The Relationship Between Coronary Collateral Circulation and In-hospital Mortality in Patients with First Acute Anterior STEMI

İlk Akut Önduvar ST Elevasyonlu Miyokart Enfarktüsü Geçiren Hastalarda Koroner Kollateral Dolaşım ile Hastane İçi Ölüm Arasındaki İlişki

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ABSTRACT

Aim: The aim of the present study is to investigate the prognostic value of Coronary Collateral Circulation (CCC) in patients with the first acute anterior wall ST Elevation Myocardial Infarction (STEMI) undergoing primary percutaneous coronary intervention (p-PCI).

Material and Method: A total of 220 Patients with first acute Anterior STEMI within first 6th hours undergoing p-PCI were divided into 2 groups with respect to absence of CCC and presence of CCC. Coronary collateral flow to the infarct related artery (IRA) was graded on baseline angiograms with the use of qualitative classification by Rentrop.

Results: A total of 220 patients mean age was of 61.4±12.3 years with first acute Anterior STEMI undergoing p-PCI were included the study. 34% of patients had CCC. The present study consisted of 64 female (29%) and 156 male (71%) patients. There were no statistically significant differences in respect to demographic characteristics, risk factors of coronary artery disease, LVEF, KILLIP classes, time from symptoms onset to PCI, door to balloon time, preprocedural and postprocedural angiographic characteristics and clinical outcomes which included cardiogenic shock on admission, cardiogenic shock in-hospital, fatal ventricular arrhythmias, complet AV block, mechanical complications and in-hospital mortality between the groups. In a stepwise backward multivariable logistic regression model, the independent prognostic indicators for in-hospital mortality were age (odds ratio [OR] 1.08, 95% CI 1.07 to 1.26, p=0.03), Time from symptoms onset to PCI (odds ratio [OR] 1.6, 95% CI 1.06 to 2.59, p=0.04) and unsuccessful p-PCI (odds ratio [OR] 3.3, 95% CI 1.04 to 10.9, p=0.04).

Conclusion: Presence of CCC was not associated with in-hospital mortality in patients presenting with first acute Anterior STEMI undergoing p-PCI within first 6th hours.

Key words: acute anterior STEMI; coronary collateral circulation; in-hospital mortality

ÖZET

Amaç: Çalışmada ilk akut önduvar ST Elevasyonlu Miyokart Enfarktüsü (STEMI) geçirip Primer Perkütan Koroner Girişim (p-PKG) uygulanmış hastalarda Koroner Kollateral Dolaşım (KKD) prognostik değerinin araştırılması amaçlanmıştır.

Materyal ve Metot: İlk akut önduvar STEMI geçiren, ilk 6 saat içinde p-PKG uygulanan toplam 220 hasta KKD varlığı ve yokluğuna göre 2 gruba ayrıldı. Başlangıç anjiogramlarında, enfarktta sorumlu artere doğru oluşan koroner kollateral kan akımı Rentrop klinik sınıflaması yöntemleri kullanılarak derecelendirildi.

Bulgular: İlk akut önduvar STEMI geçiren p-PKG uygulanan ortalaması yaşları 61,4±12,3 olan toplam 220 hasta çalışmamıza dahil edildi. Çalışmamızın %34’ünde KKD mevcuttu. Çalışmamızın kadın oranını %29, erkek oranı %71 oluşturmaktaydı. Gruplar arasında deyimifiz, ventriküler döngüsi, KILLIP sınıfları, koroner arter hastalığı risk faktörleri, sempromların başlangıcından p-PKG yapılacanın kadar geçen süre, balon-kapı süresi, periprosedürel ve postprosedürel anjiografik özellikleri ve başvuru anıtda Kardiyojenik Şok, Hastane içi Kardiyojenik Şok, Ölümü Ventrükel Arıtmiler, Kompakt AV blok, Mekanik Komplikasyonlar ve Hastane içi Ölümü içeren kliniği sonuçları arasında istatiksel olarak anlamlı farklılık mevcut olmadığı şeklinde bulduğumuz logistik regresyon analizi ve [İOR] 1,08, 95% CI 1,07 to 1,26, p=0,03), Sempromların başlangıcından p-PKG yapılacanın kadar geçen süre [İOR] 1,6, 95% CI 1,06 to 2,59, p=0,04), başarsız p-PKG [İOR] 3,3, 95% CI 1,04 to 10,9, p=0,04) hastane içi ölüm için bağımız tahmin etkileri olarak bulundu.

