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PREDICTORS OF IMPROVEMENT IN LEFT VENTRICULAR FUNCTION AFTER STENT IMPLANTATION OF CHRONIC CORONARY OCCLUSION

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Kronik koroner oklüzyonlu hastalarda, koroner stent implantasyonunun sol ventrikül fonksiyonları üzerine etkisi iyi bilinmektedir.

Bu çalışmanın amacı, çıplak ve ilaç kaplı stentlerin sol ventrikül ejeksiyon fraksiyonu (LVEF) üzerine etkisini araştırmak ve LVEF düzelmesinde etkili klinik ve anjiyografik faktörleri belirlemektir.

Kronik oklüzyon nedeniyle başarılı stent implantasyonu yapılan 304 hasta çalışılmıştır. Stent konulmadan önce ve 6 ay sonra ekokardiyografik inceleme yapılmıştır.

Kronik koroner oklüzyona stent implante edildikten sonra tüm gruplarda, LVEF de önemli artma (% 53.2±11.9 den %57.0±11.1 e, p <0.0001) ve hem LV diastol sonu volum indeksinde (85.6±18.9 ml/m² den 80.1±17.1 ml/m² e; p <0.001) ve hemde LV sistol sonu volum indeksinde (40.0±15.8 ml/m² den 34.1±14.3 ml/m² e; p <0.0001) azalma saptanmıştır. Çıplak stent grubu ile ilaç kaplı stent grubu arasında LVEF artışı yönünden anlamlı bir fark yoktu. Multivariate analizde, koroner tıkanmadan sonra 2 ay geçmemiş olanlarda bazal LVEF %50 den az olanlarda ve diyabetiklerde stent uygulamasının LVEF düzelmesinde bağımsız öngörücü olduğu saptanmıştır.

Sonuç olarak, kronik koroner oklüzyon nedeniyle yapılan stent implantasyonu stent sonrası ilk 6 ayda, bilhassa LV fonksiyonu represe olan hastalarda ve oklüzyon üzerinden 2 ay geçmemiş olan hastalarda LVEF üzerine olumlu etkiye sahiptir.

Anahtar kelimer: Coroner oklüzyon, Stent, Sol ventriküler fonksiyonu

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INTRODUCTION

Left ventricular ejection fraction (LVEF) is a powerful predictor of prognosis in patients with coronary artery disease[1,2]. Interventions that increase LVEF reduce in-hospital mortality and improve long term clinical outcomes[1,3]. There have been many reports describing late improvement in left ventricular (LV) function following early restoration of coronary artery patency after acute myocardial infarction (MI), but there are only a few studies assessing changes in LV function after revascularization of chronic total coronary occlusions (CTO)[4-13]. Percutaneous transluminal coronary angioplasty (PTCA) of CTO can be performed with a good success rate. However, the long-term improvement of LVEF after PTCA for CTO is hampered by high rates of reocclusion and restenosis[11,12,14-16]. Technological advances in interventional cardiology and the use of coronary stent implantation in patients with CTO results in a much greater increase in lumen diameter and reduces angiographic restenosis compared with PTCA alone[17,18]. There are limited datas on recovery of LV function after stent implantation in patients with CTO[7-10]. Moreover, the predictors of recovery of LV function after the stent implantation in this group of patients is not well known. So, the aim of this study was to assess the effect of coronary stent implantation on LVEF and to examine what clinical and angiographic factors may have an effect on recovery of LVEF.

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METHODS

Study population: The inclusion of patients took place between 7 April 1998 and 24 February 2006 in Sani Konukoğlu Medical Center (Gaziantep-Turkey). During

Table I: Clinical and angiographic characteristics of patients underwent stent implantation.

Baseline characteristics (n= 304)	
Age (years)	60.4±10.8
Male patients (%)	87.9
Cigarette smoking (%)	
Current	41.1
Past	42.8
Diabetic mellitus (%)	19.4
Treated hypertension (%)	44.0
Family history of CAD (%)	36.8
History of myocardial infarction (%)	54.9
Previous PTCA (%)	14.5
Previous CABG operation (%)	0
Duration of occlusion (months)	6.1±7.0
CCS class	
1, 2	37.1
3, 4	46.7
Medication at discharge	
Antiplatelet	98.0
ACE inhibitor (%)	36.2
Nitrate (%)	58.5
Beta-blocker (%)	61.8
Calcium antagonist (%)	29.6
Statin (%)	46.0
Collateral circulation (%)	60.5
Target-lesion coronary artery (%)	
Left anterior descending	40.8
Left circumflex	27.3
Right coronary	31.9
Stents per patient (%)	
1	77.3
2	21.7
3	1
Stent type (%)	
Bare Metal Stent	54.3
Drug-Eluting Stent	45.7

