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Effects of Thrombolytic Therapy on Distal Coronary Microvasculature: A Study Based on Coronary Pressure Measurements

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TROMBOLİTİK TEDAVİNİN DİSTAL KORONER MİKROSİRKÜLASYONA ETKİSİ

ÖZET

Trombolitik tedavinin (TT) başarısının en önemli belirleyicisi sağlanılan damar açıklığından çok kurtarılan miyokard kitlesinin miktarıdır. Bir kısım hastada tromboliz sonrası sağlanan anjiografik akıma rağmen doku perfüzyonunun olamayabileceği gösterilmiştir. TT sonrası miyokard canlılığı ve fonksiyonlarının en önemli belirleyicilerinden biri de distal mikrosirkülasyonun (DMV) destruksiyon derecesidir. Distal mikrosirkulasyonun kantitasyonu ve fonksiyonlarının tayini koroner kapalı basınç (CWP), kollateral akım indeksi (CFI), ve DMV'nin hiperemik situmulusa yanıtlılığının (ΔP) tespiti ile mümkün olabilir. Bu çalışmada biz miyokard infarktüslü (MI) hastalarda TT'nin DMV üzerine olan etkisini DMV'nin perfüzyon basıncı, fonksiyonları ve patentliğinin kantitatif olarak ölçülmesi yoluyla araştırdık.

Materyel ve Metod: *Bu çalışmaya infarktüsten sorumlu arterinde >%70 darlık ve TIMI (thrombolysis in myocardial infarction) II derecede akımı bulunan ve bu damarına akut MI sonrası 10 gün içerisinde PTCA ve /veya stent implantasyonu yapılan toplam 30 hasta dahil edildi. 15 hasta semptomlarının başlangıcının 6 saati içerisinde TT almıştı. Anjiografiyi takiben fiberoptik basınç ölçer kılavuz tel (pressure wire) ilerletilerek darlığın distaline yerleştirildi. Proksimal ve distal basınçlar simultane olarak bazal şartlarda ve adenosin hiperemisi altında kaydedildi. Balon ile total oklüsyon sağlandığı anda tespit edilen distal basınç CWP olarak kaydedildi. CFI, simultane olarak tespit edilen CWP'nin ortalama aortik basınca bölünmesi ile bulundu. Transstenotik basınç gradientini arttırabilme kapasitesi (sağlanabilir ΔP) veya başka bir deyişle DMV'nin yanıtlılığı, lezyonu geçen hiperemik basınç gradientinden istirahat basınç gradientinin çıkarılması ile bulundu.*

Bulgular: *TT alan grupta (grup I) ortalama CWP, CFI ve P değerleri sırasıyla 27.7 ± 9.6 mmHg, 0.29 ± 0.09 ve 22.7 ± 7.4 mmHg iken TT almayan grupta (grupII) sırasıyla 18.2 ± 6.2 mmHg, 0.19 ± 0.07 ve 12.2 ± 6.8 mmHg idi. Ortalama CWP , CFI ve ΔP değerleri grup I de anlamlı ölçüde fazla idi. Bu ortalama değerler arasındaki farklılıklar istatistiki olarak anlamlı idi (sırasıyla, $p<0.01$, $p<0.01$ ve $p<0.03$).*

Sonuç: *Trombolitik tedavi DMV üzerine koruyucu etkiye sahiptir ve bir miktar spontan rekanalizasyon sağlansa bile DMV'nin destruksiyon derecesi TT almayan hastalarda daha fazladır. TT nin etki ve yararlılığının değerlendirilmesi ve sonraki tedavi stratejilerinin belirlenmesi DMV'nin patentliğinin kantitatif tayini ile mümkündür.*

