Corrected thrombolysis in myocardial infarction frame counts in diabetic patients with angiographically normal coronary arteries

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Objectives: To evaluate corrected thrombolysis in myocardial infarction (TIMI) frame count (CTFC) in patients with angiographically normal coronary arteries and diabetes mellitus, a condition known to be associated with microvascular dysfunction.

Methods: Patients who underwent coronary angiography in Gazi University Hospital, Ankara, Turkey between January 2000 and January 2005 were studied. Corrected TIMI frame count was calculated over the left anterior descending (LAD), left circumflex (Cx) and right coronary arteries (RCA) in 118 diabetic and 122 non-diabetic patients with normal coronary angiogram.

Results: The mean CTFC values of the LAD, Cx, and the RCA were similar in diabetics and nondiabetics (21.0±7.5 versus 21.3±9.6, 23.3 ± 9.7 versus 23.5 ± 10.8, 17.9 ± 6.7 versus 18.7 ± 7.4 respectively, p>0.05 for all comparisons). In stepwise multivariate linear regression analysis, body surface area had a significant correlation with CTFC of all the 3 coronary arteries.

Conclusion: We conclude that CTFC in diabetics and non-diabetics with angiographically normal coronary arteries is similar. Since microvascular disease is an inherent component of diabetes, our finding may reflect the inadequacy of CTFC in predicting microvascular disease in diabetic patients with normal coronary angiograms.

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ABSTRACT

الأهداف: من أجل تقييم تعداد إطار انحلال الخثرة المصحح (CTFC) لدى المرضى المصابين بداء السكري والذين كانت نتيجة تخطيط الأوعية للشرايين التاجية لديهم طبيعية، هنالك حالة أخرى تعرف باتحادها مع توقف وظيفة الأوعية الدقيقة.

الطريقة: تمت دراسة حالة المرضى الذين خضعوا لتخطيط الشريان التاجي بمستشفى جامعة غازي – تركيا، خلال الفترة ما بين يناير 2000م وحتى يناير 2005م. تم حساب تعداد إطار انحلال الخثرة المصحح في احتشاء عضلة القلب (CTFC) على مدى النازل الأمامي (LAD) والمنعطف الأيسر (CX) والشرايين التاجية اليمنى (RCA) لدى 118 مريضاً بالسكري، و122 غير مصاب بالسكري ونتيجة تخطيط الشريان التاجي لديهم طبيعية.

النتائج: كانت قيم تعداد إطار انحلال الخثرة المصحح في احتشاء عضلة القلب (CTFC) الفعلية لـ(LAD) و(CX) و(RCA) مشابهة لدى مرضى السكري والغير مصابين بالسكري (21.0±7.5 versus 21.3±9.6, 23.3 ± 9.7 versus 23.5 ± 10.8, 17.9 ± 6.7 versus 18.7 ± 7.4) على التوالي (p>0.05) لجميع المقارنين. في خطوة محكمة كان لدى تحليل تراجع المتغير المتعدد الخطي ومنطقة سطح الجسم (BSA) ذات صلة ملحوظة مع تعداد إطار انحلال الخثرة المصحح (CTFC) في احتشاء عضلة القلب لجميع الشرايين التاجية الثلاثة.

خاتمة: وجدن أن تعداد إطار انحلال الخثرة المصحح (CTFC) في احتشاء عضلة القلب (CTFC) لدى المصابين بالسكري وغير المصابين والذينٍ لديهم نتيجة تخطيط الشرايين التاجية طبيعية مشابهة. نظراً لكون مرض الأوعية الدقيقة مكون وراثي للسكري، فقد تعكس دراستنا استقلالية تعداد إطار انحلال الخثرة المصحح في احتشاء عضلة القلب (CTFC) في التكهن بمرض الأوعية الدقيقة لدى المرضى المصابين بداء السكري والذين نتيجة تخطيط الشريان التاجي لديهم طبيعية.