CAD: coronary artery disease, PTCA: percutaneous transluminal coronary angioplasty, CABG: coronary artery bypass graft surgery, CCS: Canadian Cardiovascular Society, ACE: angiotensin-converting enzyme.

this time, 82615 patients underwent diagnostic coronary angiography. Among these patients, 447 patients who had CTO and angina pectoris or exercise-induced ischaemia related to the occluded artery were included in this study.

A CTO was defined as complete interruption of the vessel with Thrombolysis In Myocardial Infarction flow grade 0 that was >1 months old based on the clinical history[14]. Occlusions in patients in whom the clinical history did not allow determination of the age of the occlusion were classified as chronic. Patients who had a MI <1 month of the procedure and significant left main coronary artery disease, patients who had an estimated CTO duration <1 month were excluded. The study was approved by the local Ethics Committee and written informed consent was obtained from all patients before the procedure.

Angiography: Coronary angiography and stenting were performed according to ACC/AHA guidelines for percutaneous coronary intervention[19]. Of 447 patients with CTO, 384 patients underwent successful drug-eluting (DES) or bare metal coronary stent (BMS) implantation. The remaining 63 patients who had unsuccessful stent implantation, 34 patients underwent CABG (coronary artery bypass graft) surgery and 29 patients had medical treatment alone. Among the patients who underwent successful stent implantation, 214 patients underwent BMS implantation (Medtronic S670, Medtronic Vascular, Santa Rosa, California; Multi- Link Tristar, Guidant, Temecula, California; BX Velocity, Cordis Corp and Ephesos, Nemed Ltd, Turkey) and 170 patients underwent DES implantation (Cypher, Cordis, Johnson and Johnson Co, The Netherlands and Taxus, Boston Scientific, Boston, Massachusetts). Premedication consisted of 300 mg/day of aspirin orally and 150 mg of clopidogrel starting >24 hours before percutaneous coronary intervention. A bolus of 10,000 IU of heparin was administered after sheath insertion, with repeat bolus given as needed to maintain an activated clotting time of >250 seconds. After the procedure, aspirin 300 mg/day was continued indefinitely and clopidogrel 75 mg/day was administered for 1-6 months.

Echocardiography: Baseline echocardiography (Acuson CV70, Siemens Medical Solutions USA, Inc) was performed before percutaneous intervention. Estimates of LV end-diastolic volume index (EDVI), end-systolic volume index (ESVI), and ejection fraction (EF) were obtained from the average of three consecutive cardiac cycles taken from apical four chamber views using the modified Simpson's rule.

Follow-up: All patients were asked to return for a 6-months follow-up control, regardless of symptomatic status. Within 6 months after the stent implantation, 5 patients died, 16 patients underwent CABG surgery and 36 patients had repeat percutaneous coronary intervention. Those patients and 23 patients who did not attempt to 6-months follow up were excluded from the study. The remaining 304 patients comprise the study cohort. At 6-months follow-up, all patients were evaluated for symptoms by interview and examination and, echocardiography was repeated to

Table II: Pre and post stent implantation echocardiographic parameters

PParameters	Baseline	Follow-up	P
Left atrium, cm	3.52±0.3	3.30±0.3	0.003
IVS, cm	0.97±0.1	0.95±0.1	NS
LV EDVI, ml/m^2	85.6±18.9	80.1±17.1	<0.0001
LV ESVI, ml/m^2	40.0±15.8	34.1±14.3	<0.0001
LV EF, %	53.2±11.9	57.0±11.1	<0.0001

IVS: interventricular septum, LV: left ventricular, EDVI: end-diastolic volume index, ESVI: end-systolic volume index, EF: ejection fraction

assess recovery of LV function.

