Preoperative Serum Fibrinogen as a Predictor for Myocardial Infarction in Surgical Myocardial Revascularization

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Objective

Determine the predictive level of preoperative serum fibrinogen level for the occurrence of MI in perioperative surgical myocardial revascularization (SMR), as well as for other impacting outcomes, such as stroke, pulmonary thromboembolism (PTE), and death, separately or in combination.

Methods

A retrospective cohort study based on the heart surgery database analysis from São Lucas Hospital, at Rio Grande do Sul Catholic University with 1,471 consecutive patients submitted to extracorporeal SMR between January, 1998 and December, 2002.

Results

Perioperative MI occurred in 14% of sample patients. No association was shown between preoperative fibrinogen and perioperative MI (410.60 ± 148.83 mg/dl for the study group x 401.57 ± 135.23 mg/dl for control group – p = 0.381 – RC = 1.000 – CI95%: 0.998-1.002 – p = 0.652), combined outcome for MI, stroke, PTE, and death (411.40 ± 153.52 mg/dL for the group reporting outcome x 400.31 131.98 mg/dL for the group with no outcome – p = 0.232) and neither separately.

Conclusions

In that sample, preoperative serum fibrinogen level did not show any association with the occurrence of perioperative MI in SMR, neither with other impacting outcomes, stroke, PTE, and mortality, whether separately or as composite endpoints.

Key words

Fibrinogen, myocardial infarction, surgical myocardial revascularization.

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Thrombotic complications in surgical myocardial revascularization (SMR) stand as the major causes of mortality in this population. Among them are pulmonary thromboembolism (PTE), stroke and myocardial infarction (MI). The low incidence of PTE, described in literature as 0.5%, seems to be underestimated as a result of difficulties faced for the diagnosis of the condition, which therefore requires high degree of suspicion[1,2]. Stroke occurs in 0.4% to 6% of patients submitted to SMR. From those, up to 28% have mortality as endpoint, demonstrating how impacting such occurrence is[3]. From those serious complications, perioperative MI is the most commonly found, with incidence ranging from 5 to 15%, as reported in literature[3,4]. MI consequences may range from non-clinically relevant slight enzyme increases to low cardiac debit conditions, or malign tachyarrhythmias, followed by mortality or survival time reduction in the long run[3] - which explains the efforts put into the attempt of preventing such complication.

Since fibrinogen is an acute phase inflammatory protein, responsible for singular functions in the coagulation cascade, its association with thrombotic and inflammatory phenomena has been extensively studied[5-29]. Among those, the association with MI is, undoubtedly, the most widely assessed[5-25,30]. Fibrinogen acts as a bridge between platelet IIb IIIa glycoprotein receptor exposed on platelet surface when it is activated. Thus, it provides the aggregation of two or more cells, and the formation of a platelet thrombus. Additionally, fibrinogen also plays a key role in the final stage of the coagulation cascade, when the fibrin network is formed, thus forming fibrin monomers when cleavaged with thrombin (another important platelet activator), from X factor activation, which in its turn, originates from tissue factor.

However, in the heart surgery setting, literature makes available one study only, published by Rifón et al[31], where fibrinogen was assessed in a retrospective cohort in the preoperative SMR of 19 patients with angiographic occlusion of venous graft within a month after post-surgery, and compared with 63 controls with pervious grafts. After multivariate analysis, no statistically significant difference was found (350 ± 70 mg/dl x 380 ± 90 mg/dl – p = NS) between the groups. After extensive literature review – covering the past 30 years – no studies with more expressive samples to assess clinical outcomes could be found.

Therefore, although there are a number of observational studies and reports on the association of fibrinogen to atherothrombotic cardiovascular disease, no studies are available in the literature to relate fibrinogen and MI in perioperative SMR. Such information is extremely relevant since if preoperative risk is identified and properly managed, it may be possible to reduce that serious complication in the surgical setting.

The present study has the primary purpose of determining whether preoperative fibrinogen level is a predictor for the occurrence of MI in SMR perioperative period. As a secondary objective, the study tried to assess the association between preoperative serum fibrinogen and the occurrence of stroke, PTE and mortality, independently or associated to MI, as the combined endpoint in SMR perioperative period.

