Previous percutaneous coronary intervention may increase symptom recurrence and adverse cardiac events following surgical revascularization

Önceden geçirilmiş perkütan koroner girişim cerrahi revaskülarizasyon sonrası semptom rekürrensini ve majör kardiyak olayları artırabilir mi?

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ABSTRACT

Objective: The number of percutaneous coronary interventions (PCI) is increasing. There is limited outcome data on patients with a history of PCI and subsequently required surgical revascularization.

Methods: Overall 611 patients who survived 30 days after coronary artery bypass graft surgery (CABG) between 2001 and 2005 were evaluated. Mean follow-up was 29.4 ± 11.3 months and 45% were female. The effect of preoperative PCI as a risk factor for symptom recurrence and adverse cardiovascular events and mortality was determined.

Results: Preoperative PCI was an independent risk factor for symptom recurrence ($p<0.0001$), combined adverse cardiac events ($p<0.0001$) and slightly increased overall mortality ($p<0.04$). Comparison of patients with and without a prior PCI showed that former had significantly worse outcomes compared to the latter. Patients with history of at least one restenosis following a PCI developed significantly more adverse end points ($p<0.0001$).

Conclusion: In this study, patients with previous PCI were more likely to develop symptom recurrence and adverse cardiovascular events following CABG. This difference was more pronounced in patients who had at least one recurrent stenosis after a PCI. *(Anadolu Kardiyol Derg 2006; 6: 148-52)*

Key words: Percutaneous coronary intervention, coronary artery bypass graft surgery

ÖZET

Amaç: Perkütan koroner arter girişimlerin sayısı gün geçtikçe artmaktadır. Perkütan koroner arter girişimi yapılıp da daha sonra cerrahi revaskülarizasyon yapılan hastaların ilerideki sonuçları hakkında çok az bilgi mevcuttur.

Yöntemler: İki bin bir ile 2005 yılları arasında koroner arter baypas ameliyatı olan ve 30 gün hayatta kalan 611 hasta incelendi. Ortalama takip süresi 29.4 ± 11.3 ay idi ve hastaların % 45'i bayandı. Preoperatif perkütan koroner girişimin semptom rekürrensi, majör kardiyak olaylar ve mortalite üzerindeki etkisi incelendi.

Bulgular: Preoperatif perkütan koroner girişim semptom rekürrensini ($p<0.0001$) ve birleşik majör kardiyak olayları ($p<0.0001$) bağımsız olarak artırdı. Mortaliteyi de daha az miktarda olmak üzere artırdı ($p<0.04$). Daha önce perkütan koroner girişim olan ve olmayan hastalar karşılaştırıldığında perkütan girişim geçiren hastaların orta vade takip sonuçlarının diğerlerine göre önemli derece kötüleştiği görüldü. Perkütan koroner girişimden sonra en az bir kez restenoz olan hastalarda restenoz olmayan hastalara göre daha fazla majör kardiyak olaylar görüldü ($p<0.0001$).

Sonuç: Bu araştırmada, daha önce perkütan koroner girişim geçirmiş hastaların koroner arter baypas ameliyatından sonra daha çok semptom rekürrens ve majör kardiyak olaylara maruz kaldığını gösterdik. Bu fark perkütan koroner girişimden sonra en az bir kez reküran stenoz olan hastalarda daha bariz olarak ortaya çıktı. *(Anadolu Kardiyol Derg 2006; 6: 148-52)*

Anahtar kelimeler: Perkütan koroner girişim, koroner arter baypas cerrahisi

Introduction

Percutaneous coronary intervention (PCI) is emerging as the initial treatment modality for treatment of severe coronary atherosclerosis. Percutaneous coronary intervention indications are extended to patients who were traditionally considered at high risk for recurrent stenosis. National registry studies have reported post-stent revascularization rates between 14-30% in different patient populations (1,2). Twenty-two percent of these patients require surgical revascularization whereas 78% undergo repeat PCI (3). Most of these reinterventions are performed to the same coronary artery. Hence there will be an accu-

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mulating number of patients with history of more than one PCI to the same coronary artery. Although only 5% of patients with single vessel disease subsequently require coronary artery bypass graft surgery (CABG) after PCI (4), this figure can be as high as 20% in multi-vessel disease (5). An increasing number of CABG's will be performed in patients who have had previous PCI. History of previous PCI's with or without subsequent restenosis may have an impact on the midterm outcome following CABG. Prognostic factors following CABG have been well studied however there are no data in the literature regarding the significance of PCI on midterm outcome after CABG.

