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Prognostic factors for perioperative myocardial infarction and immediate mortality in patients who underwent coronary artery bypass graft surgery

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Acronyms
BMI: body mass index
CABG: coronary artery bypass graft
ECC: extracorporeal circulation
LCO: low cardiac output
PMI: perioperative myocardial infarction

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ABSTRACT

Introduction: Coronary artery bypass surgery is one of the mainstays of treatment in ischemic heart disease.

Objective: To identify factors that influence the occurrence of perioperative myocardial infarction and early cardiac mortality in patients who underwent coronary artery bypass graft surgery.

Method: A prospective cohort study was performed at the Department of Cardiovascular Surgery, "Cardiocentro del Hospital Clínico Quirúrgico Hermanos Ameijeiras" from March 2012 to August 2014. The sample consisted of 231 consecutive patients who met the inclusion criteria. The response variables were: sudden cardiac death early cardiac mortality and acute perioperative myocardial infarction.

Results: Age, body mass index, prolonged surgical time (p=0.023) and complications (p=0.009) were the variables independently associated with the occurrence of perioperative infarction. Odds ratio, adjusted for age and body mass index were lower than 1. According to adjusted odds ratio, variables of most influence on mortality were the presence of complications (3.753; p=0.017), prolonged surgical time (2.690; p=0.002) and low preoperative glomerular filtration rate (2.112; p=0.036).

Conclusions: Older age and higher body mass index were protective prognostic factors for perioperative acute myocardial infarction events. Prolonged surgical time and complications were independently associated with perioperative infarction and mortality after coronary artery bypass graft surgery. Low preoperative glomerular filtration rate was also associated with mortality.

Key words: Coronary artery bypass grafting, Prognostic factors, Perioperative myocardial infarction, Mortality, Coronary artery disease

Factores pronósticos para infarto de miocardio perioperatorio y mortalidad inmediata en pacientes tratados mediante revascularización miocárdica quirúrgica

RESUMEN

Introducción: La cirugía coronaria constituye uno de los pilares del tratamiento en la cardiopatía isquémica.

Objetivo: Identificar factores que influyen en la ocurrencia del infarto de miocardio perioperatorio y muerte inmediata de causa cardíaca, en pacientes tratados mediante cirugía de revascularización miocárdica.

Método: Se realizó estudio de cohorte prospectivo en el servicio de Cirugía Cardiovascular del Cardiocentro del Hospital Clínico Quirúrgico Hermanos Ameijeiras, desde marzo de 2012 hasta agosto de 2014. La muestra se constituyó por 231 pacientes consecutivos que cumplieron los criterios de inclusión. Las variables de respuesta fueron: muerte inmediata de causa cardíaca e infarto agudo de miocardio perioperatorio.

Resultados: La edad, el índice de masa corporal, el tiempo quirúrgico prolongado (p=0,023) y la aparición de complicaciones (p=0,009), fueron las variables que tuvieron asociación independiente con la ocurrencia de infarto perioperatorio. Los índices de probabilidad u oportunidad (odds ratio) ajustados para la edad y el índice de masa corporal fueron menores que 1. Según odds ratio ajustados, las variables con mayor influencia en la mortalidad fueron la presencia de complicaciones (3,753; p=0,017), el tiempo quirúrgico prolongado (2,690; p=0,002) y el filtrado glomerular preoperatorio bajo (2,112; p=0,036).

Conclusiones: La mayor edad y el mayor índice de masa corporal fueron factores pronósticos protectores para la aparición de infarto agudo de miocardio perioperatorio. El tiempo quirúrgico prolongado y la presencia de complicaciones se asociaron de manera independiente con el infarto perioperatorio y la mortalidad después de una revascularización miocárdica quirúrgica. El filtrado glomerular preoperatorio bajo, también estuvo asociado a la mortalidad.

Palabras clave: Revascularización miocárdica, Factores pronósticos, Infarto de miocardio perioperatorio, Mortalidad, Cardiopatía isquémica

INTRODUCTION

Today acute coronary event lethality doubles that from 20 years ago due to the fast population aging in some countries. Approximately one million people a year are admitted to hospitals in the United States because of ischemic heart disease[1]. In less developed countries the demographic transition leads to patterns of morbidity and mortality similar to that of developed countries. In 2020, seven out of ten deaths in Latin America will be due to noncommunicable diseases and ischemic heart disease is going to be the main cause[1].