Methods

Study design - A retrospective cohort study, with prospective data collection to put together a database.

Population - Patients submitted to isolated MRS at São Lucas Hospital at Rio Grande do Sul Catholic University (HSL-PUCRS).

Sample - Out of the 2,102 consecutive patients submitted to heart surgery at the HSL-PUCRS in the period between January, 1998 and December, 2002, 1,580 underwent SMR; from those, 1,472 were submitted to isolated SMR. Finally, 1,471 had records of preoperative fibrinogen level between 1 and 14 days before surgical procedure and were included in the study. The sample was quite representative for a cohort of patients submitted to SMR. Age range was 60.8 ± 10.1 years of age, and females accounted for 15.6%. Diabetes Mellitus was reported by 27.5% of the sample; hypertension by 67.9%; left coronary bundle branch lesion (LMCA) by 20.9%. Patients had vascular grafts at 2.96 ± 0.96. Preoperative left ventricle ejection fraction (FEVE) was 47.5 ± 12.1%; 2.5% of the patients had had previous SMR; 1.4% needed urgent surgery; 0.6% were submitted to coronary endarterectomy during surgery, and finally, a high rate (40.6%) of patients reporting preoperative unstable angina (UA) made up the sample population (Table 1).

Table 1 - General Characteristics of Sample

Characteristic	(n = 1.471)
Females (%)	15.6
Age (mean ± SD)	60.8 ± 10.1
Age > 60 years (%)	56.8
Diabetes Mellitus (%)	27.5
Arterial Hypertension (%)	67.9
Preoperative LVEF (mean ± SD - %)	47.5 ± 12.1
Ventricular Dysfunction (LVEF < 40% - %)	25.1
Number of grafts (mean ± SD)	2.96 ± 0.96
Triarterial Lesion (%)	72.3
LMCA Lesion (%)	20.9
Preoperative Unstable Angina (%)	40.6
Urgency Surgery (%)	1.4
REDO (%)	2.5
Coronary endarterectomy (%)	0.6
ECC Time (mean ± SD - minutes)	83.7 ± 29.8
Fibrinogen (mean ± SD – mg/dL)	403.0 ± 137.3

Data are expressed in percentages ou mean ± standard deviation. SD = Standard Deviation; LVEF = left ventricle ejection fraction; LMCA = left main coronary artery; REDO = re-operation; ECC = extracorporeal circulation.

Defining variables - The criteria used to define MI in SMR perioperative period were the ones widely described in literature [3,4]: 1) new, persistent Q wave shown by electrocardiogram (ECG) within 48 hours of post-surgery and associated to CK-MB > 30 U/L; 2) new and persistent left bundle branch blocking, associated to CK-MB > 30 U/L maximum serum level; 3) CK-MB > 80 U/L serum level taken isolatedly. Enzyme collection was carried out 0, 4, 8, 16, 24, 36 and 48 hours post-surgery; ECGs were carried out 0, 24 and 48 hours post-surgery. Stroke was defined as the occurrence of new neurological deficit, associated to ischemic changes at brain imaging exam (computed tomography and magnetic resonance imaging) in brain area topographically compatible with neurological condition, up to discharge. PTE was defined as the occurrence of dyspnea, chest pain or shock with no other etiology, associated to pulmonary imaging exam (thoracic computerized angiotomography, ventilation and perfusion pulmonary scintigraphy, and perfusion or pulmonary arteriography), with high probability or confirmation of PTE, up to discharge. Mortality was evaluated during the *index* hospitalization period. Composite endpoint was entered as the first occurrence of any of the endpoints under evaluation (MI, stroke, and mortality).

Planning - The analysis of the database at the HSL-PUCRS Heart Surgery Postoperative Unit (UPOCC) was carried out through preoperative values of fibrinogen, of controllable variables and of clinical outcomes for as controllable variables and clinical endpoints, such as MI, stroke, PTE and death. A review of the electronic records at HSL-PUCRS clinical analyses laboratories was carried out with the purpose of retrieving patients' fibrinogen values that might not have been available at the database.