Methods

A retrospective review of 611 consecutive patients who survived 30 days after CABG between 2001 and 2005 was performed. Preoperative characteristics, cardiovascular risk factors as well as indications for CABG were reviewed (Table 1) and entered into a database. Percutaneous coronary intervention was defined as any percutaneous coronary intervention including balloon angioplasty, intra-coronary stent placement as well as cutting-balloon, atherectomy and brachytherapy. Failed PCI was defined as angiographically proven restenosis at the site of a previous PCI early or late after the procedure requiring reintervention. Patients who required urgent or emergent revascularization due to acute ischemia during the procedure or in the first 30 days after PCI were excluded.

Follow-up was obtained through patients' hospital records, primary care physicians and cardiologists and was complete in all 611 patients. Symptom recurrence was defined as new angina or new onset congestive heart failure (CHF) observed during follow-up period. Adverse cardiovascular events were defined as myocardial infarction (MI), cerebrovascular accident (CVA), coronary reintervention (repeat PCI or CABG) and sudden cardiac death. Symptom recurrence, adverse cardiovascular events and overall mortality were included in statistical analysis.

Continuous variables were presented as mean ± standard deviation (SD). Kolmogorov Smirnov test was used to evaluate normal distribution of age as a continuous variable. The results of the test (Z= 0.835, p= 0.489) showed that age as a continuous variable showed normal distribution.

Quantitative variables were compared using Student's t-test whereas qualitative variables were compared using Chi-square test. A p value < 0.05 was considered statistically significant. Stepwise Cox Regression Analysis was utilized to determine the effects of preoperative variables on the symptom recurrence, adverse cardiovascular events and mortality.

All statistical analyses were performed using SPSS Statistical Software for Windows 10.0 (SPSS Inc. Chicago, IL). Survival curves were constructed using Kaplan-Meier method and comparisons of survival curves were done using Log Rank Analysis.

Table 1. Patient characteristics

	Patients (611), n	%
Mean age, years	67.5 ± 10.6	
Female	275	45.0
EF <30%	106	17.3
Hyperlipidemia	289	47.2
Diabetes	113	18.4
Hypertension	289	47.2
Unstable angina	24	3.9
MI <1 week	102	16.6
COPD	56	9.1
ESRD	17	2.7
PVD	51	8.3
Prior CVA	38	6.2
AHA Class III/IV	44	7.2

AHA- American Heart Association heart failure class, COPD- chronic obstructive pulmonary disease, CVA- cerebrovascular accident, EF- ejection fraction, ESRD- end stage renal disease, MI- myocardial infarction, PVD- peripheral vascular disease

Results

Mean age was 67.4 ± 10.5 years and mean follow-up was 29.4 ± 11.3 months. Of 611 patients, 190 had a history of at least one PCI prior to undergoing surgical revascularization (PCI/CABG): 153 patients underwent single vessel PCI, 30-underwent two-vessel PCI and 7 patients had three-vessel intervention. Balloon angioplasty only was performed in 25, intra-coronary stent placement in 149, cutting-balloon in 7, atherectomy in 5 and brachytherapy in 4 patients. Of these 190 patients, 69 had a history of at least one restenosis at the site of the previous PCI prior to undergoing CABG. The mean interval between the PCI procedure and CABG was 16.8 ± 4.2 months. The last procedure was used as the reference in patients who had multiple PCI.

Indication for CABG in PCI/CABG group were as follows: symptomatic restenosis only at the site of the PCI in 16, disease progression in other coronary arteries along with restenosis at the PCI site in 139 and development of new stenosis in coronary circulation other then the PCI vessel in 35 patients.

Revascularization was performed using an internal thoracic artery for left anterior descending artery and saphenous vein grafts for the remaining coronary territories. Radial artery grafts were used selectively in the absence of other conduits. Grafting strategy was not modified according to the PCI history of the particular coronary artery. Off-pump coronary artery bypass surgery was used in 16 patients none of whom had a history of PCI. Mean number of grafts was 3.4±1.3. Revascularization was complete in all but one patient. All patients were prescribed life-long postoperative aspirin as well as aggressive statin therapy throughout the study period. Perioperative complications were renal failure requiring dialysis in 2, respiratory failure in 5, MI in 4, CVA in 5 and deep sternal wound infections in 3 patients.