Sonuç: Çalışmada ilk akut önduvar STEMI geçiren, ilk 6 saat içinde p-PKG uygulanan hastalarında KKD ile hastane içi ölüm arasında ilişki tespit edilememiştir.

Anahtar kelimeler: ilk akut önduvar STEMI; koroner kollateral dolaşım; hastane içi ölüm
Introduction
Coronary Collateral Circulation (CCC) is an alternative source of blood supply for myocardium. Theoretically CCC is assumed to play an important role for keeping viability of jeopardized myocardium in critical stenosis of related epicardial coronary arteries. Protective effect of CCC on myocardium have been shown in several animal and human angiographic experimental studies1-3. Also presence of well developed CCC and its impact on jeopardized myocardium and clinical outcomes were investigated especially in studies on chronic stable coronary artery disease with total occlusion (CTO) of coronary artery4-7.

Despite advances in medical and interventional therapies, acute myocardial infarction (AMI) is still a significant cause of mortality and morbidity. Percutaneous coronary intervention (PCI) has proven to be the best therapeutic option in patients with acute ST-segment elevation myocardial infarction (STEMI). Anterior STEMI are still associated with an increased mortality compared to other forms and locations of myocardial infarction8. Thus, various clinical and angiographic parameters have been searched to predict clinical outcomes among patients with anterior STEMI in the era of PCI. CCC can be one of those parameters.

Aim of this study was evaluate the preintevention angiographic evidence of CCC and in-hospital outcomes in patients with anterior STEMI who were undergone PCI.

Material and Method
Patients with first acute anterior STEMI undergoing primary PCI (p-PCI) were enrolled in this prospective study between February 2012 and June 2015. Inclusion criteria were as follows: onset of symptoms <6 hours before p-PCI; ST-segment elevation >0.2 mV in 2 contiguous precordial V1, V2 leads and >0.1 mV in precordial V3-V6 leads with the left anterior descending artery (LAD) occlusion (Thrombolysis in Myocardial Infarction (TIMI) flow grade 0–1) as the infarct-related artery at baseline coronary angiography. Right and left coronary angiograms were obtained before the attempted angioplasty with sufficient quality to assess the presence of collateral circulation via the filling of LAD and side branches by. Exclusion criteria were prior anterior MI, venous graft-related infarcts, non-graftable collateral flow due to technical reasons, concurrent pericardial disease, chronic pulmonary disease, pulmonary hypertension, valvular heart disease (moderate to severe insufficiency and/or stenosis), acute pulmonary embolism, history of cardiac arrest before admission, renal failure (serum creatinin level >1.5 mg/dl on admission). Informed consent of each subject and approval of the Local Ethics Committee were obtained.

Coronary Angiography
Coronary angiography (CAG) was performed within 90 minutes of hospital admission. All patients received dual antiplatelet therapy with aspirin (300 mg) and clopidogrel (600 mg) or ticagrelor (180 mg) loading dose before CAG. Preprocedural anticoagulation consisted of intravenous unfractionated heparin (70 IU/kg) in all cases. Primary PCI with stent implantation was performed according to current guidelines9. The purpose of the p-PCI procedure was to obtain a residual stenosis of <20% in the infarct-related artery (IRA) by visual evaluation. An optimal angiographic result was defined as presence TIMI grade 3 flow in the LAD following p-PCI. An unsuccessful procedure was defined as a procedure resulting in TIMI grade 0–1 or 2 flow10. Use of glycoprotein IIb/IIIa inhibitors (i. e. tirofiban) was left to the discretion of the attending physician. Complete ST-segment resolution was defined as a reduction of >70% in the summed 12-lead extent of ST-segment elevation from baseline to the post-procedural electrocardiogram, which was recorded at 90th minute after the first balloon inflation.

