Survival Results of Postoperative Coronary Angiogram for Treatment of Perioperative Myocardial Ischemia Following Coronary Artery Bypass Grafting: A Single Centre Experience

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Abstract

Objectives: Although perioperative myocardial ischemia (PMI) is a well-known complication following coronary artery bypass grafting (CABG), standard strategies for its diagnosis and treatment are so far not defined. In the current study, we sought to evaluate the impact on survival of postoperative coronary angiogram for management of patients with PMI after CABG.

Methods: Overall, 4028 patients underwent isolated CABG in a single centre institution between January 2006 and September 2013. A total of 168 (4.2%) patients received postoperative coronary angiogram because of diagnosis of PMI. These patients were matched on the basis of gender, age at surgery and date of surgery with 336 (1:2 ratio) CABG patients without PMI in order to determine the impact of the PMI-management.

Results: A total of 476 grafts were examined (263 venous grafts, 196 internal mammary artery grafts and 17 radial artery grafts). Almost three-quarters of the 168 PMI patients (74.4%) underwent postoperative coronary angiogram within 24h of surgery. Normal postoperative coronary angiogram, graft failure and new native vessels occlusion were observed in 23.2%, 52.4% and 24.4% of patients respectively. A total of 30 (17.9%) patients underwent surgical revision of grafts whereas 60 (35.7%) patients were treated with percutaneous coronary intervention (PCI). 18 (10.7%) PMI patients died during the hospital stay compared to 6 (1.8%) in the non-PMI group. Survival rates at 7 years were 62.5% in the PMI group and 81.1% in non-PMI group ($p<0.001$). After multivariable adjustment PMI ($p<0.001$; HR 3.17, 95%CI 2.12-4.73) turned out to be an independent predictor of mortality. Moreover, further sub-analysis revealed that delayed postoperative coronary angiogram (>24h after surgery) was an independent predictor of poorer mid-term survival ($p=0.008$; HR 3.62, 95%CI 1.41-9.33).

Conclusions: PMI after CABG is associated with a significantly poorer survival. A prompt postoperative management must always be considered. Further prospective studies are required to confirm our results.

Introduction

Perioperative myocardial ischemia (PMI) is a well-known complication following CABG surgery. Its incidence accounts for 1-8%[1–5] and the resulting mortality rate ranges from 7 to 16%.[1,2,6,7] The diagnosis of PMI is generally based on postoperative cardiac enzyme elevation, new ECG signs of myocardial ischemia and new regional wall motion abnormalities on echocardiogram.[8] All these tools, though indispensable for the clinical diagnosis of PMI, do not add any detail regarding the status of the native vessels or number of grafts potentially responsible for PMI. Postoperative coronary angiogram can provide this information offering the opportunity for a prompt intervention that may ultimately translate into better patient outcomes.[2] The aim of the present study is to evaluate the impact on survival of postoperative coronary angiogram for management of patients with PMI after CABG.

Patients and methods

Study Population and indication to postoperative coronary angiogram:

Between January 2006 and September 2013, 4028 patients underwent isolated CABG surgery at the university hospital of Münster. A total of 168 (4.2%) patients had postoperative diagnosis of PMI and for this reason underwent postoperative coronary angiogram. The study population was divided into two groups. The first group included 168 PMI patients who underwent postoperative coronary angiogram (PMI group) and the second group 336 CABG patients without PMI (non-PMI group) matched on the basis of gender, age at surgery and date of surgery in a 1:2 ratio. The matching was done manually by a researcher on a separate spreadsheet from which all other variables were excluded. Clinical data were extracted from our prospective institutional database. The University of Münster Ethical Committee and Institutional Review Board approved the study and patient consent was waived. The attending cardiac surgeon, anaesthesiologist and cardiologist were always involved in the indication for postoperative coronary angiogram. This mainly included the following criteria: progressive postoperative elevation of cardiac enzymes regardless of electrocardiographic/echocardiographic correlations, ECG changes suggestive of myocardial ischemia (such as ST segment alteration) or major ventricular arrhythmia of unclear cause. An abnormal postoperative angiogram was defined as either graft failure (i.e. early graft occlusion or stenosis) or new native vessel occlusion.

