM is known to stimulate angiogenesis at least in the retina. But the functionally more important collateral vessels of the heart are not product of angiogenesis but rather of "arteriogenesis". In this study we investigated the effect of DM on coronary collaterals that are product of arteriogenesis. Coronary angiography, the most commonly used technique for studying collateral circulation, may not be accurate in assessing collateral circulation because most collaterals are situated intramurally or too small to visualize angiographically [10]. Intracoronary pres-

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sure measurement is a new technique to provide accurate and quantitative information about the collateral circulation [11-14], and it can be easily applied during the coronary intervention. We therefore sought the effects of DM on coronary collateral vessels in patients with CAD by using intracoronary pressure measurement technique.

METHODS

Patient Population

We studied 40 patients with CAD referred to Istanbul Faculty of Medicine between november 1998- october 1999 who met the following criteria: 1) clinically stable angina pectoris 2) ischemic symptoms lasting over 3 months period 3) verified myocardial ischemia by at least one non-invasive test 4) more than 70% stenosis in one coronary artery 5) underwent PTCA and/or stent implantation for this vessels.

Measurements of collateral blood flow

Left and right coronary arteriography was performed in all patients. After angiography fiberoptic pressure monitoring guide-wire (Pressure wire, 0.014 in. RADI Medical System, Uppsala, Sweden) was advanced and positioned distal to the stenosis to be dilated, The same wire was used as a guide wire for angioplasty catheter. During the angioplasty or stent implantation procedure and total occlusion with balloon, distal pressure was recorded as coronary wedge pressure (CWP:Pocclusion). As a more valuable parameter, collateral flow index (CFI) was determined by the ratio of simultaneously measured CWP (Pocc:mmHg) to aortic pressure (Pa,mmHg,obtained from the guiding catheter) (CFI: CWP/Pa). We neglected the measurement of the central venous pressure because we did not include the cases in whom this pressure is expected to be elevated.

Statistical analysis Statistical analysis was performed by using SPSS for windows. Data were expressed as mean ± SD. A p value < 0.05 was considered significant. The difference between groups were evaluated by chi-square analysis for categorical variables and student t test for continuous variables.

RESULTS

Baseline Characteristics

The study population was expressed as two groups according to whether they had DM or not. As shown in table 1 and table 2, the two groups was well matched in terms of baseline clinical and angiographic characteristics.

Pressure measurements of collateral circulation

The mean value of CWP was 18.1 ± 8.6 mmHg in diabetic group and 26.8 ± 9.6 mmHg in non-diabetic group and this difference was statistically significant

Table 1. Baseline Clinical Characteristics

	Diabetic Group (n: 20)	Non-Diabetic Group (n: 20)
Age, years	57.1±10.2	60.3±9.4
Male/female	12/20	13/20
Risk factors		
Dyslipidemia	8(40%)	10(50%)
Hypertension	11(55%)	10(50%)
Smoking	13(65%)	15(75%)
Duration of ischemic symptoms	3.2±0.4 months	3.1±0.5 months

No differences between two groups

Table 2. Angiographic Characteristics

	Diabetic Group (n: 20)	Non-Diabetic Group (n: 20)
Stenotic artery		
Left anterior descending	9(45%)	10(50%)
Left circumflex	5(25%)	6(30%)
Right coronary	6(30%)	4(20%)
Diameter stenosis (%)	78.7±12.1	77.3±13.3

No differences between the two groups

($p<0.05$). The mean value of CFI was significantly higher in non-diabetic group as well. (0.17 ± 0.08 in diabetic group and 0.25 ± 0.09 in non-diabetic group, $p<0.05$, table 3).

DISCUSSION

In the presence of an epicardial narrowing, collateral channels develop, and contribution of collateral flow to myocardial flow increases progressively [1]. Because the presence of well developed collaterals correlates strongly with recurrent myocardial ischemia, it has been postulated that the ischemic myocardial cells produce angiogenic growth factors. It is well known that the collateral "stem" which connects the

Table 3. Results of pressure measurements

	Diabetic Group (n: 20)	Non-diabetic group (n: 20)	p
mean CWP (mmHg)	18.1 ± 8.6	26.8 ± 9.6	<0.05
mean CFI	0.17 ± 0.08	0.25 ± 0.09	<0.05

collateral network with the normal arteries is surrounded by normal tissue that does not belong to the region of the occluded artery. For this reason, collateral growth does not seem to be determined by the myocardium in its direct vicinity [15]. The pressure difference between stenotic and normal vascular regions induces an increase in blood flow velocity in the rudimentery anostomoses and connections. The increased shear stress in turn activates the endothelium, leading to expression of adhesive molecules, subsequent monocyte attachment and production of growth factors. Over the past decade, numerous angiogenic factors have been purified, and their amino acid sequence have been determined with gene cloning [16]. In a canin model of myocardial ischemia, intracoronary infusion of vascular endothelial growth factor in to ischemic territory has been shown to accelerate native collateral development [17]. Endothelium has a pivotal role in collateral development and nitric oxide effects vascular endothelial growth [18]. High levels of glucose concentration lead to endothelial dysfunction [19-20] and nitric oxide production is also impaired in DM [21]. Taken together, these two factors can probably be considered as a support for our finding that was the poor collateral development seen in patients with DM (table 3). Only limited data are available on the effect of DM on collateral development. Previously, in one small clinic [22] and a postmortem study [23] it has been shown that DM has negative effect on collateral development. At last, in another study, 306 patients were analyzed according to Rentrop classification for collateral artery formation and it was found that in subjects with DM, the collateral vessel development is severely impaired compared with nondiabetic patients [24]. In this large study, the degree of collateral development was assessed angiographically. But, coronary angiography, the most commonly used technique for studying collateral circulation, may not be accurate in assessing collateral circulation because most collaterals are situated intramurally or too small to visualize angiographically [10]. Cohen et al. demonstrated that angiographically well developed collateral vessels are regularly found only in patients with greater than 80 percent stenosis of a major coronary artery [25]. It was already shown by Pijls et al. that the relation between the degree of visibility of collaterals on the angiogram and calculated CFI , is rather variable and warns against relying upon the angiogram alone to assess development of coronary collaterals. Therefore, the collaterals visualized by angiographically may not accurately quantify collateral circulation. The value of distal coronary occlusion pressure as an index of collateral flow at coronary occlusion, has been investigated by Schaper in experimental models and was recognized by Gruentzig, King, Meier and other investigators in the early days of angioplasty [26-27]. But its clinical usefulness, however, remained limited until development of pressure monitoring guide wire technologies. In this study collateral circulation was assessed quantitatively and objectively by using intracoronary pressure measurement techniques. We also included relatively more homogenous subjects who had one vessel disease and presented with stable ischemic symptoms lasting over 3 months. It is well known that collateral growth, expansion and maturation take at least one month whereas ischemia is only transient. It can be anticipated that these inclusion criterias affect the grade of collateral development in each group in the same degree as well. We choosed single vessel disease as an inclusion criteria and pressure measurements were performed in this ischemia related artery which give information only about the myocardial region that could be collateralized. So, our result gained more accuracy by means of above mentioned contributing factors inspite of relatively low number of patient included in this study.

In conclusion; in this study poorer development of coronary collaterals in patients with DM confirmed and extended those of the results of previous reports. This study objectively and quantitatively demonstrated that the coronary collateral vessel development is impaired in diabetic patients compared with nondiabetic patients.

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