Corrected thrombolysis in myocardial infarction (TIMI) frame count (CTFC) is a valuable tool to evaluate angiographic outcomes following reperfusion,[1] and it has a prognostic importance.[2,3] It was also shown that CTFC of nonculprit arteries in patients with acute myocardial infarction was significantly higher compared with the normal arteries in the absence of acute myocardial infarction.[1] Moreover, CTFC has recently been shown to be higher in patients with metabolic syndrome and normal coronary angiograms, implying that CTFC may show microvascular dysfunction of the coronary bed in the absence of atherosclerotic lesions in the epicardial coronary arteries.[4] Type 2 diabetes mellitus is a disease that is well known to be associated with microvascular dysfunction.[5-7] To our knowledge, no study has yet investigated CTFC in diabetic patients with angiographically normal coronary arteries. The aim of this study was to investigate the CTFC in diabetic and non-diabetic patients with normal coronary angiograms.

Methods. In this retrospective study, participants were identified through a review of our angiography database of 7141 patients who underwent coronary angiography from January 1, 2000 to January 1, 2005. Two groups were selected according to the following criteria: 1. The non-diabetic group consisted of patients with no previous diagnosis of diabetes and a pre-procedural fasting blood glucose level <110 mg/dL. 2. The diabetic group consisted of patients documented with type 2 diabetes requiring either diet or medication for treatment. All participants had normal epicardial coronary arteries on the coronary angiogram and a normal echocardiogram. Normal coronary angiogram was defined as a complete absence of even minimal luminal irregularities in any of the epicardial coronary arteries. Normal echocardiogram was defined as the absence of valvular heart disease, myocardial hypertrophy, and global or regional wall motion abnormalities. The only exclusion criterion was an inadequate visualization of any coronary artery for frame counting. We also recorded body surface area (BSA), history of hypertension, smoking history, lipid parameters, creatinine levels, and angiographic hemodynamic data including heart rate, aortic systolic pressure and aortic diastolic pressure. The local ethical committee approved the study protocol. A CTFC was determined for each coronary artery in each patient according to the method first described by Gibson et al.[1] In the first frame used for TIMI frame counting, a column of nearly full or fully concentrated dye touches both borders of the coronary artery origin and moves antegrade. In the last frame, dye just begins to enter a standard distal landmark in the artery. These standard distal landmarks are as follows: in the left anterior descending artery (LAD), the distal bifurcation; in the circumflex artery (Cx), the most distal branch of the obtuse marginal branch with the longest total dye path; in the right coronary artery (RCA), and the first branch of the posterolateral artery. These frame counts are corrected for the longer length of the LAD by dividing by 1.7 to achieve the CTFC. Since cinefilming rate is 25 frames in our laboratory, we made a second correction by the formula [(30/25) x CTFC observed] to get comparable results with the 30 frames cinefilming rates with which most studies in the literature were carried out.[1]

Data were analyzed using SPSS version 10 (SPSS Inc., Chicago, Illinois) for Windows (Microsoft, Redmond, Washington). Data were presented as means ± standard deviations for continuous variables and as absolute numbers (percentages) for categorical variables. Comparisons between the 2 groups were performed using the t-tests for continuous variables and chi square tests for categorical variables. A multivariate linear regression analysis was performed by using CTFC for LAD, Cx, and RCA as dependent variables and all others variables as independent variables. A stepwise method was used, with a value of $p<0.05$ required for entry and a value of $p<0.10$ is required for retention of variables in the model. A p value of <0.05 was considered statistically significant.

Results. A total of 273 (133 diabetics, 140 non-diabetics) patients were eligible for our study. Fifteen from diabetic group, 18 from non-diabetic group were excluded because of inadequate visualization of any coronary artery for frame counting. Therefore, a total of 240 patients (118 diabetics, 122 non-diabetics) were included in the study. Baseline characteristics are shown in **Table 1**. Diabetic patients had higher BSA, heart rates and triglyceride levels, but lower total cholesterol, low density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol levels as compared with the non-diabetics. Diabetic patients were more likely to be hypertensive and less likely to be smoker. The fasting plasma glucose levels were higher in the diabetic group. The 2 groups were similar on age, gender, serum creatinine, aortic systolic and diastolic pressures (**Table 1**). In the diabetic group, 55 (46.6%) patients were receiving only diet therapy, 53 (44.9%) were on oral antidiabetics and 10 (8.5%) were on insulin therapy. Corrected TIMI frame count values were similar in the 2 groups (**Figure 1**). The mean CTFC in the LAD was 21.0 ± 7.5 frames in the diabetic group and 21.3 ± 9.6 frames in the non-diabetic group (p=0.824). The mean CTFC in the CX was 23.3 ± 9.7 frames in the diabetic group and 23.5 ± 10.8 frames in the non-diabetic group (p=0.857). The mean CTFC in the RCA was 17.9 ± 6.7 frames in the diabetic group and 18.7 ± 7.4 frames in the