Statistics: The baseline characteristics of the population were analyzed using summary statistical measures. Categorical variables were presented numerically and continuous variables were presented as mean ± SD. The change in echocardiographic parameters before and 6 months after stent implantation was examined by paired Student t test, and the differences in LVEF changes between groups were examined by unpaired Student t test. The Chi square test was used for testing categorical variables. To identify "independent" prognostic factors of LVEF improvement, multivariate linear regression analyses were performed. All measures with a univariate p value <0.20 were considered for inclusion into multivariate analysis. A p value <0.05 was considered significant. All statistical analyses were performed using commercially available SPSS version 10.0.

RESULTS

Baseline characteristics: Baseline characteristics of the patients are summarized in in Table I. Most patients were men (87.9%) with a mean age of 60.4±10.8 years. Nineteen percent of the patients had diabetes mellitus (DM) and 44.0% of the patients was under antihypertensive treatment. About 55% of patients had a previous MI in the territory of the occluded artery. The mean duration of occlusion was 6.1±7.0 months. The occluded vessel was the left anterior descending artery in 40.8%, the left circumflex artery in 27.3% and the right coronary artery in 31.9%. In 77.3%, a single stent and in 22.7%, more than one stent was used per patient. The implanted stent type was BMS in 54.3% and DES in 45.7%.

Echocardiography: At 6-month follow-up we observed a significant improvement in LV function as shown by a decrease in LV EDVI and LV ESVI, and an increase in LVEF (p<0.0001) (Table II). Left atrial diameter was significantly decreased after 6-month follow up (p<0.005).

Univariate analysis of change in LVEF in study subgroups: Table III summarizes the univariate comparisons of change in LVEF between different study subgroups. After 6-month follow up a greater recovery of LVEF was detected in non-diabetic patients compared to those diabetic patients (p<0.04). Improvement in LVEF was observed both in patients with (p<0.05) and without hypertension (p<0.001). Although the treatment with angiotensin converting enzyme (ACE) inhibitors was associated with a greater magnitude of improvement in LVEF, the difference between patients with ACE inhibitors treatment and those without ACE inhibitors treatment did not reach statistical significance (P=0.06). A significant improvement in LVEF was observed from baseline to 6-month follow-up in both Canadian Cardiovascular Society (CCS) angina class 1, 2 and CCS class 3, 4 groups (p<0.001 and p<0.05 respectively). The intergroup differences in improvement of LVEF were not statistically significant. Regarding the baseline LVEF, patients with basline LVEF >50% showed a significant improvement in LVEF while no significant changes were observed in patients with baseline LVEF >50% (p<0.0001 and p>0.05 respectively). After 6-month follow up a greater recovery of LVEF was detected in patients with occlusion duration <2 months than those with duration >2 months (p<0.01). No difference in the improvement of LVEF was noted between BMS or DES groups. However, the patients receiving multiple stents showed a greater improvement in LVEF than those patients with single stent implantation (p<0.05).

Multivariate predictors of improvement in LVEF: Multivariate regression analysis showed that baseline LVEF <50%, DM absence and occlusion duration <2 month to be independent predictors of improvement in LVEF (Table IV).

DISCUSSION

Successful PTCA of CTO and improvement in LV

Table III: Comparision of baseline and six-month follow-up LV EF results according to variables.

