Orjinal Araştırma / Original Article

Changes in Non-culprit Lesion Severity on Follow-up Coronary Angiography after Primary Percutaneous Coronary Intervention

Primer Perkütan Koroner Girişimlerde Sorumlu Olmayan Lezyonların Kontrol Koroner Anjiyografide Değişimleri

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Abstract

Aim: Non-culprit lesion severity has often been exaggerated at the time of acute ST segment elevation myocardial infarction (STEMI). We aimed to determine changes in non-culprit lesions severity on follow-up coronary angiography (CAG) and independent predictors of these changes.

Material and Method: We retrospectively evaluated the changes in non-culprit lesion stenosis on follow-up CAG which was done within 2 months after primary percutaneous coronary intervention (P-PCI) in patients presenting with STEMI.

Results: 154 patients were included in this study and 207 non-culprit lesions (percentage diameter stenosis (PDS) ≥50%) were compared using quantitative coronary analyses (QCA). Minimal lumen diameter (1.30±0.38 mm vs. 1.54±0.46 mm, p<0.001) and reference vessel diameter (2.88±0.66 mm vs. 2.92±0.64 mm, p=0.001) were increased significantly and PDS (54.49±9.38 vs. 47.5±11.17, p<0.001) and percentage area stenosis (78.38±8.65 vs. 71.29±11.84, p= <0.001) were decreased significantly. There was no significant change in lesion length (13.52±5.59 mm vs. 13.25±5.31 mm, p= 0.078). 65 (31.4%) of these significant lesions (PDS ≥50% by QCA) were regressed (less than 50%) on follow-up CAG. In multivariable analyses; current smoking, clopidogrel use after the P-PCI and history of coronary artery disease were the independent predictors of decrease in PDS.

Conclusion: Significant exaggeration of non-culprit lesion stenosis severity occurs at the time of acute STEMI.

Keywords: Primary percutaneous coronary intervention; multi-vessel disease; non-culprit lesion; quantitative coronary analysis

Öz

Amaç: Akut ST segment yükselmeli miyokard enfarktüsü (STEMI) sırasında sorumlu olmayan lezyonlar sıklıkla olduklarından daha ciddi görünürler. Kontrol koroner anjiyografi (KAG)'de sorumlu olmayan lezyonların şiddetindeki değişiklikleri ve bu değişikliklerin bağımsız prediktörlerini belirlemeyi amaçladık.

Gereç ve Yöntem: STEMI ile başvuran ve primer perkütan koroner girişimden (P-PKG) sonraki 2 ay içinde kontrol KAG yapılan hastalarda sorumlu olmayan lezyonlardaki değişiklikleri retrospektif olarak değerlendirdik.

Bulgular: Bu çalışmaya 154 hasta dahil edildi ve 207 (yüzde çap darlığı (YÇD) ≥50%) sorumlu olmayan lezyon kantitatif koroner analizler (QCA) kullanılarak karşılaştırıldı. Minimal lümen çapı (1,30±0,38 mm'ye karşı 1,54±0,46 mm, p <0,001) ve referans damar çapı (2,88±0,66 mm'ye karşı 2,92±0,64 mm, p=0,001) önemli ölçüde arttı ve YÇD (54,49±9,38'e karşı 47.5±11,17, p <0,001) ve yüzde alan darlığı (78.38±8.65 vs. 71.29±11.84, p= <0,001) anlamlı olarak azaldı. Lezyon uzunluğunda anlamlı değişiklik izlenmedi (13,52±5,59 mm'ye karşı 13,25±5,31 mm, p= 0,078). Bu önemli lezyonların 65'i (% 31.4) (QCA'ya göre YÇD ≥% 50) kontrol KAG'de geriledi (% 50'den az). Çok değişkenli analizlerde; mevcut sigara kullanımı, P-PKG'den sonra klopidogrel kullanımı ve koroner arter hastalığı öyküsü, YÇD'deki azalmanın bağımsız prediktörleri idi.