During follow-up 34 patients developed angina, 7 developed CVA, 12 developed MI and 9 developed CHF and thirty- two patients required coronary reintervention (29 repeat PCI and 3 redo CABG). The indications for reintervention were recurrent angina in 18, MI in 12, and new onset CHF with demonstrable new ischemic myocardium on the myocardial perfusion scan in two patients. A total of 41 coronary territories (coronary arteries or bypass grafts to the stenosed coronary arteries) needed reintervention. Of these, 24 coronary territories had a PCI preoperatively and 17 had no PCI performed prior to the CABG (p= 0.274).

Overall, 34 patients died during follow-up. Cardiac deaths were observed in 14 patients (sudden cardiac death in 7, end stage ischemic cardiomyopathy in 3, in-hospital ventricular fibrillation in 1, pulmonary edema in 1, acute MI in 1, and severe

aortic stenosis in 1 patient who declined reoperation). One of these developed new onset CHF at 32 months and underwent a PCI and died at 56 months. Another patient developed MI at 2 months postoperatively and underwent PCI and subsequently expired at 18 months. Four additional patients developed symptoms (3 angina and 1 congestive heart failure) 8 months to 51 months prior to death.

The cause of death was non-cardiac in 20 patients (metastatic prostate cancer 1, lung cancer 1, metastatic breast cancer 1, colon cancer 1, cerebrovascular accident 3, auto accident 1, sepsis 2, end stage lung disease 3, end stage renal disease 2, pulmonary embolus 1, upper gastrointestinal bleeding due to anticoagulation 1, pancreatitis 1 and pneumonia 2).

We evaluated the effects of individual preoperative characteristics and cardiovascular risk factors as well as significant intraoperative variables on symptom recurrence, adverse cardiovascular events and mortality using Multivariate Cox Regression analysis. A history of preoperative PCI was found to be an independent risk factor for symptom recurrence (p<0.0001, OR 4.81 [2.75-8.41], 95% CI) (Table 2) and adverse cardiovascular events (p<0.0001, OR 6.03 [3.27-11.11], 95% CI) (Table 2). These patients also had a slightly increased overall mortality (p<0.04, OR 2.72 [1.37-5.42], 95% CI) (Table 2) during follow-up. We also compared PCI/ CABG and CABG alone groups for the incidence of preoperative risk factors and number of grafts (Table 3). Patients were otherwise similar except for significantly less incidence of hyperlipidemia and diabetes in PCI/CABG group. Individual end points were then analyzed with respect to PCI history (Table 4). The PCI/CABG patient group was found to have increased incidence of all of the end points except for CHF.

Table 2. Cox regression analysis results according to PCI history

		B	SE	Sig.	Exp (B)	95 % CI	
						Lower	Upper
Symptom recurrence	Radial	1.272	0.382	0.000	3.571	1.666	7.651
	PCI	1.573	0.285	0.000	4.812	2.755	8.412
	COPD	1.540	0.304	0.000	4.675	2.592	8.423
Adverse cardiac events	Radial	0.936	0.373	0.012	2.550	1.228	5.296
	Statin	-0.727	0.307	0.018	0.483	0.265	0.883
	PCI	1.797	0.312	0.000	6.031	3.273	1.111
	COPD	1.296	0.327	0.000	3.653	1.923	6.941
	EF<30%	0.927	0.300	0.002	2.527	1.405	4.547
Mortality	Radial	1.511	0.547	0.006	4.533	1.551	13.25
	PCI	1.003	0.350	0.004	2.727	1.372	5.420
	Smoker	1.331	0.493	0.007	3.786	1.441	9.950
	EF<30%	1.503	0.347	0.000	4.496	2.275	8.883

COPD- chronic obstructive pulmonary disease, EF- ejection fraction, PCI- percutaneous coronary intervention, Radial- radial artery, Smoker- active tobacco user

Table 3. Comparison of preoperative risk factors and number of grafts between patients with and without history of PCI