Anahtar kelimeler: *Trombolitik tedavi, mikrosirkülasyon, koroner basınç*

Reperfusion therapy has improved survival in acute myocardial infarction and the survival benefit is strongly dependent on success of the reperfusion therapy [1-4]. However early reperfusion does not guarantee, the recovery in left ventricular function in clinical trials [5-8]. The collateral circulation is an alternative source of blood supply to myocardium jeopardized by abruptly occluded vessels, preventing myocardial death and favoring myocardial recovery after reperfusion therapy. However, the functional significance of collateral circulation in myocardial infarction (MI) has been a matter of debate [9-12]. The vascular network of the collaterals together with the surrounding vascular bed constitute the distal microvasculature. Intracoronary pressure measurement is a new technique to provide quantitative and functional information about the collaterals and microvasculature [13,14]. This technique can be easily applied during the coronary intervention. The most important determinant of the success of thrombolytic therapy is the amount of salvaged myocardial mass rather than accomplished vessel patency. Using contrast echocardiography, it has been shown that the "no- reflow" phenomenon at the myocardial level in a group of patients who had angiographic evidence of epicardial reflow after thrombolysis [8]. It

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may be due to microvasculatory stasis, distal fibrin embolisation, destruction of microvasculature or a combination of these processes. One of the most important prognostic determinants of myocardial viability and function after thrombolysis is the degree of destruction of DMV. The collateral growth and maturation takes 2-5 weeks after myocardial infarction. Because, culprit lesion occupies only small intraluminal area [15] and that is probably insufficient to induction of collateral development in the preinfarction period, pressure measurements (CWP,CFI) performed in the IRA early after MI quantifies mainly the pressure reflected from the distal microvasculature more than the collaterals. Function and integrity of the DMV after MI can also be determined by assessing of the response of distal capillary network related to infarcted segment to vasodilator stimuli. If in the presence of stenosis in IRA and only small pressure gradient (ΔP) can be provoked across the lesion, this is indicative for severe resistive vessel dysfunction and increased resistance due to microvascular destruction. In this study we investigated the effects of thrombolytic therapy on DMV by quantitative measuring of the perfusion pressure, function and patency of distal microvasculature in patients with MI.

METHODS

Study Patients. We studied 30 patients with first MI and no previous angina, referred to Istanbul Faculty of Medicine between November 1998 - August 1999 and who met the following criteria: 1) more than 70% residual stenosis in IRA 2) thrombolysis in myocardial infarction (TIMI) grade II flow in IRA 3) underwent PTCA and /or stent implantation for this residual lesion in IRA within 10 days after AMI. Exclusion criteria was defined as the presence of heart failure. All of the patients had ST elevation on their surface ECG at admission. Fifteen of 30 patients had received thrombolytic therapy with tissue plasminogen activator (tPA) within six hours of their symptoms beginning. Remaining half of them had not received thrombolytic therapy due to presence of contrandications (1 patient had previous gastrointestinal system bleeding, 3 patient had previous cerebro-vascular accident) or late admission to the hospital (eight patients who presented 12 hours after the onset of symptoms had pathologic Q wave on their surface ECG at admission). In the coronary care unit all patients had received conventional drug therapy in accordance with guidelines for treatment of AMI [16].

Quantification of patency and pressure of microvasculature. Left and right coronary angiography was performed in all patients. TIMI flow grade was assessed as previously defined [4]: Grade 0 - no perfusion, Grade 1- penetration without perfusion, Grade 2 - partial perfusion, Grade 3 - complete perfusion. After coronary angiography, fiberoptic pressure monitoring guide-wire (Pressure wire, 0.014 inch, Radi) was advanced and positioned distal to the stenosis to be dilated. The same wire was used as a guide wire for angioplasty catheter. Proximal aortic (Pa) and distal pressures (Pd) were recorded simultaneously under baseline and hyperemic conditions. Distal pressure was recorded from pressure wire and proximal pressure was recorded from guiding catheter. Adenosin was the hyperemic agent used and given a dose of 20 μg intracoronary bolus for left system and 15 μg for RCA. During the angioplasty procedure and total occlusion with balloon inflation, distal pressure was recorded as coronary wedge pressure (CWP). Coronary flow index (CFI) was determined by the ratio of simultaneously measured CWP to aortic pressure. 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. Because we assumed that coronary artery occlusion in itself is a potent vasodilatory stimulus, no additional vasodilatory drugs were administered during balloon occlusion. Transstenotic pressure gradient acrossed the lesion calculated during baseline and hyperemic conditions by substraction of simultaneously measured distal pressure (Pd) from aortic pressure (Pa). Capability to increase pressure gradient (achievable ΔP) or with an other word, responsiveness of DMV was assessed by substraction of resting pressure gradient from provoked (hyperemic) pressure gradient across the lesion.