Cuba does not escape these statistics, 17% of the adult population suffers from ischemic heart disease. Heart diseases are the second leading cause of death in the workforce, with 22.651 deaths from this cause in 2013, which is related to the increase in average and life expectancy of the Cuban population[2].

Surgery has been one of the mainstays treatments for ischemic heart disease in the last fifty years. It includes two types: one intended to improve the coronary blood flow of the territories irrigated by arteries with significant stenosis (coronary artery bypass graft [CABG] surgery), and another which aims to repair heart structures damaged by ischemic events (surgery for mechanical complications of acute myocardial infarction and ischemic cardiomyopathy). CABG is the most common cardiothoracic surgery. Approximately 550.000 patients undergo CABG in the United States every year. European developed countries perform over 250 operations per million inhabitants[3]. In Cuba, it is the second most performed heart surgery representing 35-40% of operations with extracorporeal circulation (ECC). The Cardiology Division from the "Hermanos Ameijeiras" hospital, founded in 1984, has over 25 years of experience in CABG having already achieved significant results. More than 700 coronary artery bypass procedures were performed along the first 20 years. Numbers have increased since 2004, to stabilize more than 150 procedures a year, of which about 50% are made with beating heart. Current mortality rates for elective CABG in Cuba are ranging around 8%[4].

Ischemic heart disease remains the leading cause

of death worldwide, so the analysis of results in coronary surgery has become very important also because of the volume of cases represented by this type of intervention in cardiac surgery as well as the issue related to the cost per patient. Risk assessment is an important aspect of current clinical practice and a useful tool for both, physician and patient. Numerous methods have been developed for risk stratification of adverse events, mainly based on the anatomical complexity or clinical risk, which have proven useful in the decision-making process. These methods frequently used in clinical settings, are risk models to assess the immediate or short term —inpatient or after 30 days—, and middle and long term results (≥ 1 year). Current risk stratification methods do not incorporate some important variables and although risk models provide useful information for predicting mortality and major adverse events, to date there is no model available to predict what patients would have quality of life benefits[5].

In addition to mortality it is important to identify prognostic factors that influence the occurrence of acute perioperative myocardial infarction (PMI), as it has a negative impact in terms of morbidity and mortality in patients treated with CABG. Approximately 15% of patients undergoing heart surgery who develop PMI suffer cardiogenic shock. In addition, up to 49% of patients with PMI have adverse cardiac events after 2 years.

Predictor models of mortality and other adverse cardiac events in cardiac surgery have been made from certain population groups, in a defined period of time, and have taken into account variables that were previously selected in other different settings. It is therefore important to wonder whether these studies results could be applied to different population groups, which were operated on at another time, and therefore, whether it would be feasible introducting new variables (not established in conventional risk scores) that could influence the prognosis of these patients.

For these reasons, this research aimed to identify factors influencing prognosis, occurrence of PMI and early cardiac death in patients treated with CABG in the "Hermanos Ameijeiras" Hospital.

METHOD

A prospective cohort research was conducted with 231 patients diagnosed with ischemic heart disease who were treated with CABG in the Division of Cardiovascular Surgery from the Cardiology Division at *Hospital Clínico Quirúrgico Hermanos Ameijeiras* from March 2012 to August 2014.

Patients were selected from a study population consisted of all patients diagnosed with ischemic heart disease requiring surgical treatment in the Division of Cardiovascular Surgery from the above-mentioned hospital.

Exclusion criteria

Patients who a) because of their place of residence would hamper the monitoring activities and assistance to consultations, b) did not wish to participate in the study and c) required combined surgery.

Variables

Preoperative: Sex, age, personal and family medical history, hemochemical lab test results, smoking, anthropometric measures, previous interventions, angina functional class, QRS duration, left ventricular systolic function and number of involved coronary vessels.

Intraoperative: Surgery support, surgical times, ECC time, cardiac arrest induction time, number of anastomosis, type of bypass and surgical accidents.

Immediate postoperative period: Intubation time, complications and stays in both Surgical Intensive Care Unit and Hospital.