Sonuç: Akut STEMI sırasında sorumlu olmayan lezyonlardaki darlıkların derecesi önemli ölçüde daha artmış olarak izlenmektedir.

Anahtar kelimeler: Primer perkütan koroner girişim; çoklu damar hastalığı; sorumlu olmayan lezyon; kantitatif koroner analiz

INTRODUCTION

Acute coronary syndrome (ACS) is a continuum disease process and complete coronary occlusion in the absence of collateral perfusion results in ST-segment elevation myocardial infarction (STEMI). STEMI comprises approximately 25% to 40% of ACS presentations.[1,2] Prompt restoration of myocardial perfusion is vital and primary percutaneous coronary intervention (P-PCI) is the preferred mode of reperfusion.[3,4] Approximately 50% of STEMI patients have significant stenoses in one or more non-culprit arteries[5,6] at the time of P-PCI. Coronary flow also globally slows in acute myocardial infarction (AMI), and relief of the culprit artery stenosis by PCI restores flow in the non-culprit artery as well.[9] Non-culprit stenosis severity may be exaggerated on angiographic assessment at the time of AMI.[7,8] ACS are usually triggered by acute thrombosis, superimposed on a ruptured or eroded atherosclerotic plaque.[10,11] The thrombotic response to plaque rupture is very a dynamic process may result in generation of vasoconstrictors such as thrombin, serotonin and thromboxane A and often associated with vasospasm and distal embolization.[12] Endothelial dysfunction associated with increased risk of thrombosis and abnormal vasomotor response via mediators such as prostacyclin, endothelin-1 and decreased secretion of nitric oxide.[13] Increased sympathetic activity has been documented during acute myocardial infarction and this may cause coronary vasoconstriction in the presence of endothelial dysfunction. Also, activation of the circulating renin-angiotensin system occur during severe ischemia. This neurohormonal activation leads to systemic and possibly to coronary vasoconstriction.[14,15] All of these mechanisms involved in pathogenesis of ACS are possibly contributing to exaggeration of non-culprit vessel stenosis severity during STEMI. Significant stenosis has generally been defined as >50% diameter stenosis of non-culprit artery. [8,9,16] We performed a retrospective analysis of patients who underwent P-PCI for STEMI with significant non-culprit lesions and had another elective coronary angiogram (CAG) within 60 days. We sought to determine changes in non-culprit vessel lesions severity and independent factors associated with these changes.

MATERIAL AND METHOD

Patient population

We reviewed data of all patients who presented with STEMI and underwent P-PCI and had an elective follow-up CAG within 2-60 days between December 2010 and July 2012 at our Hospital. This study was conducted according to the Declaration of Helsinki and approved by the Hospital Clinical Research Ethics Committee (IRB number: 2013/13). Written informed consent was obtained from all patients before the procedures. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study; all study analyses, the drafting and editing of the manuscript, and its final contents.

Patient selection

>18 year-old patients who presented with STEMI and underwent P-PCI within the first 12 hours of the onset of typical ischemic chest pain and found to have significant (visually estimated diameter stenosis of ≥50% on the P-PCI) non-culprit lesions and had an elective follow-up CAG within 2-60 days were included in this study. Patients who had non-culprit lesions with chronic total occlusion (100% stenosis), instent stenosis, CABG to non-culprit arteries and non-matching projections (>5° difference in any plane between P-PCI and follow-up CAG) were excluded from this study. Patients who had follow-up CAG done for ACS were also excluded from this study.