Variable	Baseline LV EF (%)	Follow-up LV EF (%)	p Value
Male gender			
Yes (n= 268)	53.1±12.2	56.9±12.2	0.926
No (n= 36)	53.8±11.7	57.7±11.0	
Diabetes mellitus			
Yes (n= 58)	51.5±12.0	53.8±11.8	0.040
No (n= 246)	53.6±12.1	57.7±11.7	
Treated hypertension			
Yes (n= 135)	50.9±12.5	53.9±12.2	0.119
No (n= 169)	55.0±11.1	59.5±10.8	
Previous myocardial infarction			
Yes (n= 168)	50.2±12.7	53.9±12.6	0.873
No (n= 136)	56.9±10.8	60.8±11.0	
Treatment of ACE inhibitors			
Yes (n = 114)	51.4±13.3	56.1±12.7	0.058
No (n = 190)	54.3±11.2	57.5±11.9	
Treatment of nitrate			
Yes (n = 182)	50.9±13.6	55.0±13.7	0.381
No (n = 122)	56.6±11.8	60.0±11.5	
Treatment of blockers			
Yes (n = 186)	53.8±11.6	57.9±11.3	0.342
No (n = 118)	52.2±12.3	55.6±12.6	
Treatment of calcium antagonist			
Yes (n = 92)	55.7±12.5	58.6±11.9	0.217
No (n = 212)	52.1±12.8	56.3±12.3	
Treatment of statin			
Yes (n = 142)	52.6±12.1	56.7±12.5	0.460
No (n = 162)	53.7±11.9	57.3±12.3	
Baseline angina class			
CCS class 1, 2 (n = 155)	54.0±12.2	58.4±11.6	0.156
CCS class 3, 4 (n = 149)	52.4±11.8	55.5±11.3	
Occlusion duration			
2 month (n = 158)	52.1±12.1	57.2±11.0	0.004
>2 month (n = 146)	54.4±11.8	56.8±11.3	
Baseline LV EF (%)			
<50 (n = 141)	43.7±8.9	51.0±10.5	0.0001
>50 (n = 163)	61.4±6.8	62.2±6.6	
Collateral circulation			
Yes (n = 186)	53.1±11.9	56.8±12.0	0.838
No (n = 118)	53.4±11.8	57.3±12.1	
Target-lesion coronary artery			
Left anterior descending (n = 121)	52.3±12.7	55.9±12.5	0.692
Left circumflex (n = 84)	54.2±11.2	58.2±11.0	
Right coronary (n = 99)	53.4±11.1	57.3±11.0	
Stents per patient			
1 (n = 235)	54.6±11.4	57.8±10.9	0.012
2 (n = 69)	48.4±11.8	54.2±11.6	
Stent type			
Standard stent (n= 165)	53.4±11.7	56.7±11.3	0.197
Drug-eluting stent (n= 139)	52.9±11.9	57.4±10.6	

ACE: angiotensin-converting enzyme, CCS: Canadian cardiovascular society, LV EF: left ventricular ejection fraction

Table IV: Multivariate predictors of improvement in LV EF.

Predictors	Beta Coefficient	p Value
Hypertension existence	-0.213	0.098
Diabetes mellitus existence	-0.245	0.027
ACE inhibitors use	0.274	0.122
Baseline angina class (CCS class 1, 2)	0.223	0.246
Occlusion duration (<2 month)	0.282	0.017
Baseline LV EF (<50)	0.349	0.0001
Multiple stent implantation	0.230	0.135
Drug-eluting stent implantation	0.280	0.180

ACE: angiotensin-converting enzyme, CCS: Canadian cardiovascular society, LV EF: left ventricular ejection fraction

recovery after percutaneous revascularization has been demonstrated in several studies[11,12,14]. PTCA, however, associated with a high rate of restenosis and late vessel occlusion. Recent studies have shown that improvement in LV function has indeed observed only in patients without reocclusion[11,12]. The stent implantation following percutaneous recanalization of CTO decreases restenosis and reocclusion rates and therefore, increases the overall improvement in LV function[8,9,17,18]. In accordance with previous reports we demonstrated both a reduction in LV volume and a significant improvement in LV function at follow-up after successful recanalization of CTO[8,9,11]. We also confirmed that the most powerful determinant of improvement in LVEF at 6-month follow up was baseline LVEF <50%[9,11]. Previous reports has been suggested that poor LV function in patients with coronary artery disease might be associated with perfusion defects[9,11,20]. Such patients may have stunned or hibernating viable myocardium that recover after revascularization. Moreover, ventricles with low LVEF have much room to improve further after revascularization of a coronary occlusion.

In our study, multivariate analysis showed duration of occlusion to be independently predictive of improvement in LV function. There have been only two studies in literature assessing the relation between duration of coronary occlusion and improvement of LV function after percutaneous revascularization of CTO[9,11]. Dzavik et al. demonstrated that duration of occlusion was independently predictive of improvement in LV function in patients with CTO submitted to percutaneous revascularization, as was the case in the present study[9]. In contrast to those results, however, Sirnes et al. did not found any relation between duration of coronary occlusion and LV recovery after percutaneous revascularization of CTO[11]. Sirnes et al. conducted their study in a relatively small study population and 29 % of the patients underwent PTCA without stent implantation. This may be the reason for a diminished ability to detect a relationship between duration of coronary occlusion and recovery of LV function. Ours and Dzavik et al.'s findings indicate that dysfunctional but viable myocardium may persist several months after coronary artery occlusion, suggesting that reperfusion of the target artery within 2 months may restore the persistent hibernating myocardium leading to recovery of LV function and preventing ventricular dilatation.