Response variables related to prognosis: Early cardiac death and PMI.

PMI: Classified as type 5 according to the third universal definition of acute myocardial infarction[6], that related to CABG and defined by elevated cardiac biomarkers levels 10 times higher to 99th percentile of the upper reference limit in patients with normal baseline cardiac troponin (<99th percentile) during the first 48 hours after CABG. In addition, one of the following: a) new pathologic Q waves or new left bundle branch block; b) new occlusion of the native coronary artery or graft, angiographically demonstrated or c) imaging evidence of new loss of viable myocardium or new regional wall motion abnormalities.

Early mortality: occurred in the first 30 days after

CABG[6].

Techniques for primary data collection

Patient data was collected during their stay in the pre-operative area, operating room, Surgical Intensive Care Unit, postoperative care unit and outpatient consultation, and was compiled in a research folder to be subsequently entered in the database.

Follow-up

All patients received clinical follow-up in the after surgery recovery room or outpatient. The occurrence of adverse events (mortality and PMI) was obtained by reviewing medical records and death certificates during the first 30 days after surgery.

Information processing and analysis

A database was compiled in Excel and it was statistically processed using SPSS version 11.

Summary measures for qualitative (percentages) and quantitative variables, mean and standard deviation were used when followed a normal distribution, otherwise, mean with interquartile range.

Chi-square test (χ^2) was used to compare proportions in the case of 2x2 contingency tables with continuity correction; Fisher's exact test was used when there was a 25% or more expected frequencies. Chi-square (χ^2) without correction test was applied for rows and columns contingency tables. Mann-Whitney U test was used to compare means due to the small sample of patients with PMI and those deceased. To determine the influence of possible factors influencing the prognosis for the presence of PMI and mortality, multiple logistic regression with dichotomous response was used.

Table 1. Univariate analysis for factors related to the presence of perioperative AMI. *Hospital Hermanos Ameijeiras*. Havana, 2015.

Variables	Perioperative AMI		p*
	Yes (n=31) (mean ± SD)	No (n=200) (mean ± SD)	
Age (years)	62,1 ± 9,3	63,4 ± 8,8	0,517
BMI (kg/m^2)	25,8 ± 4,2	27,2 ± 3,9	**0,048**
Waist circumference (cm)	94,2 ± 7,2	97,1 ± 6,9	**0,015**
Surgical time (hours)	6,4 ± 2,0	5,7 ± 1,4	0,078
Intubation time (hours – mean[IR])	6,2 (9,0)	6,1 / 3,1	0,083
SICU stay (hours – mean[IR])	69,0 (57,2)	67,2 / 40,9	0,952
Hospital stay (days – mean[IR])	27,2 (11,7)	33,9 / 17,2	0,088
CPB time (min)**	151,6 ± 50,1	123,5 ± 47,6	0,061
Cardiac arrest induction time (min)**	72,1 ± 24,4	77,0 ± 29,3	0,513
Emergency surgery (n[%])	26 (83,9)	187 (93,5)	0,075[c]
Elective surgery (n[%])	5 (16,1)	13 (6,5)	

* Mann-Whitney U test, ** AMI: n=14 / No AMI n=89
c: Fisher's exact test
AMI, acute myocardial; BMI, body mass index; ECC, extracorporeal circulation; IR, interquartile range; SD, standard deviation; SICU, Surgical Intensive Care Unit.

Ethical considerations

The research was conducted in compliance with the provisions of the International Code of Medical Ethics and the four ethical principles. Patients were explained the purpose of the study and their written and signed informed consent was taken into account.

RESULTS

There was significant association between body mass index (BMI) and patients who did or did not suffered PMI (25.8±4.2 *vs.* 27.2±3.9 kg/m^2; p=0.048). A significant association (p=0.015) was also found with respect to the waist circumference: 94.2± 7.2 vs. 97.1±6.9 cm (Table 1). The PMI probability value associated with the Mann-Whitney U test for surgical time, intubation, hospital stay and ECC time approached the level of statistical significance with values of 0.078, 0.083, 0.088, and 0.061; respectively. For the type of surgery, the probability value associated with the Fisher's test also approached statistical significance (p=0.075).