Coronary Collateral Circulation
Coronary collateral flow to the infarct-related artery was graded on baseline angiograms with the use of a four-degree qualitative classification by Rentrop and Cohen2: 0 - no collateral vessels; 1 - filling of side branches of infarct related artery (IRA) via collateral channels without visualization of the epicardial segment; 2 - partial filling of the epicardial segment of IRA via collateral channels; 3 - complete filling of the epicardial segment of IRA via collateral channels. Two experienced cardiologists assessed the coronary angiograms in a blinded fashion and reached a consensus regarding the TIMI flow grade, the collateral flow grade and myocardial blush grade. Patients were divided into 2 groups based on level of CCC as follows: absence of coronary collateral flow (Rentrop 0) and presence of coronary collateral flow (Rentrop 1, 2, 3) Angiographic myocardial blush was graded in a core
laboratory according to the method described by van’t Hof11: 0, no contrast density or persistent staining; 1, minimal contrast density; 2, moderate contrast density, but less than that obtained during angiography of a non-IRA; or 3, normal contrast density, comparable to that obtained during angiography of a non-IRA.

**Echocardiography**

Following successful recanalization of LAD, a significant improvement of the LV function can be observed echocardiographically approximately 3–5 hours after the intervention. Therefore, standard two-dimensional echocardiography with a digital ultrasonic device system (iE33; Philips, Netherlands) was performed for each patient in left lateral decubitus position 5 hours after p-PCI. At least 5 consecutive beats were recorded, and the average of values was used for statistical analyses. All recordings were made using a sweep speed of 100 mm/s, with an electrocardiogram (lead II). Echocardiographic evaluation of the LV function was completed by the assessment of systolic and diastolic diameters, systolic and diastolic volume. Modified Simpson’s method was used to assess the left ventricular ejection fraction (LVEF).

**In-hospital clinical course**

Adjunctive medical therapy followed the standards of the coronary care unit. The primary objective of this study was to examine in-hospital death. Secondary objectives were to examine the occurrence of advanced heart block, ventricular arrhythmias (ventricular fibrillation and ventricular tachycardia) requiring treatment, hypotension necessitating intraaortic balloon pump (IABP) or pharmacological hemodynamic support. Mechanical complications included free wall rupture, ventricularseptal rupture and severe mitral regurgitation secondaryto corda tendinea or papillary muscle rupture. Cardiogenic shock was characterized by hypotension (defined as systolic blood pressure below 90 mmHg lasting more than 15 minutes or above 90 mmHg under positive inotrop/vasopressor treatment and IABP support), and elevated LV filling pressures in association with signs of tissue hypo-perfusion (cold extremities, cyanosis, oliguria or altered mental status) which were not caused by extra-cardiac causes.

All statistical analyses were performed using the IBM SPSS software (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) Continuous variables were presented as mean ± SD whereas categorical variables as count and percentages. The Kolmogorov-Smirnov test was used to evaluate the distribution of continuous variables. Continuous variables were compared with Student’s t test or Mann-Whitney U test according to the distribution of the data. Categorical variables were compared with chi-square or Fisher’s exact tests when ever appropriate. Univariate and multivariate logistic regression analyses were conducted to assess association of CCC and inhospital mortality. In stepwise multivariate regression analysis (Backward, Wald), effect size was adjusted for all variables with a univariate significance level of <0.2. Adjusted odds ratios (OR), along with their 95% CIs were presented. A 2-tailed p value of <0.05 was considered statistically significant.

**Results**

A total of 220 patients 34% of patients had CCC, mean age was of 61.4±12.3 years with first acute Anterior STEMI undergoing p-PCI were included the study. The present study consisted of 64 female (29%) and 156 male (71%) patients. There were no statistically significant differences in respect to demographic characteristics, risk factors of coronary artery disease, LVEF, KILLIP classes, time from symptom onset to PCI and door to balloon time between the groups. Also there were no statistically significant differences in respect to antiagregant therapies, other medications given in the hospital and IABP support between the groups (Table 1). There were not found statistically significant differences in respect to number of diseased coronary arteries, preprocedural TIMI flow and MBG grade and postprocedural TIMI flow (successful/unsuccesful PCI) between the groups (Table 2). Clinical outcomes were shown in Table 3. There were not found statistically significant differences when compared to the groups with clinical outcomes which included cardiogenic shock on admission, cardiogenic shock in-hospital, fatal ventricular arrhythmias, complete AV block, mechanical complications and in-hospital mortality. In a stepwise backward multivariable model, when all univariate (p<0.05) predictors of in-hospital mortality were considered, the independent prognostic indicators were age (odds ratio [OR] 1.08, 95% CI 1.07 to 1.26, p=0.03, Time from symptoms onset to PCI; odds ratio [OR] 1.6, 95% CI 1.06 to 2.59, p=0.04) and unsuccessful p-PCI (OR 3.3, 95% CI 1.04 to 10.9, p=0.04).
### Table 1. Baseline clinical, echocardiographic characteristics and in-hospital therapy