In the present study DM appears to be independently predictive of improvement in LV function. Our results are consistent with those of previous reports[20,21]. Sugioka et al. indicated that CABG was inadequate for improving LV function in diabetic patients with severe ventricular dysfunction at the baseline[21]. Hu et al. reported that LVEF improvement was observed in non-diabetic patients but not in diabetic patients after percutaneous revascularization of left main coronary artery[20]. It appears that DM itself may cause metabolic myocardial damage and microvascular functional abnormalities and thus may impair the recovery of LVEF after coronary revascularization. Moreover, higher restenosis rate after percutaneous stent implantation in diabetic patients compared with those non diabetic patients may also affect improvement of LV function after percutaneous revascularization[22].

Regarding CSS class, Dzavik et al. reported that LVEF was improved more in patients with less severe angina[9]. However, Sirnes et al. reported that patients with angina pectoris CCS class 0-2 before PTCA had the same increase in LVEF as those with CCS class >2[11]. The results of the present study are in accordance with the results of Sirnes et al. We found similar increase in LVEF in patient with angina pectoris class CCS class 1-2 and CCS class 3-4. It seems that CSS class is not a predictive parameter in LV EF recovery after coronary revascularization.

There are conflicting reports on the influence of collaterals on recovery of LV EF in coronary occlusions. Some authors have reported that the presence of well-developed collaterals was an important factor in determining LV function in patients with coronary occlusions[23,24]. In contrast, other authors have reported no effect of collaterals on baseline function or improvement of LVEF after reperfusion[25]. In our study, we found that collateral circulation had no influence on LV recovery after revascularization in patients with coronary occlusions. It appears that the presence of coronary collaterals is not mandatory for the functional recovery in patients with CTO.

Many authors have reported the MI to be a factor affecting LVEF after coronary revascularization[5, 26]. In those studies it was stated that patients with a history of MI would have less viable ischemic myocardium and, thus it would be less likely to benefit from coronary revascularization. On the other hand, some other authors have reported that there was no significant difference in recovery of LVEF after revascularization of coronary occlusion between patients with old MI and those without previous MI[9,11]. In accordance with later reports, we did not found significant difference in recovery of LVEF between patients with history of MI >2 months and those without history of MI. The reason for these discrepancies may be explain with heterogeneous of the study groups.

DES implantation, which enhances long-term patency of the occluded vessel compared with BMS implantation, might be advantageous[27]. There is only one study in literature comparing improvement of LV function after DES and BMS implantatation in patients with CTO. In this study, Nakamura et al. have reported that improvement in LV function after DES stent implantation was better than BMS implantation[7]. In our study, we found a higher increment of EF in patients revascularizated with DES stents compared with BMS stents, however, the difference that did not reach statistical significance. This may have been in part because we performed follow-up echocardiography at 6-month and most of restenosis were detected at an earlier stage and, therefore, only a small percentage of restenotic lesions were found to be severely narrowed which may influence LV function.

It is well known that ACE inhibitor improves LVEF in patients with LV dysfunction[28,29]. In the present study drug treatment with ACE inhibitor did not enhance recovery of LV function in multivariate analysis. The reason for this contrary may be due to the patients in our study had less LV systolic dysfunction as compared with the patients in the large ACE inhibitor trials[28,29]. Moreover, the effect of ACE inhibitor on improvement of LV function seems most striking in the early months after initiation of treatment. Most of the patients in our study had started ACE inhibitors months before percutaneous coronary stent implantation.

LIMITATIONS

There are several limitations of this study. First, we did not have a control group with no intervention; thus no treatment effect on LV function can be ascribed directly to the revascularization procedure. Second, coronary angiography was not repeated at 6-months follow up; thus, restenosis could not be excluded. Third, all patients in this study had angina pectoris or a positive exercise stress test. However, many patients with CTO have no myocardial ischaemia related to the occluded artery. Thus, the possible benefit in LV function after stent implantation of CTO in ischaemic patients demonstrated in this study cannot be generalized to patients without ischaemia.

CONCLUSION

Stent implantation of CTO improves LVEF and decreases LV volumes during 6 months follow-up after coronary stent implantation. Improvement in LV function is most pronounced in patients with low baseline LVEF and those with coronary occlusion within 2 months. The presence of diabetes mellitus impairs recovery of LVEF after coronary revascularization. However, CSS class, presence of coronary collaterals or history of MI >2 months have no effect on improvement of LV function.

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