Procedural details

Primary PCI was performed by the percutaneous femoral approach and all patients received a chewable 300 mg aspirin and clopidogrel 600 mg loading dosage before the procedure. The culprit lesion was identified as the site of acute occlusion or impaired Thrombolysis in Myocardial Infarction 3 flow.[17] Non-culprit lesions were defined as lesions in an artery other than the infarct related artery with smooth angiographic borders and no associated thrombus. Heparin (100 IU/kg I.V.) was administered when the coronary anatomy was defined. P-PCI was performed only for culprit lesions. After angioplasty, all patients were admitted to the coronary care unit, where 100 mg aspirin and 75 mg clopidogrel were continued in all patients. The use of glycoprotein IIb/IIIa inhibitors was up to the discretion of the operator.

Quantitative coronary analysis (QCA) measurements

All P-PCI angiograms were reviewed by two experienced operators to find those patients who had a significant non-culprit lesion (visually estimated diameter stenosis of ≥50%). Angiographic images before any intracoronary nitrates were administered were used for comparisons. Coronary angiography (Siemens Artis Zee Ceiling, Erlangen, Germany) was performed in multiple orthogonal projections and non-culprit lesion severity was analyzed with validated QCA 2D coronary quantification software (Scientific QCA Analysis, Siemens, Erlangen, Germany).[18] The contrast filled catheter tip was traced and used for calibration. End-diastolic images in the least foreshortened view were used for the quantitative measurement. Projection that showed the most critical stenosis was chosen and orthogonal projection was identified. Average of the measurements from these 2 projections was obtained. Analysis was performed by two experienced operators and the average of the two was calculated. İnterobserver agreements were 94% and 91% for MLD and PDS, respectively.

Data Collection and Definitions

Patients' demographic and clinical characteristics were obtained from patients' charts and electronic medical record system. Following information was gathered: age, gender, co-morbidities and risk factors for coronary artery disease (CAD) (smoking history, family history, diabetes mellitus,

hypertension, and hyperlipidemia), history of CAD (previous MI, PCI and CABG), time elapsed to follow-up CAG, MI territory, angiographic and procedural details (culprit lesion, non-culprit lesions, PTCA, tirofiban and stent use on P-PCI) and medications on PPCI and follow-up CAG. Angiographic data of the patients were obtained from catheter laboratory records and electronic medical record system. Angiographic images of primary PCI and follow-up CAG were used for QCA. Minimal lumen diameter (MLD), percentage diameter stenosis (PDS), percentage area stenosis (PAS), reference vessel diameter (RVD) and lesion length (LL) were the parameters assessed by QCA.

MLD, RVD and LL defined as the smallest lumen diameter in the segment of interest, the averaged diameter of the coronary artery assumed without atherosclerotic disease and length of the stenosis as measured by 2 points where the coronary margins change direction creating a shoulder between the angiographically normal subsegment and the diseased subsegment respectively. Percentage diameter stenosis and percentage area stenosis are calculated as follows: $100\% \times (RVD-MLD)/RVD$ and $100\% \times (RVD^2 - MLD^2)/RVD^2$ respectively.

STEMI defined as ST segment elevation of at least 1 mm in two or more contiguous leads (2 mm for V1–V3) or new-onset left bundle branch block.[3]

Lesion not responsible for the acute STEMI is defined as non-culprit lesion. Significant lesion is defined as >50% diameter stenosis of artery by QCA.

The primary goal was to assess the changes in non-culprit vessel lesion severity by QCA and secondary goal was to assess the independent predictors of these changes.

Statistical analysis

Continuous variables are expressed as means±SD, and categorical variables are expressed as percentages. Univariable analyses (using the chi-square or the Fisher exact test and McNemar test for paired categorical variables and the t test or Mann-Whitney U test for continuous variables) were performed to identify demographics, baseline clinical characteristics, and peri-procedural variables associated with changes in non-culprit vessel lesion severity (MLD, RVD, PDS, PAS and LL). Angiographic data between the two procedures were compared using paired t tests and changes in medications were compared using McNemar test. Uni-and multivariable predictors of changes in in non-culprit vessel lesion severity were assessed by logistic regression analysis and odds-ratios (OR) are reported. A backward stepwise multivariable logistic regression model was carried out to assess the independent relationship between variables (demographics, baseline clinical characteristics and changes in medications) and changes in non-culprit vessel QCA parameters. Variables exhibiting a P value of <0.1 in the univariable analysis were entered into the multivariable logistic regression model. For all tests, 2-sided P values <0.05 were considered as significant. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 17.0 for Windows (SPSS Inc, Chicago, Illinois, USA).