Table 1 - Baseline characteristics.

Characteristics	Non-diabetic group (n=122)	Diabetic group (n=118)	*P*-value
Age (years)	54.4±9.9	55.7±9.2	0.289
Male gender (%)	62 (50.8)	49 (41.5)	0.149
BSA (m^2)	1.85±0.18	1.90±0.17	0.058
Hypertension (%)	68 (55.7)	83 (70.3)	0.019
Smoking (%)	34 (27.9)	18 (15.3)	0.018
Total cholesterol (mg/dL)	207.6±41.5	196.1±36.9	0.028
LDL-cholesterol (mg/dL)	132.0±34.7	120.0±27.8	0.009
HDL-cholesterol (mg/dL)	46.6±12.6	42.7±10.0	0.015
Triglycerides (mg/dL)	150.3±81.3	183.6±129.0	0.021
Fasting plasma glucose (mg/dL)	103.6±2.7	144.6±43.8	<0.001
Serum creatinine (mg/dL)	0.98±0.65	0.90±0.17	0.155
Aortic systolic pressure (mm Hg)	135.3±15.9	135.5±19.8	0.935
Aortic diastolic pressure (mm Hg)	79.0±8.6	79.2±9.3	0.838
Heart rate (beats/minute)	75.6±7.3	78.0±8.7	0.019

Data listed as absolute numbers (percentages) or means ± standard deviation. BSA - body surface area, HDL - high-density lipoprotein, LDL - low-density lipoprotein

non-diabetic group (p=0.411). Results of multivariate analyses are shown in **Table 2**. The only variable having significant correlation with CTFC of all 3 coronary arteries was the BSA. Aortic diastolic pressure was negatively correlated with CTFC of LAD and Cx. Age was positively correlated with CTFC of Cx and RCA.

Discussion. The CTFC, which counts the numbers of cine frames required for dye to reach standardized distal landmarks, was developed by Gibson et al,[1] to provide an objective and quantitative index of angiographic coronary blood flow. Technically, dye injection rates and catheter sizes have no effect on CTFC,[8] but use of nitrate increases and tachycardia decreases CTFC significantly.[9] Also, if the dye is given first of diastole instead of systole, CTFC will be lower.[9] In several studies, it was used in acute coronary syndromes to assess coronary blood flow and lower CTFCs (faster flow) are associated with improved outcomes.[2,3,10]

Recently, Turhan et al[4] have shown that CTFC was significantly higher in patients with metabolic syndrome compared with control subjects. In their study, both groups had angiographicaly proven normal coronary

