Thrombolysis in myocardial infarction frame count in coronary arteries without visible atherosclerosis in coronary angiography of patients with stable coronary artery disease

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ABSTRACT

الأهداف: التحقيق في انحلال الخثرة في إطار تعداد (TFC) احتشاء عضلة القلب (TIMI) في الشرايين التاجية بدون حدوث تصلب مفصلي في تخطيط الشريان التاجي لدى المرضى المصابين بأمراض الشريان التاجي المستقر (CAD).

الطريقة: تم تقييم حالة 83 مريضاً (متوسط العمر 10±58، 31 (37%) ذكور). الذين خضعوا لتقييم تخطيط الشريان التاجي للذبحة الصدرية المستقرة بعيادة القلب بجامعة غازي – أنقرة – تركيا، خلال الفترة ما بين عام 2006م وحتى عام 2007م. تم تحديد 40 مريضاً بشرايين تاجية سليمة كمجموعة أولى، والمجموعة الثانية بعدد 43 مريضاً الذين لديهم شريان تاجي واحد طبيعي في وضع مستقر (CAD). تم تحديدهم كتضيق بنسبة 50% أو أكثر من ذلك على الأقل في شريان رئيسي واحد. تم تقييم تيار الدم والانصباب للجهاز القلبي الوعائي بواسطة استعمال طريقة (TFC).

النتائج: في المجموعة الثانية، تم تقييم (TFC) في هبوط الشريان الأمامي الأيسر (LAD) لدى 15 مريض، (TFC) للشريان المقوس (CX) لدى 18 مريض، و(TFC) للشريان التاجي الأيمن (RCA) لدى 10 مرضى. في المجموعة الثانية (TFC) لهبوط الشريان الأمامي الأيسر (12±37 مقابل 12±29، p=0.015) و (8±22 مقابل 9±18 ، p=0.035) للشريان المقوس، كانت أعلى بشكل ملحوظ من أولئك المرضى في المجموعة الأولى. كان (TFC) لـ(RCA) متشابهاً بين المجموعتين (9±17 مقابل 8±17، p=0.990). بعد تعديل عوامل الخطر بواسطة تحليل الخمود متعدد التغير بين (TFC) والإحصائيات السريرية كانت غير ملحوظة إحصائيا.

خاتمة: يخفض (TFC) هبوط الشريان التاجي الأمامي الأيسر (LAD) و(CX)، الذي ليس لديه مرض في الشريان التاجي في أمراض الشريان التاجي المستقرة (CAD). كان التحسن المتنبأ به (CAD) بغض النظر عن القياسات السريرية.

Objectives: To investigate the thrombolysis in myocardial infarction (TIMI) frame count (TFC) in the coronary arteries without visible atherosclerosis in coronary angiography of patients with stable coronary artery disease (CAD).

Methods: Eighty-three patients (mean age 58±10, 31 [37%] males), who underwent coronary angiographic evaluation for stable angina in Gazi University, Ankara, Turkey, Cardiology clinic between 2006-2007 were enrolled. Forty patients with normal coronary arteries were defined as group I. Group II consisted of 43 patients, who have one normal coronary artery in the setting of stable CAD defined as stenoses 50% or greater in at least one major coronary artery. Coronary blood flow and microvascular perfusion was evaluated by TFC.

Results: In group II, the TFC of left anterior descending artery (LAD) in 15 patients, TFC of circumflex artery (CX) in 18 patient, and TFC of right coronary artery (RCA) in 10 patients were evaluated. In group II, the TFC of LAD (37±12 versus 29±12, p=0.015) and CX (22±8 versus 18±9, p=0.035) were significantly higher than those in group I. The TFC of RCA was similar between groups (17±9 versus 17±8, p=0.990). After the adjustment of the risk factors by multivariate regression analyses, the association between TFC and clinical characteristic was statistically non-significant.

Conclusion: The TFC decreased in angiographically normal LAD and CX arteries in the setting of stable angina pectoris. The important predictor was CAD alone, irrespective of the clinical parameters.

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The thrombolysis in myocardial infarction (TIMI) frame count is a useful quantitative method to evaluate the coronary blood flow.[1] In previous studies, where TIMI frame count (TFC) of the culprit artery in the setting of acute myocardial infarction (AMI) was higher as compared to nonculprit ones, it was assumed that nonculprit arteries had normal coronary blood flow.[2] Coronary blood flow was shown to be impaired in nonculprit arteries in the presence of AMI as compared to normal coronary arteries.[3] The aim of our study was to evaluate the flow in the coronary arteries without visible atherosclerosis in coronary angiography of patients with stable coronary syndromes and at least one major epicardial coronary artery with significant lesions by using TFC.