RESULTS

A total of 1442 consecutive patients who presented with STEMI and underwent P-PCI between December 2010 and July 2012 at a single tertiary care center were retrospectively reviewed. There were 749 (51.9%) patients with operator-reported multi-vessel disease. Initially, 195 patients were identified who had elective follow-up CAG within 2-60 days after primary PCI for non-culprit lesion PCI or before scheduled coronary artery by-pass graft (CABG) surgery. Six patients had instent stenoses, 2 patient had CABG to non-culprit vessels, 4 patients had chronic total occlusion (100% stenosis) and 29 patients had non-matching projections (>5° difference in any plane). After exclusion of those 41 patients, final study population consisted of 154 patients. Of those 154 patient included in this study had total of 207 significant non-culprit lesions.

Demographics and Baseline Clinical characteristics of the study population are shown in **Table 1**. Mean age was 56.1±9.5 (33-88) and 131 (85.1%) of the patients were male. TIMI 3 flow was achieved in all patients after P-PCI. Sixty-four (41.5%) patients had acute anterior MI. Time to follow-up CAG was 25.5±14.2 days (2-60).

Table 1. Patients' Demographics and Baseline Clinical characteristics	
Demographics and Baseline Clinical characteristics	**Study population (n=154)**
Age (yrs)	56.1±9.5 (33-88)
Male	131 (85.1%)
Diabetes mellitus	42 (27.3%)
Hypertension	74 (48.1%)
Current smoker	99 (64.3%)
Hyperlipidemia	83 (53.9%)
Family history of CAD	49 (31.8)
History of CAD	46 (29.8%)
Previous MI	25 (16.2%)
Previous PCI	19 (12.3%)
Previous CABG	2 (1.3%)
Anterior MI	64 (41.5%)
Time to follow up CAG (day)	25.5±14.2 (2-60)
Culprit Vessel	
LAD	64 (41.5%)
Cx	34 (22.1%)
RCA	56 (36.4%)
Non-Culprit Vessel	
LAD	79 (38.2%)
Cx	53 (25.6%)
RCA	75 (36.2%)
Number of Non-Culprit Vessels	
1 Vessel	112 (72.7%)
2 Vessel	33 (21.4%)
3 Vessel	7 (4.5%)
4 Vessel	2 (1.3%)

CABG: coronary artery bypass graft surgery, CAD: coronary artery disease, Cx: circumflex artery, LAD: left anterior descending, MI: myocardial infarction, PCI: percutaneous coronary intervention, PTCA: percutaneous transluminal coronary angioplasty, RCA: right coronary artery.

on presentation and TIMI 3 flow was achieved either by simple balloon dilatation and/or thrombus aspiration. Lesion length, RVD, MLD, mean vessel diameter (meanD), and area of stenosis were compared during P-PCI and follow-up CAG. They also found that there was no significant change in lesion length.

RVD was increased significantly on follow-up CAG in our study similar to the reported by Sahin et al.[19] However, Hanratty et al.[8] and Cristea et al.[20] found that there was no change in RVD. Hanratty et al.[8] included 48 patients with 59 non-culprit lesions suitable for analysis in their study. Between infarct and non-infarct angiograms there was a significant change in minimal lumen diameter (1.53±0.51 mm vs. 1.78±0.65 mm, p <0.001) and percentage diameter stenosis (49.3±14.5% vs. 40.4±16.6%, p <0.001) of the nonculprit lesion without significant change in reference segment diameter. Twenty-one percent of patients had lesions >50% at AMI that were <50% at non-AMI angiography. Infarct versus non-infarct setting was the only significant independent predictor of change in non-culprit stenosis. PDS was decreased significantly in our study consistent with the observations of Hanratty et al.[8] and Sahin et al.[19] MLD was increased and PDS was decreased significantly in our study on follow-up CAG. Hanratty et al.[8] and Sahin et al.[19] also reported similar significant changes in MLD and PDS. We also found that current smoking, history of CAD and clopidogrel use after the P-PCI were independent predictors of both increase in MLD and decrease in PDS in multivariable analysis.