| Variables                                | Coronary collateral circulation | p value |
|------------------------------------------|---------------------------------|---------|
|                                          | Absent (n=144)                  | Present (n=76) |         |
| Age (years)                              | 60.5±11.9                       | 63.3±13.2 | 0.11    |
| Male [n (%)]                             | 116 (80.6)                      | 57 (75.0) | 0.34    |
| Hypertension [n (%)]                     | 44 (30.6)                       | 20 (26.3) | 0.51    |
| Hyperlipidemia [n (%)]                   | 32 (22.2)                       | 14 (18.4) | 0.50    |
| Diabetes Mellitus [n (%)]                | 31 (21.5)                       | 16 (21.1) | 0.93    |
| Smoke [n (%)]                            | 65 (45.1)                       | 35 (46.1) | 0.89    |
| Family History of CAD [n (%)]            | 59 (41.0)                       | 29 (38.2) | 0.68    |
| Previous PCI [n (%)]                     | 18 (12.5)                       | 10 (13.2) | 0.89    |
| Time from symptoms onset to PCI (hours)  | 3.1±1.11                       | 3.17±0.95 | 0.15    |
| Door to balloon time (minutes)           | 42±6.2                         | 41.7±6.3  | 0.24    |
| LV EF (%)                                | 41.0±10.5                      | 45.2±10.0 | 0.06    |
| KILLIP Class                             | 0.80                            |          |         |
| KILLIP I                                 | 87 (60.4)                       | 46 (60.5) |         |
| KILLIP II                                | 39 (27.1)                       | 22 (28.9) |         |
| KILLIP III                               | 7 (4.9)                         | 3 (3.9)   |         |
| KILLIP IV                                | 11 (7.6)                        | 5 (6.6)   |         |
| In-hospital therapy                      |                                 |           |         |
| Aspirin [n (%)]                          | 137 (95.1)                      | 71 (93.4) | 0.59    |
| ACEI-ARA [n (%)]                         | 91 (63.2)                       | 49 (64.5) | 0.85    |
| Clopidogrel [n (%)]                      | 123 (85.5)                      | 64 (84.3) | 0.80    |
| Ticagrelol [n (%)]                       | 21 (14.5)                       | 12 (15.7) | 0.68    |
| Statin [n (%)]                           | 128 (88.9)                      | 68 (89.5) | 0.89    |
| Glycoprotein IIb/IIIa inhibitor [n (%)]   | 40 (27.8)                       | 24 (31.6) | 0.58    |
| IABP [n (%)]                             | 20 (13.8)                       | 9 (11.8)  | 0.80    |

Data are expressed as mean ± SD for normally distributed data or count (percentage) for categorical variables; ACEI-ARA, angiotensin-converting enzyme inhibitor-angiotensin II receptor antagonist; CAD, coronary artery disease; IABP, intra-aortic balloon pump; LV EF, Left ventricular ejection fraction; MI, Myocardial infarction; PCI, Percutaneous coronary intervention.

### Table 2. Preprocedural and postprocedural angiographic characteristics related to coronary collateral circulation

| Variable                               | Coronary collateral circulation | p value |
|----------------------------------------|---------------------------------|---------|
|                                        | Absent (n=144)                  | Present (n=76) |         |
| Number of diseased coronary arteries   |                                 |           | 0.25    |
| 1 [n (%)]                              | 90 (62.5)                       | 41 (53.9) |         |
| 2 [n (%)]                              | 39 (27.1)                       | 25 (32.9) |         |
| 3 [n (%)]                              | 15 (10.4)                       | 10 (13.2) |         |
| TIMI flow before PCI                   |                                 |           | 0.98    |
| TIMI 0 [n (%)]                         | 123 (85.4)                      | 65 (85.5) |         |
| TIMI 1 [n (%)]                         | 21 (14.6)                       | 11 (14.5) |         |
| MBG grade before PCI                   |                                 |           | 0.59    |
| MBG 0–1                                | 132 (91.7)                      | 68 (89.5) |         |
| MBG 2                                  | 12 (8.3)                        | 8 (10.5)  |         |
| TIMI flow after PCI                    |                                 |           | 0.95    |
| Unsuccessful (TIMI 0–1) [n (%)]        | 15 (10.4)                       | 8 (10.5)  |         |
| Successful (TIMI 2–3) [n (%)]          | 129 (89.6)                      | 68 (89.5) |         |