Statistical Analysis:

Normal distribution of data was assessed with the Shapiro-Wilk test. Data are summarized as mean ± standard deviation. Categorical variables are expressed as frequencies and were compared with Fisher's exact test. Comparisons of continuous variables between groups were performed by unpaired two-tailed t-tests. The effect of PMI on perioperative time courses of CK, CK-MB and cTnI levels was analysed by repeated measures analyses of variance in which the correlation between time points was taken into account. Mauchly's Test of Sphericity indicated that the assumption of sphericity had been violated, therefore degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity. Primary endpoints were in-hospital and mid-term mortality. Follow-up was conducted by inquiry at residential registrations offices for each individual patient. Clinical follow-up was completed on 10^{th} of February 2016. Cumulative survival curves were computed according to Kaplan-Meier method considering the time of surgery as the time of origin. Predictors of mortality were identified in a multivariable Cox regression comprising the entire cohort of PMI and non-PMI patients. Furthermore, an additional multivariable Cox regression including only PMI patients was performed to assess the impact of early postoperative coronary angiogram and other patient characteristics on mortality in this cohort. In order to account for variables derived from the early postoperative period (such as indication to postoperative coronary angiogram and early complications) time of origin was set at 48 hours after surgery for both Cox regression models. The proportionality assumption was assessed by analysing the interaction of each candidate predictor with time. For all statistical tests, a two-tailed p-value <0.05 was considered significant. Data analysis was performed using IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

Results

Patient baseline characteristics and intraoperative data are presented in *Tables 1 & 2* respectively.

Angiogram findings, treatment and in-hospital outcomes:

Indications for postoperative coronary angiogram in PMI patients included postoperative elevation of cardiac enzymes in 112 (66.6%), signs of ischemia in ECG in 84 (50.0%) and major ventricular arrhythmia in 14 (8.3%) patients. 68 (40.1%) patients had an isolated cardiac enzyme elevation. *Figure 1* displays the mean postoperative levels of CK, CK-MB and cTnI on arrival at the intensive care unit (0h) and 6, 12, 24, 48 and 72 hours after surgery. Repeated measures ANOVA showed that there was a significant effect of PMI on the postoperative course of CK [$F=7.6$ ($df=1.9,685$), $p=0.001$], CK-MB [$F=43.9$ ($df=2.5,625$), $p<0.001$] and cTnI [$F=25.2$ ($df=2.9,455$), $p<0.001$] levels. Of the 168 PMI patients, 125 (74.4%) underwent postoperative coronary angiogram within 24h of surgery. A total of 476 grafts were examined (263 venous grafts, 196 internal mammary artery grafts and 17 radial artery grafts). Normal postoperative coronary angiogram, graft failure and new native vessels occlusion were reported in 23.2%, 52.4% and 24.4% of patients respectively. A total of 30 (17.9%) PMI patients underwent surgical revision of grafts whereas 60 (35.7%) patients were treated with PCI. The remaining 78 (46.4%) patients were treated conservatively. Left anterior descending artery bypass grafts were most commonly revised (46.2%) followed by right coronary artery grafts (22.0%). Circumflex, marginal, left main coronary and diagonal artery grafts were revised in 13.2%, 12.1%, 4.4% and 2.2% of cases respectively. A total of 18 (10.7%) PMI patients died during the hospital stay compared to 6 (1.8%) in the non-PMI group. PMI patients who underwent CABG revision after postoperative coronary angiogram had the highest in-hospital mortality (13.3%) followed by PCI patients (11.7%) and those who were treated conservatively (9.0%). Major postoperative complications among the 168 PMI patients included as follows: low cardiac output syndrome in 50 (29.8%), need for postoperative extracorporeal membrane oxygenation (ECMO) in 18 (10.7%), respiratory failure with need for reintubation in 27 (16.1%), postoperative bleeding with need for resternotomy in 14 (8.3%) and central neurological complications in 8 (4.8%) patients.