 Natural progression of coronary artery disease involves two distinct processes. First, fixed and almost irreversible process that causes gradual luminal narrowing slowly over decades (atherosclerosis). Second, a dynamic and potentially reversible process that causes rapid coronary occlusion (thrombosis or vasospasm, or both). Thus, symptomatic coronary lesions contain a variable mix of chronic atherosclerosis and acute thrombosis but, because the exact nature of the mix is unknown in the individual patient, the term atherothrombosis is frequently used. Generally, atherosclerosis predominates in lesions responsible for chronic stable angina, whereas thrombosis constitutes the critical component of culprit lesions responsible for the ACS.[11,12,21,22]

Individuals using clopidogrel after the P-PCI were more likely to have increase in MLD and decrease in percentage diameter stenosis, OR (Odds Ratio): 20.0 (95% CI: 2.34 - 170.53, p= 0.006) and OR: 26.63 (95% CI: 3.06 - 231.30, p= 0.003), respectively. This significant improvement in non-culprit vessel stenosis with the use of clopidogrel can be due to the inhibition of platelet functions which result in inhibition of this second dynamic and reversible process of atherothrombosis at the time of P-PCI as described above.

Individuals with a current smoking history were more likely to have increase in MLD and decrease in percentage diameter stenosis, OR: 10.36 (95% CI: 4.06 - 26.41, p <0.001) and 10.42 times (95% CI: 4.09 - 26.53, p <.001), respectively. Cigarette smoking plays a direct role by constricting coronary arteries

through nicotine-mediated action on alpha-adrenergic receptors and by induction of endothelial dysfunction by nicotine and oxidizing chemicals.[23,24] Therefore, smoking is more likely to cause rapid and reversible coronary occlusion in patients with ACS rather than the fixed stenosis.

Individuals with a history of CAD were less likely to have increase in MLD and decrease in percentage diameter stenosis, OR: 0.21 (95% CI: 0.084 - 0.559, p= 0.002) and 0.26 (95% CI: 0.098 – 0.689, p= 0.007), respectively. Individuals with a known history of CAD are more likely to have predominantly atherosclerotic lesions. These are generally fixed fibroproliferative and hardly reversible lesions that cause slow gradual stenosis.

CONCLUSION

Exaggeration of non-culprit lesion stenosis severity occurs at the time of acute STEMI. Deferring the revascularization decision making and further evaluation of these lesions with FFR or intravasküler ultrason may result in more accurate evaluation of the lesions and prevent unnecessary PCI.

Limitations

Retrospective and monocentric characters are the limitations of our study.

ETHICAL DECLARATIONS

Ethics Committee Approval: Study was approved by the Republic of Turkey Ministry of Health, University Of Health Sciences, Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Clinical Research Ethics Committee (IRB number: 2013/13).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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REFERENCES

1. Mandelzweig L, Battler A, Boyko V, et al. The second Euro Heart Survey on acute coronary syndromes: characteristics, treatment, and outcome of patients with ACS in Europe and the Mediterranean Basin in 2004. Eur Heart J. 2006;27:2285-93.

2. Yeh RW, Sidney S, Chandra M, et al. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med. 2010;362:2155-65.

3. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33(20):2569-619.

4. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;127:e362-425.

5. Widimsky P, Holmes DR Jr. How to treat patients with ST-elevation acute myocardial infarction and multi-vessel disease? Eur Heart J 2011;32:396-403.