Laboratory analysis - Blood samples to dose fibrinogen serum level were collected from all patients included in the study between 1 and 14 days before surgical procedure through the *Clauss* method through turbidimetry reading and the use of Coag-A-Mate MTX™ equipment and Fibriquik™ reactant, a thrombin reactant compound (100 U NIH/mL), fibrinogen reference calibration (buffer solution, human plasma, and stabilizers) and *Veronal of Owren* buffer solution (0.28M sodium barbital).

Control of variables - The following variables were controlled, as described in the literature as predispositional for the occurrence of the outcome (perioperative MI), which is to say, possible misguiding factors: age, gender, LVEF, LCBB lesion, UA, coronary endarterectomy, urgency surgery, REDO, number of grafts, and time of extracorporeal circulation (ECC). The time for aortic clamp was not included in the analysis, since this variable keeps the same time pattern behavior as ECC (r = 0.82). In the analysis model, the number of grafts replaced the occurrence of three-vessel disease, since this is a continuous variable showing the same behavior pattern (r=0.88).

Statistical analysis - Sample size was calculated based on the results of a pilot study[32] where the incidence of perioperative MI was 23% and 13% for study and control groups, respectively, and odds ratio (OR) for the association between fibrinogen and the outcome under discussion was 1.89. Considering $p < 0.05$ as significant, and an 80% power to estimate a 10% difference between the groups, Epi-info program helped reach a total number of 1,350 patients required so that analysis results could either confirm or deny - with statistical significance - study hypothesis.

The statistical analysis was carried out using SPSS 11.0 software, with descriptive analysis of general data, Pearson correlation coefficient for the exclusion of same behavior pattern variables in the analysis model, univariate analysis through chi-square for categorical variables, Student *t* test for continuous variables, and logistic regression multivariate analysis for variables presenting $p < 0.2$ in univariate analysis. Final results were presented through odds ratio (OR), with 95% confidence intervals (CI). Statistical significance was defined as $p < 0.05$ for the multivariate analysis.

Ethical considerations - As this is a research based on medical records of patients not easily found, with no informed address or who are already deceased, and therefore not available for signature, the Informed Consent was not included. Additionally, the heart surgery data base at the UPOCC/HSL-PUCRS has been approved by the Ethics Committee at the same hospital. The study was examined and approved of by the Research Ethics Committee at HSL-PUCRS and at the Cardiology Institute University Cardiology Foundation (IC-FUC).

Results

Of the 1,471 patients included in the study, 206 (14%) reported perioperative MI; 2.79% presented stroke; 2.92% reported PTE; and 7.41% had mortality as endpoint. Combined endpoints occurred in 22.7% of the sample (Table 2). In the univariate analysis, some statistically significant differences were found between the groups with and without perioperative MI, as expected. In group 1 (with MI) mean number of grafts was higher (3.21 ± 0.96 x 2.92 ± 0.95 - $p < 0.001$), as well as LMCA lesions (29.1% x 19.6% - $p = 0.002$), preoperative UA: (50.5% x 39.0% - $p = 0.002$) and time of ECC: (95.7 ± 32.8 minutes x 81.7 ± 28.8 minutes – $p < 0.001$). No statistically significant difference was found between the groups with and without perioperative MI in regard to gender, age, LVEF, urgency surgery, REDO, and combined coronary endarterectomy (Table 3).

Mean preoperative fibrinogen did not show statistically significant difference when the two groups were compared – with or without perioperative MI (410.60 ± 148.83 mg/dl x 401.57 ± 135.23 mg/dl – p = 0.39) (Table 3). Even after sample categorization in percentiles for serum fibrinogen level, the decreasing order comparison of both the first quartile and the first decile and the remaining of the sample did not show significant difference (Table 4).

Although negative to univariate analysis, the association of preoperative fibrinogen to perioperative MI was carried out through logistic regression multivariate analysis, since many characteristics were different in both groups. In addition to fibrinogen, other variables were included in the equation: gender, age, LMCA lesion, preoperative UA, coronary endarterectomy, REDO, number of vascular grafts, and ECC time. After logistic regression analysis, 6 variables were identified as independent predictors for the occurrence of perioperative MI in SMR: female gender, LMCA lesion, preoperative UA, REDO, ECC time, and the number of grafts. The association between preoperative serum fibrinogen level and the occurrence of perioperative MI was kept null after the adjustment for possible misguiding factors included in the regression model (OR = 1.000 - IC95%: 0.998-1.002 – p = 0.652) (Table 5).