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

RESULTS

Baseline characteristics. The study population was divided into two groups according to whether they received thrombolytic therapy (TT) or not. As shown in table 1 and Table 2 there were no significant differences between the two groups with respect to age, gender, risk factors and angiographic characteristics.

Pressure measurements of the DMV. The mean values of CWP (27.7 ± 9.6 mmHg versus 18.2 ± 6.2 mmHg, $p<0.01$) and CFI (0.29 ± 0.09 versus 0.19+0.07, $p<0.01$) were significantly higher in the group of patients who received thrombolytic therapy (group I). Also, the mean value of achievable transstenotic gradient (ΔP) was statistically significantly higher in the group I (22.3 ± 7.4 mmHg versus 12.2 ± 6.8 mmHg, $p<0.03$, table 3)

Table 1. Baseline clinical characteristics

	Group I	Group II
	Thrombolytic therapy (+) n= 15	Thrombolytic therapy (-) n=15
Age, yrs	56.2 ± 11.3	55.7 ± 12
Male/female	11/4	10/5
Risk factors		
Diabetes mellitus	4(26%)	5(33%)
Dyslipidemia	5(33%)	7(46%)
Hypertension	8(53%)	6(40%)
Smoking	6(40%)	7(46%)
Multivessel disease	3(20 %)	4(26%)

No differences between the two groups.

Table 2. Angiographic characteristics

	Group I n= 15	Group II n=15
Infarct- related artery		
Left anterior descending	7(46%)	8(53%)
Left circumflex artery	4(26%)	3(20%)
Right coronary artery	4(26%)	4(26%)
Diameter stenosis, %	73.3±14.1	75.2±12.3
TIMI flow grade	2.1±0.9	2.0±0.7

No differences between the two groups.

Table 3. Results of pressure measurements

	Group I (n: 15)	Group II (n: 15)	p
mean CWP (mmHg)	27.7 ± 9.6	18.2 ± 6.2	< 0.01
mean CFI	0.29 ± 0.09	0.19 ± 0.07	< 0.01
mean ΔP	22.3 ± 7.4	12.2 ± 6.8	< 0.03

DISCUSSION

The myocytes are organized within the capillary network and are connected to the capillary wall by collagen struts [17]. Each myocyte is lined by at least one capillary. This close anatomical structure suggest on intense functional link. Survival of myocardial cells depends on coronary flow at the microvascular level. After MI, destruction of distal microcirculatory bed supplied by IRA results in myocyte death and loss of myocardial mass. 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 and Meier in the early days of angioplasty [18-19]. However, distal occlusion pressure (CWP), which was determined by intracoronary pressure measurement in IRA early after MI, gives information not only about collateral circulation but also DMV supplied by IRA. Although, some collaterals are seen in nearly 40 percent of patients with an acute occlusion [20], the incidence of collateral development 2 weeks after MI is significantly lower in patients with subtotal occlusion [21]. In our study, pressure measurements were performed early after MI (within 10 days) and one of the our inclusion criteria was, TIMI-2 grade flow in IRA. Nevertheless, some of the collateral vessels could also be developed after MI but, collateral growth and maturation takes at least 2-5 weeks after myocardial infarction. The culprit lesion may occupy only small intraluminal area in the pre-infarction period [15] and that is probably insufficient to induction of collateral development in the infarcted territory. Because of all these reasons, it is not expected to presence of well developed collaterals in infarcted region in our study group. Therefore, pressure measurements (CWP,CFI) that were performed in the IRA early after MI, reflects mainly the status of the distal microvasculature. Perfusion studies of dog [22] and human [23] hearts reveals that there are no microvascular connections at the boundaries between regions perfused by large coronary arteries. Because, there is no anostomose between two microvasculatory territories, pressure measurements which are performed in IRA gives information only about the DMV territory perfused by this artery.