Effect of PMI on late outcome and predictors of mid-term survival:

Follow-up data were available for 489 (97.0%) patients of the entire cohort. After a mean follow-up of 5.54 years, 375 (76.7%) out of 489 patients were alive, 104 (63.8%) in the PMI group and 271 (83.1%)

in the non-PMI group. Survival rates at 7 years were 62.5 % in the PMI group and 81.1% in non-PMI group respectively (Log-rank test: p<0.001) *(Figure 2).* Excluding in hospital deaths and considering only the discharged patients, survival rate differences remained still significant (p<0.001) *(Figure 3).* After correcting for the baseline differences (PMI vs non-PMI group) *(Table 1)* Cox regression analysis revealed that the occurrence of PMI was an independent risk factor for mid-term mortality (p<0.001; HR 3.17, 95%CI 2.12-4.73). Moreover, further sub-analysis considering only PMI patients revealed that delayed postoperative coronary angiogram (>24h after surgery) turned out to be an independent predictor of poorer mid-term survival (p=0.008; HR 3.62, 95%CI 1.41-9.33). Further risk factors of the conditional Cox regression analysis as well as of the Cox regression sub-analysis of PMI patients are provided in *Table 3*. Repeat CABG, PCI and conservative treatment (p=0.92) resulted in similar survival. *(Figure 4)*

Discussion

PMI is one of the most life-threatening complications following CABG. Typical causes of PMI are graft-related including kinking, spasm and anastomotic occlusion/stenosis, or non-graft related including new occlusion of native vessels or incomplete revascularization.[9–13] The associated mortality rate ranges between 7 and 16%[1,2,6,7] and it is out of debate that an early identification of ischemic causes by postoperative coronary angiogram can lead to prompt intervention potentially limiting the detrimental effect of ischemia. Despite this, literature still offers only few reports on this issue and standard procedures for the treatment of PMI are not yet defined.[2,9] Davierwala et al.[2] reported a PMI rate of 5.3% with an in-hospital mortality rate of 7.3% among PMI patients. In their study, patients with an abnormal angiogram (63.9%) had a higher mortality (9.3%) compared to patients with a normal angiogram (3.5%). Moreover, postoperative coronary angiogram performed 30 hours after CABG resulted in a significantly worse outcome (p=0.02; OR 2.9, 95%CI 1.2-7.2). These findings suggested the importance of expeditious management of PMI[2]. In our cohort, the incidence of PMI was similar (4.2%) to the one reported by Davierwala et al.[2], however the rate of abnormal angiograms was higher (76.8%) and consequently we reported an increased mortality (10.7% vs 7.3%). These slight differences could find their explanation in the more liberal indication to postoperative coronary angiogram resulting in a higher rate of normal angiograms and a slightly lower mortality. Moreover, our multivariable analysis confirmed that delayed postoperative coronary angiogram (over 24 hours after CABG) resulted in a significantly worse survival *(Figure 5).* This can be explained by the fact that a prompter intervention can limit the effects of ischemia as indicated by the negative prognostic impact of cTnI levels at 24 hours after surgery. However, despite prompt intervention, survival in PMI patients was still significantly lower than in non-PMI patients and this difference still remained evident after in-hospital deaths were excluded. On the contrary, Davierwala et al.[2] observed a similar survival between discharged patients and those who showed no evidence of PMI. Such differences may be due to a different approach to revascularization, indications and therapeutic management of PMI and ultimately the different statistical analysis. Moreover, the significantly higher rate of postoperative major complications after PMI can constitute a burden for patients after discharge resulting in a lower mid-term survival.

Regarding the comparison of outcomes among the undertaken procedures (revision of CABG vs. PCI vs. conservative treatment) after postoperative coronary angiogram, Thielmann et al.[3] reported a non-significant difference in in-hospital and 1-year mortality among the three treatments. Consistent with this, Davierwala et al.[2] also showed that mortality among PMI patients was not influenced by the treatment method (p=0.1). In same line, our analysis shows similar survival outcomes regardless of the intervention after postoperative coronary angiogram. However, this may be owing to different conditions underlying PMI. In this regard, several angiographic variables were taken into account in the multivariable model but the method of repeat revascularization was mostly chosen according to the finding, i.e. anastomotic stenosis or kinking were treated exclusively by revision CABG, whereas incomplete revascularization was treated by PCI. Therefore, a comparative analysis of revision CABG and PCI is not feasible. This study is of retrospective design with its inherent disadvantages and many different physicians including surgeons, cardiologists and anesthesiologists were involved in the care of patients. Thus, despite standard internal policies of treatment, we cannot exclude the presence of additional biases.