	PCI History			
	No (n=421)	Yes (n=190)		p
Age, years	67.43 ± 9.54	66.86 ± 12.04	t:0.551	0.582
Follow-up period, months	38.2 ± 13.2	36.7 ± 13.2	t:1.28	0.200
Female sex, n (%)	186 (44.2)	89 (46.8)	X2 0.375	0.540
ESRD, n (%)	15 (3.6)	2 (1.1)	X2 3.050	0.081
Unstable angina, n (%)	17 (4.0)	7 (3.7)	X2 0.043	0.835
PVD, n (%)	36 (8.6)	15 (7.9)	X2 0.074	0.786
Hypertension, n (%)	209 (49.6)	80 (42.1)	X2 2.985	0.084
Diabetes, n (%)	92 (21.9)	21 (11.1)	X2 10.130	0.001**
Active smoker, n (%)	14 (3.3)	12 (6.3)	X2 2.873	0.090
Hyperlipidemia, n (%)	238 (56.5)	51 (26.8)	X2 46.29	0.001**
Ejection fraction<30%, n (%)	69 (16.4)	37 (19.5)	X2 0.868	0.351
COPD, n (%)	35 (8.3)	21 (11.1)	X2 1.808	0.277
Previous MI, n (%)	113 (26.8)	41 (21.5)	X2 1.923	0.166
Graft >3, n (%)	346 (82.2)	152 (80.0)	X2 0.415	0.520

** p < 0.01
COPD- chronic obstructive pulmonary disease, ESRD- end stage renal disease, MI- myocardial infarction, PVD- peripheral vascular disease

In order to be able to understand the effect of recurrent stenosis following a PCI on the defined end points, failed PCI was then entered as an individual parameter in a separate Multivariate Cox Regression analysis. A history of preoperative failed PCI was found to be an independent risk factor for symptom recurrence (p<0.0001, OR 40.36 [9.58-170.04], 95% CI) (Table 5), adverse cardiovascular events (p<0.0001, OR 14.09 [5.57-35.62], 95% CI) (Table 5) as well as overall mortality (p 0.01, OR 32.51 [4.27-247.07], 95% CI) (Table 5). Patients with a history of failed PCI were also more likely to develop all of defined end points except CVA (Table 6).

Survival free from any adverse cardiovascular event (MI, coronary reintervention, CVA and sudden cardiac death) was lower in patients with a history of PCI and was even lower in patients with history of failed PCI (p=0.001) during follow-up (Fig. 1).

Discussion

The number of PCI is increasing with changing cardiology practice patterns and introduction of drug-eluting stents. A 10% increase in PCI is predicted in coming years (6). This procedure is being used more often for patients and coronary lesions that were considered unsuitable in the past. Therefore patients who had a previous PCI will be an increasing part of cardiac surgeons' practice in the near future. In this study, we found increased incidence of postoperative symptom recurrence, adverse cardiovascular events and mortality following surgical revascularization in patients with history of PCI. The reason for this finding maybe several fold.

Large-scale clinical studies indicate that 20%-40% of pati-

Table 4. Evaluation of cardiovascular end points according to PCI history

	PCI (n=190)	No PCI (n=421)	X2	p
Angina, n (%)	22 (11.6)	12 (2.9)	18.981	0.0001***
CHF, n (%)	5(2.6)	4 (1.0)	2.550	NS
MI, n (%)	9 (4.7)	4 (1.0)	9.015	0.003**
Reintervention, n (%)	23 (12.1)	9 (2.1)	26.207	0.0001***
CVA, n (%)	6 (3.2)	2 (0.5)	7.292	0.007**
Sudden cardiac death , n (%)	5 (2.6)	2 (0.5)	5.376	0.033*
Death, n (%)	19 (10.0)	15 (3.6)	10.323	0.0001***

* p<0.05
** p<0.01
*** p<0.0001
CHF- congestive heart failure, CVA- cerebrovascular event, MI- myocardial infarction

Table 5. Cox regression results according to failed PCI history

		B	SE	Sig.	Exp (B)	95 % CI	
						Lower	Upper
Symptom recurrence	Failed PCI	3.698	0.734	0.000	40.360	9.581	170.04
	COPD	0.764	0.381	0.045	2.146	1.017	4.259
Adverse cardiac events	Failed PCI	2.640	0.472	0.000	14.091	5.572	35.62
	COPD	1.072	0.360	0.000	2.930	1.421	6.030
Mortality	Failed PCI	3.480	1.030	0.000	32.51	4.27	247.07
	EF<30 %	1.010	0.460	0.020	2.750	1.11	6.83

COPD- chronic obstructive pulmonary disease, EF- ejection fraction, PCI- percutaneous coronary intervention