The most important determinant of the success of thrombolytic therapy is the amount of salvaged myocardial mass rather than accomplished vessel patency. After MI, hyperemic and basal flow reduced and resistive vessel dysfunction occurs in infarcted region due to partial obliteration of the DMV [24]. This resistive vessel dysfunction blunts the hyperemic response and distal pressure does not decrease properly in response to adenosine hyperemia. The response to vasodilatory stimuli and the ability to increase a transstenotic gradient (achievable ΔP), is not only a measure for the residuel significance of infarct related stenosis but also an indicator of patency rate of DMV. It may be anticipated that, if in the presence

of a residuel stenosis in an IRA and only small pressure gradient can be provoked across the lesion, this is indicative for severe microvasculatory damage. On the other hand, if a considerable gradient can be provoked in such case, this indicates protected DMV and viable myocardium that justifies revascularization [25]. In our study, significantly higher pressure gradient could be provoked in the group of patients who had received TT suggested that more patent and protected DMV (table III).

Using contrast echocardiography, it has been demonstrated that lack of tissue perfusion in the face of restored angiographic flow occured in some patients after thrombolysis [8]. This is very important finding that it provides support for veritable epicardial - myocardial dissociation [26]. The most important cause of this phenomenon is the destruction of DMV due to intracapillary erythrocyte, granulocyte or debris accumulation, inspite of restored antegrad flow after thrombolysis. No-reflow or low-reflow phenomenon was also shown after succesful primary PTCA [27]. Because, thrombotic occlusion is a dynamic process, patients appears to have repetitive cycles of spontaneous reperfusion and reocclusion just before and the course of AMI. Distal embolization may also occur during this spontaneous repetitive cycles. Microvascular stunning and myocyte swelling which may lead to microvascular compresion can also be another responsible factor for epicardial-myocardial dissociation after reperfusion. These hypothesies may also be partly adapted to the cases in whom had residual stenosis in IRA. Even if some degree of recanalization could be achieved by using TT or spontaneously, integrity of DMV is still remain as determinative factor for left ventricular function. The degree of benefit from revascularization also depends on status of the DMV. It is well known that some degree of spontaneous recanalization may occur in the IRA due to activation of endogenous anti-thrombotic mechanism [28-29]. The coronary blood flow fills the intramyocardial blood pool and partially runs through the coronary microvasculature in to venous circulation. In patients with diffusely damaged DMV, which results in considerable reduction of the distal intramyocardial blood pool. The pressure reflected from intramyocardial blood pool, which is measured in distal to residual stenosis during balloon inflation (CWP,CFI), decreases proportional to the degree of DMV damage. Therefore, lower CWP and CFI values, which were determined in the group who had not received TT, may indicate further reduction of intramyocardial blood pool and further destuction of DMV in this group. In our study, two of the groups had same angiographic inclusion criterias that were more than 70% stenosis and TIMI grade II flow in IRA. But the group who received thrombolytic therapy had significantly higher CWP and achievable pressure gradient (ΔP) values that indicate more protected and patent DMV (table III). This differences can be attributed to positive effects of TT on DMV.

With an another point of view, distal embolization of thrombus or plaque contents to small vessels may also results in occlusion of collateral blood flow and infarct area is deprived of protective effects of collaterals. In one study it has been shown that, the distribution of collateral blood flow within the infarct area is related to myocardial viability [30]. In our study, CFI , which is a quantitative index of collateral blood flow, was also significantly higher in the group who had received TT. This finding also provides support to beneficial effect of TT on myocardium in terms of collateral blood flow in the infarcted territory even if it could have preformed or developed even after MI (within 10 days)

Conclusion. Thrombolytic therapy has a protective effect on DMV and even if some degree of recanalization occurs spontaneously, the destruction of DMV couldn't be prevented without TT. Evaluation of the effects and efficacy of TT and designation of the subsequent treatment strategies may be possible by quantitative determination of the patency of DMV.

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