Methods. Forty patients who underwent coronary angiography and were found to have totally normal coronary arteries (group I), and 43 patients with stable angina pectoris who underwent coronary angiography and were found to have 2 major epicardial coronary arteries with significant stenoses (50% or greater), and one normal coronary artery (group II) was studied in Gazi University, Ankara, Turkey, Cardiology Clinic between 2006-2007. Exclusion criteria were: 1) Significant stenosis within a major side branch of the normal major coronary artery, 2) Collaterals provided by the normal major coronary artery, 3) Acute coronary syndromes, 4) History of percutaneous coronary intervention, 5) History of coronary bypass surgery, 6) Chronic renal failure, 7) Coexisting significant valvular lesions, and 8) Impaired left ventricular systolic function. Selective coronary angiography was performed in all patients using the Judkins' technique in multiple angulated views by 6 French diagnostic catheters without any premedication. The TIMI frame count was calculated for each major coronary artery by using a previously defined method.[1] This method determines the number of cine-frames, in which the contrast material reaches specific distal coronary landmarks in the left anterior descending coronary artery (LAD), left circumflex coronary artery (CX), and the right coronary artery (RCA). The distal coronary landmarks were the distal bifurcation at the apex of the LAD, the distal bifurcation of the major obtuse marginal, or the main CX, the site of origin of the first branch at the crux, or its posterolateral extension for RCA. A TFC for each coronary artery was calculated by subtracting the first frame from the last frame. In the case of the LAD, TFC was corrected by dividing by 1.7 to determine the corrected TIMI frame count (CTFC). The TFC of the normal coronary artery in group I patients were compared with that of the corresponding vessel in group II patients. The study was approved by the ethics committee and informed consent was taken from the patients.

Data analysis was performed by using SPSS for Windows, version 11.5. Whether the continuous variables were normally distributed or not were determined by using Shapiro Wilk test. Data were shown as mean ± standard deviation for normally distributed variables, and as median with interquartile range for non-normally distributed variables. Nominal data were expressed as a number of patients and percentages. The differences between 2 independent groups were evaluated by Student's t test when the data were normally distributed, and by Mann Whitney U test, when not. Pearson's Chi-square, or Fisher's Exact test were applied for categorical comparisons, where appropriate. The degree of association between continuous variables was calculated by Pearson's correlation coefficient. Multiple stepwise linear regression method was used to determine the independent predictors that effected TFC levels. Coefficient of regression and 95% CIs (Confidence Intervals) for all significant independent variables were calculated. Logarithmic transformations were applied for all dependent variables in multiple linear regression analyses due to the non-normally distributed data. Odds ratio and 95% CIs for each independent variables were calculated. Any variable whose univariate test had a p-value of <0.25 was accepted as a candidate for the multivariate model along with all variables of known clinical importance. A p-value of <0.05 was considered statistically significant.

Results. The clinical characteristics and laboratory findings of patients are shown in **Table 1**. Accordingly, the patients in group II were significantly older and were more likely to be males and smokers, and had lower cholesterol levels probably due to a higher rate of statin use as compared to controls. In group II, the normal coronary artery was LAD in 15, CX in 18, and RCA in 10 patients. The TFC values regarding the LAD and the CX arteries of patients in group II were significantly higher as compared with group I, whereas there was no such difference regarding the TFC values in the RCA in the 2 groups (**Table 1**). Although, age appears as a significant predictor of TFC score in LAD and CX in multivariate analyses shown in **Table 2**, age is a demographic rather than a clinical characteristic. After adjustment for age, gender, smoking status, and cholesterol levels, the differences regarding the CTFC values between the 2 groups were still significant for the LAD and the CX and non-significant for the RCA (**Table 2**).

Discussion. It is well known that the risk factors of atherosclerosis impair endothelial function; however, the coronary microvascular dysfunction has not been demonstrated through TFC values of normal arteries of

Table 1 - Clinical characteristics of the patients.

Clinical characteristics	Group I (n=40)	Group II (n=43)	*P*-value
Age (year)	54±8	62±10	<0.001
Gender (male [%])	10 (32%)	21 (68%)	0.021
Hypertension (%)	17 (39%)	27 (61%)	0.051
Diabetes mellitus (%)	5 (39%)	8 (62%)	0.323
Family history (%)	7 (41%)	10 (59%)	0.354
Smoking (%)	8 (30%)	19 (71%)	0.017
T. chol (mg/dl)	210±46	191±36	0.041
HDL (mg/dl)	45±13	43±11	0.472
TG (mg/dl)	140±56	120±40	0.067
LDL (mg/dl)	142±54	145±57	0.791
Statin use	14 (35%)	18 (42%)	0.339
TFC			
LAD	29±12	37±12 (n=15)	0.015
CX	18±9	22±8 (n=18)	0.035
RCA	17±8	17±9 (n=10)	0.990

T. chol - total cholesterol, HDL - high density lipoprotein, TG - triglyceride, LDL - low density lipoprotein, TFC - TIMI frame count, LAD - left anterior descending, CX - circumflex, RCA - right coronary artery

Table 2 - The association of most significant risk factors and the TIMI frame count values of left anterior descending and circumflex after adjustment by multivariate analyses.