In conclusion, PMI after coronary artery bypass grafting is associated with a significantly poorer in-hospital and mid-term survival. However, the present results suggest that early postoperative coronary angiogram and treatment of causes underlying PMI may significantly attenuate the detrimental effects of myocardial ischemia and improve the outcome of these patients. Further prospective investigations are warranted in order to verify these results and to define standard treatment strategies.

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Table 1. Patient baseline characteristics

	PMI [n=168]	No PMI [n=336]	p-value
Age (years)	67.0±10.2	67.2±9.9	0.86
Female	42 [25]	84 [25]	1.0
BMI	27.28±4.3	27.62±3.8	0.37
Diabetes mellitus	42 [25]	101 [30.1]	0.25
Systemic hypertension	158 [94]	315 [93.8]	1.0
Dyslipidemia	148 [88.1]	295 [87.8]	1.0
Smoking history	87 [51.8]	159 [47.3]	0.35
COPD	15 [8.9]	21 [6.3]	0.28
Cerebral vascular disease	32 [19.0]	52 [15.5]	0.34
Peripheral vascular disease	19 [11.3]	50 [14.9]	0.34
Renal disease	20 [11.9]	51 [15.2]	0.35
LVEF <50%	29 [17.3]	81 [24.1]	0.087
Three vessel disease	113 [67.3]	199 [59.2]	0.081
Emergency admission	27 [16.1]	33 [9.8]	0.057
Preoperative myocardial infarction	38 [22.6]	75 [22.3]	1.0

Values are expressed as mean±SD or n [%]. BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction.

Table 2. Intraoperative data

	PMI[n=168]	No PMI[n=336]	p-value
Off pump	19 [11.3]	32 [9.5]	0.53
Surgery duration (min)	243.3±70.3	217.6±53.5	<0.001
Aortic cross-clamp time (min)	60.1±30.4	52.8±27.2	0.006
Heart-lung machine time (min)	100±50.2	87.6±43.9	0.004
Number of grafts	2.83±0.83	2.73±0.89	0. 20

Values are expressed as mean±SD or n [%].

Table 3.

Multivariable predictors of mid-term mortality in the entire cohort (n=504)	Hazard ratio	95%CI	p-value
PMI	3.17	2.12-4.73	<0.001
Age at surgery	1.09	1.06-1.11	<0.001
LVEF <50%	1.88	1.22-2.91	0.005
Multivariable predictors of mid-term mortality in PMI patients (n=168)			
PCA >24 hours after surgery	3.62	1.41-9.33	0.008
Age at surgery	1.06	1.01-1.11	0.014
LVEF <50%	4.50	1.97-10.25	<0.001
Need for postoperative ECMO	4.43	1.34-14.65	0.015
cTnI 24h after surgery	1.02	1.01-1-04	0.008

LVEF indicates left ventricular ejection fraction; PCA, postoperative coronary angiogram; ECMO, extracorporeal membrane oxygenation; cTnI, cardiac Troponin

Figure Legends

Figure 1: CK, CK-MB and cTnI levels on arrival at the intensive care unit and 6, 12, 24, 48 and 72 hours after surgery. Error bars denote the standard error of the means.

Figure 2: Survival including in-hospital mortality. Matched population of patients that underwent isolated CABG (no-PMI); patients with perioperative myocardial ischemia (PMI).

Figure 3: Survival excluding in-hospital mortality. Matched population of patients that underwent isolated CABG (no-PMI); patients with perioperative myocardial ischemia (PMI).

Figure 4: Survival in PMI patients according to the treatment method. Revision coronary artery bypass grafting; PCI, percutaneous coronary intervention; no intervention

Figure 5: Survival according to the timing of postoperative coronary angiogram (PCA). Matched population of patients that underwent isolated CABG (no-PMI); PMI patients that underwent PCA within 24 hours (PCA<24h) after surgery; PMI patients that underwent PCA more than 24 hours (PCA>24h) after surgery.