Tables 2 and 3 show the significant association of QRS width (101.0±14.5 *vs.* 94.2±20.4 ms; p=0.016), operative time (6.9±2.1 vs. 5.7±1.4 hours; p= 0.012) and diabetes mellitus (p=0.025) with mortality. This means that the longer the QRS and surgical time duration, plus the presence of diabetes, the higher mortality will be. For glomerular filtration, the value of death probability associated with the Mann-Whitney U test

Table 2. Univariate analysis for factors related to early mortality.

Variables	Mortality		p*
	Yes (n=22) (mean ± SD)	No (n=209) (mean ± SD)	
Age (years)	63,23 ± 9,7	63,20 ± 8,7	0,817
BMI (kg/m^2)	28,2 ± 4,09	26,9 ± 3,93	0,152
Waist circumference (cm)	100,3 ± 8,5	100 ± 9,3	0,619
Glomerular filtration (ml/min/m^2 - mean[IR])	76,7 / 34,4	86,3 / 33,3	0,088
LVEF (%)	55,6 ± 15,8	59,4 ± 10,5	0,599
Number of vessels	3,9 ± 0,9	3,8 ± 1,2	0,685
QRS width (ms)	101,0 ± 14,5	94,2 ± 20,4	**0,016**
Surgical time (hours)	6,9 ± 2,07	5,7 ± 1,4	**0,012**
ECC time (min)	141,3 ± 54,3	125,8 ± 48,1	0,313
Anoxic arrest time (min)	69,1 ± 30,8	77,2 ± 28,4	0,311

* Mann-Whitney U test.
BMI, body mass index; ECC, extracorporeal circulation; IR, interquartile range; LVEF, left ventricle ejection fraction; min: minutes; SD, standard deviation.

Table 3. Univariate factors related to early mortality analysis.

	Mortality				p
	Yes (n=22)		No (n=209)		
	Nº	%	Nº	%	
STEACS	9	40,9	119	56,9	
NSTEACS	3	13,6	8	3,8	0,077[b]
CSA	10	45,4	82	39,2	
Prior PTCA	1	4,5	27	12,9	0,488[c]
Complete CABG	16	72,7	157	75,1	1,000[a]
Incomplete CABG	6	27,3	52	24,9	
Urgent SI	18	81,8	195	93,3	0,077[c]
Elective SI	4	18,2	14	6,7	
HT	18	81,8	175	83,7	0,766[c]
DM	13	59,1	68	32,5	**0,025**[a]

a: Chi-square test (χ2) with continuity correction. b: χ2 without continuity correction. c: Fisher's exact test.
CABG, coronary artery bypass grafting; CSA, chronic stable (effort) angina; DM, diabetes mellitus; HT, Hypertension; NSTEACS, non-ST-segment elevation acute coronary syndrome; PTCA, percutaneous transluminal coronary angioplasty; SI, surgical intervention; STEACS, ST-segment elevation acute coronary syndrome.

Table 4. Results of multiple logistic regression to the presence of perioperative AMI.

Variables	OR	OR[a]	95% CI	p
Age	0,935	0,554	0,883 - 0,990	**0,021**
BMI (kg/m^2)	0,856	0,540	0,753 - 0,972	**0,017**
Surgical Time	1,428	1,717	1,050 - 1,942	**0,023**
QRS width (ms)	1,015	1,336	0,991 - 1,038	0,222
Beating heart[b]	1,047	1,024	0,427 - 2,566	0,919
Circulatory support[b]	0,178	0,671	0,016 - 2,000	0,162
Complications	4,790	2,116	1,489 - 15,405	**0,009**
Smoking	0,341	0,607	0,112 - 1,039	0,058
LVEF	1,011	1,129	0,973 - 1,050	0,577

a: OR standardized, b: binary variable that corresponds to transoperative support with ECC (0.351) as reference category.
BMI: body mass index; CI: confidence interval; LVEF, left ventricular ejection fraction; OR: odds ratio.

Table 5. Multiple logistic regression results for early mortality.