Dependent variables	Independent variables	Coefficient Regression (B)	*P*-value	95% Confidence Interval for (B)	
				Lower Bound	Upper Bound
LAD-TFC	CAD	0.455	<0.001	0.221	0.689
	Age	-0.022	<0.001	-0.034	-0.010
	Male gender	-0.326	0.006	-0.552	-0.100
CX-TFC	Age	-0.013	0.041	-0.025	-0.001
	HDL-C	0.015	0.013	0.003	0.026
	CAD	0.200	0.004	0.066	0.335

Log-transformed data were used in multiple linear regression analysis, HDL-C - High density lipoprotein, TFC - TIMI frame count, LAD - left anterior descending, CX - circumflex, RCA - right coronary artery, CAD - coronary artery disease

stable coronary patients before. The main finding of this study is that, the quality of blood flow, as demonstrated by TFC, is disturbed in the LAD and CX, but remains unchanged in the RCA in patients with stable angina pectoris, and coexistent significant stenoses in 2 major epicardial coronary arteries. In this study, we evaluated the coronary flow in a normally appearing coronary artery in patients with coexisting significant double-vessel disease and stable coronary syndromes. The TIMI frame count is used to evaluate microvascular blood flow and microvascular perfusion.[1,2] Higher values represent slow coronary flow and impaired perfusion. Gibson et al[3] demonstrated that in the setting of acute myocardial infarction, the coronary flow slowed in the nonculprit arteries. They suggested that acute MI slowed coronary blood flow globally due to hemodynamic impairment. In multivariate analysis after correcting for hemodynamic alteration during acute MI, coronary blood flow in nonculprit arteries remained slower in the setting of AMI; the nonculprit artery had the slowest flow when the LAD was the culprit artery, as compared to the situation where the nonLAD arteries were the culprit vessel. It has been reported in the RESTORE study[4] that percutaneous coronary intervention increases blood flow velocity in nonculprit arteries. The TIMI 14 trial[5] demonstrated that lower systolic pressure and lower heart rate were associated with slower coronary blood flow in nonculprit arteries in the setting of AMI. All these findings can be explained by an overall hemodynamic effect of acute MI, which reduces cardiac output and leads to impaired coronary blood flow both in culprit and nonculprit arteries.[5] In our study, where we studied only patients with stable coronary syndromes and normal left ventricular functions, the derangement of TFC in the normally appearing coronary artery cannot

be described to be a global hemodynamic impairment. Moreover, we found that the flow in the normal RCA remained normal in the presence of coexisting stenoses in the LAD and CX arteries, but the flow in the normal LAD and the normal CX were found to be impaired in the presence of coexisting stenoses in the remaining 2 coronary arteries. Although, it can be speculated that atherosclerosis impairs blood flow in normally appearing coronary vasculature, this differential influence deserves an explanation. This again may be explained by a greater degree of hemodynamic impairment leading to a decrease in overall coronary flow in cases where the culprit artery is the LAD, and thus, the ischemic area is large. Chatzizisis et al[6] suggested that there are significant differences regarding hemodynamic and anatomic characteristics between the left and the right coronary arteries, which may lead to atherosclerosis more frequently in the left than in the right coronary artery. In the left coronary artery, blood flow increases in diastole and decreases in systole. Oscillatory shear stress and multiform coronary flow during cardiac cycle in the left coronary tree may contribute to a propensity to the development of atherosclerosis in the left coronary artery when compared to the right. De Bruyne et al[7] evaluated coronary flow and fractional flow reserve (FFR) and found that FFR was significantly lower in the coronary arteries without visible atherosclerosis in coronary angiography of patients with diffuse coronary atherosclerosis. This study showed that atherosclerotic epicardial coronary arteries without significant segmental stenoses may lead to abnormal resistance to coronary flow.[7] Gould et al[8,9] demonstrated myocardial perfusion defects from base to apex in patients with atherosclerosis, but without significant regional perfusion defects. It has been assumed that diffuse atherosclerosis may cause microvascular disease and paradoxical vasoconstriction and lead to coronary flow impairment in the absence of significant coronary stenoses.[10-13]

In conclusion, TFC was shown to be impaired in angiographically normal coronary arteries of patients with coexisting significant double-vessel disease in the setting of stable angina pectoris. The differential finding of a preserved TFC in the RCA when the other 2 coronary arteries are significantly stenosed needs to be verified by further research. The small population size, the absence of intracoronary ultrasonography (IVUS) to define normal coronary arteries and lack of doppler wire for more reliable information are the major study limitations. The small number of vessels compared would need confirmation in larger trials.

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