Table 6. Evaluation of individual end points according to history of failed PCI

	History of failed PCI (n=69)	No history of failed PCI (n=121)	χ^2	P
Angina, n(%)	20 (29.0)	2 (1.7)	32.064	0.0001***
CHF, n(%)	5 (7.2)	0	9.005	0.003**
MI, n(%)	8 (11.6)	1 (0.8)	11.091	0.0001***
Reintervention, n(%)	21 (30.4)	2 (1.7)	34.212	0.0001***
CVA, n(%)	2 (2.9)	4 (3.3)	0.024	NS
Sudden cardiac death, n(%)	5 (7.2)	0	9.005	0.003**
Death, n(%)	18 (26.1)	1 (0.8)	31.155	0.0001***

** p<0.01
*** p<0.0001
CHF- congestive heart failure, CVA- cerebrovascular accident, MI- myocardial infarction

ents will eventually develop restenosis after a PCI (6), more frequently with complex lesions (7) as well as after multiple PCI and other adjunctive procedures i.e. atherectomy and brachytherapy (8). Percutaneous coronary intervention is more frequently associated with incomplete revascularization in multi-vessel coronary artery disease (5) and carries a small but real risk of morbidity and mortality. Asymptomatic restenosis and silent myocardial ischemia are also common following PCI and are associated with worse patient outcome (9,10,11). The cumulative incidence of shortcomings and procedure related adverse events of multiple PCI could have an impact on the prognosis of these patients.

We also observed that symptom recurrence, adverse cardiac events and mortality were more frequent in patients who had PCI with subsequent restenosis in the same vessel (failed PCI). Restenosis after PCI may be a risk factor for intimal hyperplasia and increased inflammation at the graft anastomotic site after bypass grafting. This may signify an accelerated vessel wall response to endothelial disruption and might be the likely reason for high incidence of recurrent symptoms in the PCI/CABG group. It has also been demonstrated that development of restenosis in one vessel following a PCI may be a risk factor for stenosis in other vessels following subsequent PCI (12). The incidence of graft stenosis/closure after CABG may be increased by the same mechanism and hence may explain significantly increased incidence of adverse cardiac events in these patients. However, we cannot prove this presumption since coronary angiography was not performed in all patients.

Patients with a history of failed PCI also had significantly higher incidence of sudden cardiac death as well as overall mortality. The reason for this finding maybe increased atherosclerotic load and accelerated overall atherosclerosis progression in this patient population.

The effect drug eluting stents on the long-term outcome following PCI is emerging. Drug-eluting stents may decrease the incidence of subsequent restenosis and therefore may prevent subsequent revascularizations and improve prognosis.

Patients who undergo CABG after having a PCI and especially a failed PCI may have increased risk of adverse cardiac events and worse outcomes. Restenosis after PCI may be a risk factor for increased symptom recurrence and adverse cardiac events after CABG. This may be due to an accelerated reaction to intimal disruption and vessel wall injury in these patients.

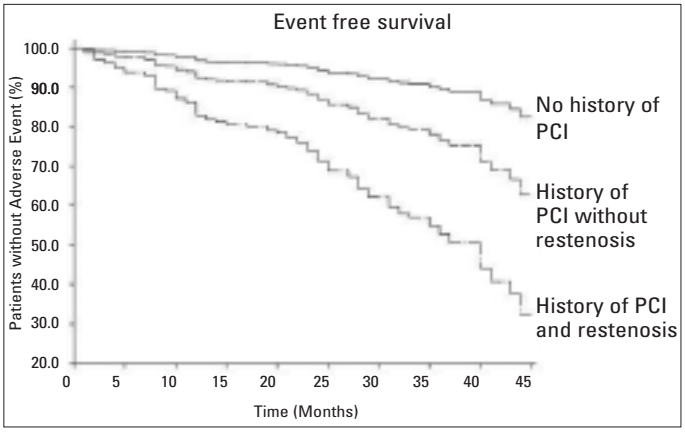

Figure 1. Comparison of adverse cardiovascular event free survival in three groups of patients

There should be a low threshold for reintervention in patients who had a history of PCI and subsequent restenosis prior to CABG. These patients may need closer follow-up for early detection of symptom recurrence and adverse cardiac events.

Percutaneous coronary intervention is considered to be an alternative to CABG and one might also be able to identify the group of patients who have higher risk of restenosis following PCI i.e. diabetics, patients with heavily calcified coronaries and diffuse three vessel atherosclerosis. These patients may be served better with CABG as the initial mode of revascularization. This might prevent the associated risks and complications of repeated PCI procedures.

Although the boundaries between percutaneous coronary intervention and surgical revascularization is more blurred then ever, evidence still supports coronary artery bypass surgery for three vessel coronary atherosclerosis.

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