Variables	OR	OR[a]	95% CI	p
Age	1,025	1,242	0,947 - 1,109	0,543
BMI (kg/m^2)	1,063	1,274	0,907 - 1,246	0,451
QRS width (ms)	1,011	1,254	0,985 - 1,039	0,406
Preoperative GF (ml/m^2/min)	1,022	2,112	1,001 - 1,043	**0,036**
STEACS[b]	3,421	1,300	0,482 - 24,268	0,219
NSTEACS[b]	0,461	0,680	0,132 - 1,605	0,224
Prior PTCA[b]	0,150	0,538	0,007 - 3,058	0,218
LVEF (%)[b]	0,985	0,849	0,941 - 1,032	1,032
Beating heart[c]	1,779	1,333	0,503 - 6,296	0,371
Circulatory support[c]	0,488	0,847	0,051 - 4,653	0,533
Surgical time	1,919	2,690	1,279 - 2,881	**0,002**
Complications	15,821	3,753	1,628 - 153,782	**0,017**

a: OR standardized, b: binary variable that corresponds to the diagnosis with chronic stable angina of effort as reference category, d: binary variable corresponding to transoperative support with the ECC as reference category.
BMI: body mass index; CI confidence interval; GF: glomerular filtration; LVEF, left ventricular ejection; NSTEACS, non-ST-segment elevation acute coronary syndrome; OR: *odds ratio*; PTCA, percutaneous transluminal coronary angioplasty; STEACS, ST-segment elevation acute coronary syndrome.

result (p=0.088), and in the case of the type of surgery the probability value associated with the Fisher test result (p=0.077), were close to the significance level.

Variables that were independently associated with the occurrence of PMI (Table 4) were: older age (p=0.021), higher BMI (p= 0.017), largest surgical time (p= 0.023) and the presence of complications (p= 0.009). Although age and BMI adjusted odds ratio (OR) were less than 1, so these variables had a protective effect at higher age and BMI, less probability to have a PMI, when all other variables are held constant. Surgical time behaved as a non-protective prognosis factor; as it increases, the opportunity to present a PMI also increases, when all other variables are held constant. Same happened with complications, as patients who presented them had nearly 5 times a greater chance of having a PMI when all other variables are held constant. According to the result of the adjusted standardized OR, variables with greater influence on the probability of having PMI were complications with 2.116 and surgical time, with 1.717.

Variables that had an independent relationship with very early mortality (Table 5) were, longer surgical time (p=0.002), low preoperative glomerular filtration rate (p=0.036), and the presence of complications (p=0.017). The lower the preoperative glomerular filtration and surgical time, the highest probability of dying when other variables are held constant; and when complications occur, the chance of dying rises about 16 times, when other variables are held constant. The confidence interval for this

variable is very wide denoting much imprecision due to the small sample of deceased in which only one presented no complications. According to the adjusted standardized OR result, variables with most influence on the probability of dying were in order of magnitude, the occurrence of complications (3.753), longer surgical time (2.690) and low preoperative glomerular filtration (2.112).

DISCUSSION

95-Parsonnet score includes obesity among its negative factors (BMI>30); however, Moulton *et al.*[7] published one of the first works about this issue in 1996. Among their findings, except sternotomy infections and atrial arrhythmias, they found that obesity was not a significant risk factor. Subsequent studies confirm the increased risk of surgical wound infection without increasing mortality. Schwann *et al.*[8], in a prospective study of 3.560 patients who were to undergo CABG, found that mortality, PMI, stroke, need for blood transfusions and hospital stay were higher in the group of patients with BMI<24 kg/m^2. Brandt *et al.*[9], found that those same complications were not significantly higher in the population of surgical patients with obesity (BMI>30). Similar results were published by Potapov *et al.*[10] and Reeves *et al.*[11], who concluded that patients with a low BMI had a higher risk of postoperative adverse events, including PMI, than obese ones (BMI>35).

A study carried out in Brazil, aiming to relate BMI with postoperative CABG events, concluded that there was no statistically significant association between obesity and overweight with the increased frequency of postoperative complications[12]. This study results coincide with what is published in literature, where BMI behaves as an independent protective factor for adverse events, including PMI. Moreover, the fact that BMI behaves that way in this study can be explained by the small number of this surgical complication (31 patients out of 231), in a sample where practically everyone is overweight or obese.