6. Cavender MA, Milford-Beland S, Roe MT, Peterson ED, Weintraub WS, Rao SV. Prevalence, predictors, and in-hospital outcomes of non-infarct artery intervention during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction (from the National Cardiovascular Data Registry). Am J Cardiol 2009;104:507–13.

7. Kahn JK. Evidence for dynAMEc coronary vasoconstriction of non-infarct vessels during acute myocardial infarction. Cathet Cardiovasc Diagn. 1995;36(4):371-3.

8. Hanratty CG, Koyama Y, Rasmussen HH, Nelson GI, Hansen PS, Ward MR. Exaggeration of nonculprit stenosis during acute myocardial infarction: implication for immediate multivessel revascularization. J Am Coll Cardiol. 2002;40:911-6.

9. Gibson CM, Ryan KA, Murphy SA, et al. Impaired coronary blood flow in nonculprit arteries in the setting of acute myocardial infarction. The TIMI Study Group.Thrombolysis In Myocardial Infarction. J Am Coll Cardiol 1999;34: 974–82.

10. Glass CK, Witztum JL. Atherosclerosis: the road ahead. Cell 2001;104:503–516.

11. Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. Circulation 2001;104:365–372

12. Falk E, Shah PK, Fuster V. Atherothrombosis and thrombosis-prone plaques. In: Fuster V, Alexander RW, O'Rourke RA, et al., eds. Hurst's the Heart, 2004. New York: McGraw-Hill, pp. 1123–39.

13. Bogaty P, Hackett D, Davies G, Maseri A. Vasoreactivity of the culprit lesion in unstable angina. Circulation 1994;90:5-11.

14. Remme WJ, Kruijssen DA, Look MP, Bootsma, de Leeuw PW: Systemic and cardiac neuroendocrine activation and severity of myocardial ischemia in humans. J Am Coll Cardiol 1994;23:82-91

15. Slavíková J, Kuncová J, Topolcan O. Plasma catecholamines and ischemic heart disease. Clin Cardiol 2007;30:326–330.

16. Wald DS, Morris JK, Wald NJ, et al. Randomized trial of preventive angioplasty in myocardial infarction. N Engl J Med. 2013 Sep 19;369 (12):1115-23.

17. Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial. Phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. Circulation 1987;76:142-5.

18. Salvatore Davide Tomasello, Luca Costanzo, Alfredo Ruggero Galassi. Quantitative Coronary Angiography in the Interventional Cardiology, Advances in the Diagnosis of Coronary Atherosclerosis, Prof.Suna Kirac (Ed.), 2011. ISBN: 978-953-307-286-9, InTech, Available from: http://www.intechopen.com/books/advances-in-the-diagnosis-of-coronary-atherosclerosis/quantitativecoronary-angiography-in-the-interventional-cardiology

19. Sahin M, Demir S, Kocabay G, et al. Coronary vessel diameters during and after primary percutaneous coronary artery intervention. Herz 2014;39(4):515-21.

20. Cristea E, Stone GW, Mehran R et al. Changes in reference vessel diameter in ST-segment elevation myocardial infarction after primary percutaneous coronary intervention: implications for appropriate stent sizing. Am Heart J 2011;162(1):173–7.

21. Libby P. Inflammation in atherosclerosis. Nature 2002;420: 868–74.

22. Davies MJ. The pathophysiology of acute coronary syndromes. Heart 2000;83:361–66.

23. Nicod P, Rehr R, Winniford MD, Campbell WB, Firth BG, Hillis LD. Acute systemic and coronary hemodynamic and serologic responses to cigarette smoking in long term smokers with atherosclerotic coronary artery disease. J Am Coll Cardiol 1984;4(5):964–71.

24. Puranik R, Celermajer DS. Smoking and endothelial function. Progress in Cardiovascular Diseases 2003;45(6):443–58.