Data are expressed as mean ± SD for normally distributed data or count (percentage) for categorical variables; MBG, myocardial blush grade; PCI, Percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.
Discussion

In the present study, we found that the presence of CCC to the ischemic myocardium in the early hours of infarction was not an independent predictor of inhospital mortality in patients with anterior STEMI undergone PCI. However by multivariate analysis, age, unsuccessful primary angioplasty and time from symptoms onset to PCI were independent predictor of mortality in our study. Although EF didn’t reach statistical significance between the groups, it was detected higher in the group with CCC which may be limiting the infarct size.

In patients with acute STEMI, a relevant protective role of collaterals has been observed as smaller infarct size, preservation of post-MI cardiac function, reduction in post-MI ventricular dilatation and post-infarct aneurysm formation. Increased collateral flow was also associated with less need for IABP post-PCI and better myocardial blush grade. However, the impact of the CCC on short and long term prognosis of MI is unclear.

Although the exact underlying mechanism for the protective role of collaterals are unclear, different mechanisms have been proposed in the literature. Acute myocardial ischaemia it self leads to QT interval prolongation and QT dispersion, which is associated with fatal arrhythmias. In a study, it was shown that CCC reduced further QT prolongation during vessel occlusion and this may contribute to the reduced mortality in patients with a well-developed CCC. The collateral circulation has been also demonstrated to have clinical benefits regarding smaller infarct size, preservation of post-MI cardiac function, and reduction in post-infarct ventricular dilatation. Over the long term, these effects are likely to contribute to a reduced mortality.

Despite the above mentioned mechanisms, clinical trials revealed conflicting results. A meta-analysis of 12 studies and 6529 patients showed that the CCC is associated with relatively improved survival. The result was consistent both in patients underwent PCI or a diagnostic angiogram only, or in case of collaterals detected visually or with CFI. Subgroup analyses indicated a clearly prolonged survival of well-collateralized patients with stable CAD while the analyses for subacute and acute MI showed comparable risk reductions but without statistical significance. Another a meta-analysis of nine studies comprising 6791 patients showed that the coronary collateral circulation was associated with relatively improved survival and fewer re-infarctions with statistical significance.

Several factors may cause these conflicting results. Firstly different study population such as patient with stable CAD, acute MI and subacute MI were included in these meta analysis. Also in most of the studies involving acute STEMI, localization of the myocardial infarction was not specified. Whereas, it is known that anterior wall STEMI have highest in-hospital mortality among patients with acute STEMI. There are only a few studies investigated impact of CCC on in hospital mortality in the literature. One of these studies enrolled 190 patients with anterior STEMI treated by primary angioplasty within the first 6 h of the onset of symptoms investigated association between CCC and in-hospital outcomes. Collateral flow to the infarct-related artery before angioplasty was angiographically assessed by Rentrop classification, 65 patients (36%)
Limitation
This study included only patients who were able to visit hospitals within 24 hours after anterior STEMI onset, and who could be undergone emergent coronary angiography which revealed complete occlusion of IRA; therefore, there could be a selection bias in this study and it is not clear whether identical conclusions can be drawn for all patients with STEMI. Angiographically detected collateral flow provides only an estimate of existing absolute collateral flow since only collaterals 100 µm or more in diameter can be identified. Collateral flow can also be evaluated with methods such as myocardial contrast echocardiography, cardiac nuclear imaging, and pressure-derived collateral flow index with better quantification but indirectly. However their routine uses in clinical practice are not feasible in the setting of acute myocardial infarction treated with PCI.

Conclusions
The result of this study involving the patients with first acute anterior STEMI revealed that the presence of CCC before PCI may not be associated with in-hospital mortality in contemporary PCI era. Association CCC and mortality should be investigated by large-scale studies.

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