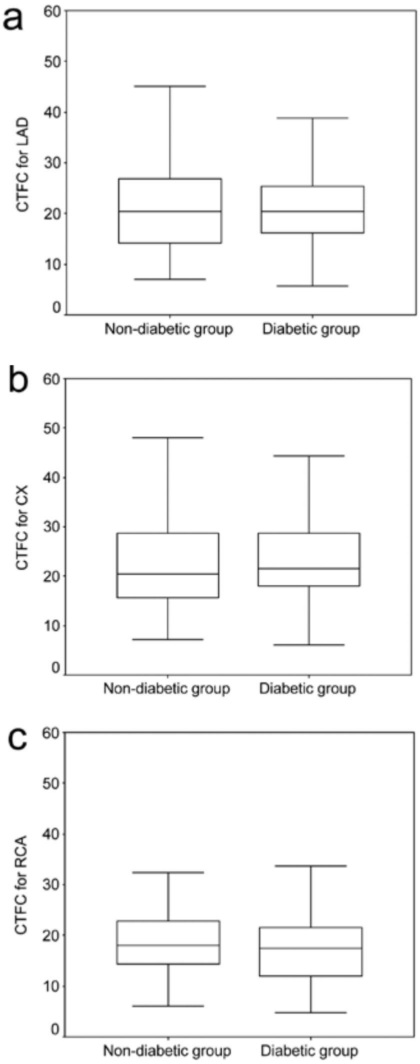

Figure 1 - Box–whisker plot of the corrected thrombolysis in myocardial infarction (TIMI) frame count (CTFC) for the a) left anterior descending artery (LAD), b) circumflex artery (Cx), and c) right coronary artery (RCA) in diabetic and non-diabetic patients.

Table 2 - Multivariate analyses using the corrected thrombolysis in myocardial infarction (TIMI) frame count in the 3 major epicardial arteries as outcome variable.

Variables	Coefficients	*P*-value
LAD		
BSA (m^2)	12.686	0.004
Aortic diastolic pressure (mm Hg)	-0.191	0.025
Cx		
BSA (m^2)	20.543	<0.001
Age (years)	0.205	0.030
Aortic diastolic pressure (mm Hg)	-0.197	0.046
RCA		
BSA (m^2)	13.005	<0.001
Age (years)	0.201	0.002

BSA - body surface area, Cx - circumflex artery, LAD - left anterior descending artery, RCA - right coronary artery arteries, so they ascribed their findings to microvascular disease. Although diabetes mellitus is one of the most common causes of microvascular disease,[5] we could not demonstrate any increase in CTFC. Our CTFC results in both diabetic and non-diabetic patients were comparable prior to the values reported by Gibson et al.[1] To our knowledge, at least 2 studies examined the baseline coronary flow in diabetics. Yokayama et al,[11] have shown that baseline myocardial blood flow in diabetic patients without symptoms and signs of ischemia was similar to non-diabetic patients. Akasaka et al,[12] have shown that diabetics with normal coronary angiograms have lower coronary flow reserve compared to non-diabetics with normal coronary angiograms. However, lower coronary flow reserve was due to both increased baseline coronary flow and decreased maximal hyperemic coronary flow in diabetics. These changes were even more pronounced in diabetics with retinopathy.[12] In multivariate analysis, the only variable associated with the CTFC of all major epicardial arteries was the BSA. This result is in agreement with those of Faile et al,[13] which may also in part explain higher CTFC found in metabolic syndrome. In our study, aortic diastolic pressure was negatively correlated with CTFC of LAD and CX but not the RCA. This result contrasts with those of Faile et al,[13] who found a positive correlation. The finding in our study may be explained by the higher diastolic pressure causing higher driving pressure across the coronary capillary bed resulting in a higher flow. Lack of association of diastolic pressure with CTFC of RCA may be due to a unique feature of flow in the RCA, which is less dependent on diastolic phase of cardiac cycles.[14] Increasing age was associated with higher CTFC in the RCA and CX. Faile et al,[13] also reported higher CTFC in the LAD and CX with increasing age. Our study represents the largest study of CTFC in diabetic patients with angiographically normal coronary arteries. In contrast, to previous studies,[1,8,13] we included only patients with completely normal coronary angiograms defined as complete absence of even minimal luminal irregularities in any of the coronary arteries, since angiographicaly visible atherosclerosis in a coronary artery predicts to diffuse involvement of the remainder of coronary tree with atherosclerosis.[15] This issue may be important because it was shown that angiographicaly invisible diffuse atherosclerosis may exert resistance to coronary flow.[16] The major limitations of this study are those inherent to retrospective studies. This study shows that CTFC in all major coronary arteries is similar in diabetic and non-diabetic patients with angiographically normal coronary arteries. Also in our study, BSA was significantly correlated with the CTFC of all major coronary arteries. Therefore, BSA should be taken into account in studies comparing different groups of CTFC.

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