Moreover, as Brandt *et al.*[9] described, Al-Alao and collaborators found that age older than 75 years greatly influenced patient to develop a PMI, with OR 2.8, (95% CI: 2.0-4.0; p<0.001), results that differ from this research, where the average age of patients with and without PMI showed very little difference (62.1± 9.3 vs. 63.4±8 8) −that could justify the finding− was lower than the one reported in that study, and constituted a protective factor.

A prolonged surgical time may favor or increase myocardial ischemia and, at the same time, the occurrence of PMI; it also leads to a decreased contractility that can produce a low cardiac output (LCO) state, that may require a prolonged ECC time, the inability to get out of it or the need of mechanical circulatory support; and the prolongation of ECC is also a PMI risk. The aforesaid coincides with the findings in this study and other publications[13,14].

It is necessary to highlight the high association between the occurrence of PMI and other complications such as LCO, where an ischemic process produces a contractile heart failure and, at the same time, a drop of coronary flow derived from this LCO state; ventricular arrhythmias, of which it is known that one of their mechanisms of production is ischemia, also favor coronary flow fall of and death. The presence of bleeding due to hematologic dysfunction, state of severe hypotension and hypertension are complications associated with the appearance of PMI, resulting from the contribution or increase in myocardial oxygen demand[15,16].

In the univariate analysis this study showed that the longer duration of preoperative electrocardiographic QRS interval was associated with increased mortality in the CABG immediate postoperative, although patients had a preserved left ventricle ejection fraction; although it was not independently associated with mortality, probably because of the sample size and the small number of this fatal event. These patients may present prevalence of ventricular mechanical dyssynchrony, leading to decreased myocardial contractile effectiveness. These mechanisms probably contribute to postoperative hemodynamic instability which, at the same time, is associated with increased early mortality[17].

Diabetes mellitus has been identified as a strong independent predictor of initiation and progression of cardiovascular disease and has been recognized as a risk factor for mortality after CABG[18], which coincides with the results of this research. A study in the *Cardiocentro Ernesto Che Guevara*, Santa Clara, Cuba, by Coll Muñoz *et al.*[19], after multivariate analysis between mortality and different covariates found that the variables which significantly affected the risk of dying were: history of diabetes mellitus (OR= 9.5; p=0.031) and chronic obstructive pulmonary

disease (OR=5.3; p=0.031).

Data from observational studies indicate that there is an increased risk of fatal perioperative complications in patients with low preoperative glomerular filtration. Renal failure is associated with an increased risk of early mortality and greater in-hospital stay[20,21]. A study by Pivatto Júnior *et al.*[22], related to mortality predictors, found that kidney dysfunction, with low preoperative glomerular filtration, pre (relative risk 6.33, 95% CI: 3.25-12 4; p= 0.001) and postoperative (relative risk 7.36, 95% CI: 3.71-14.6; p<0.001) was significantly associated with early mortality. The results described are consistent with those of the present investigation.

Prolonged surgical times are associated with increased incidence of PMI and other complications that, at the same time, are directly related to mortality[23]; which also coincides with this investigation results. In a multicenter study conducted in Brasil[24], the number of complications was related to the occurrence of postoperative death. In those who died, 59.5% had five or more complications, and less than 1% had not. Among the survivors, complications did not appear in 39.7%, and only 6.8% had five or more of them. Therefore, the postoperative complications record is also an indicator of prognosis. The main ones were those related to LCO, similar to the results obtained in this work. LCO syndrome is not uncommon during postoperative CABG. A study evaluating 814 patients between 2002 and 2003, in São Paulo, showed that this syndrome was responsible for 54.2% of deaths in the postoperative period and was present in 16.1% of operated patients[25].

It is important to remark that the fact that mortality in this study is higher than the annual average of *Hospital Hermanos Ameijeiras* in patients with CABG, is attributed to the time the study began, and because it is a prospective cohort design, it included three months in which mortality occurrence was above the annual (January to December each year), informed by the hospital in such operations 4.1% in 2012; 6.0% in 2013 and 5.8% in 2014.

CONCLUSIONS

Acute PMI was independently associated with younger age, lower BMI, prolonged surgical time and the onset of complications. Older age and higher BMI were protector prognostic factors. The probability of dying after CABG was independently influenced by prolonged surgical time, low preoperative glomerular filtration and the presence of complications

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