As for other endpoints of interest, neither did preoperative fibrinogen show any association with perioperative stroke (440.63 ± 157.71 mg/dl x 401.75 ± 136.47 mg/dl – p = 0.074), perioperative PTE (426.05 ± 165.99 mg/dl x 402.13 ± 136.24 mg/dl – p = 0.260), intra-hospital mortality (408.72 ± 162.68 mg/dl x 402.36 ± 135.01 mg/dl – p = 0.642) or composite endpoints of MI, stroke, PTE, and mortality (411.40 ± 153.52 mg/dl x 400.31 ± 131.98 mg/dl – p = 0.232) (Table 6).

Table 2 - Incidence of Endpoints in Sample

Endpoint	(n = 1,471)
Perioperative MI (%)	14.00
Perioperative stroke (%)	2.79
Perioperative PTE (%)	2.92
In-hospital death (%)	7.41
Composite Endpoint (%)	22.70

Data are expressed in percentages. MI - myocardial infarction; PTE - pulmonary thromboembolism; composite outcome - MI + stroke + PTE + in-hospital mortality.

Table 3 - Baseline Demographics of Sample With and Without Perioperative MI

Variable	With MI	Without MI	p
Females (%)	18.4	15.1	0.226*
Age (mean)	61.67	60.71	0.215**
LVEF (mean ± SD - %)	48.47	47.42	0.336**
Ventricular Dysfunction (LVEF < 40% - %)	22.2%	25.6%	0.385*
Number of grafts (mean ± SD)	3.21 ± 0.96	2.92 ± 0.95	< 0.001*
LMCA Lesion (%)	29.1	19.6	0.002*
Preoperative UA (%)	50.5	39.0	0.002*
Urgency Surgery (%)	1.9	1.3	0.437*
REDO (%)	4.4	2.2	0.067*
Coronary endarterectomy (%)	1.5	0.5	0.094*
ECC Time (mean ± SD – minutes)	95.7 ± 32.8	81.7 ± 28.8	<0.001**
Fibrinogen (mean ± SD – mg/dL)	410.60 ± 148.83	401.57 ± 135.23	0.381**

** Analysis was carried out through chi-square. ** Analysis was carried out through student t test. *** Variables included in the logistic regression model are expressed in bold type. LVEF - left ventricle ejection fraction; SD - standard deviation; LMCA - left main coronary artery; UA - unstable angina; REDO - re-operation; ECC - extracorporeal circulation.*

Table 4 - Association between fibrinogen and myocardial infarction perioperative after sample categorization through percentiles

Percentile	Fibrinogen	MI (%)	OR	CI 95%	p
90	> 577 mg/dL	18.4	1.44	0.92 – 2.25	0.14
	< 577 mg/dL	13.5			
75	> 466 mg/dL	14.5	1.06	0.76 – 1.48	0.74
	< 466 mg/dL	13.8			

** Values are expressed in odds ratio (OR) percentage and 95% confidence interval (CI).*

Table 5 - Independent Predicting Variables for the Occurrence of Perioperative Myocardial Infarction in Surgical Myocardial Revascularization

Variables included in equation	OR	95% IC	p
REDO	2.070	1.050 – 4.080	0.036
LMCA Lesion	1.692	1.160 – 2.467	0.006
Females	1.572	1.034 – 2.391	0.034
Preoperative UA	1.533	1.102 – 2.134	0.011
Increased number of grafts	1.336	1.118 – 1.596	0.001
ECC prolonged time	1.013	1.008 – 1.018	<0.001
Coronary endarterectomy	2.314	0.550 – 9.730	0.252
Age	0.996	0.979 – 1.012	0.594
Fibrinogen	1.000	0.998 – 1.002	0.652

** Data with statistical significance are in bold type. * Values are expressed in odds ratio (OR) percentage and 95% confidence interval (CI).*

Table 6 - Association of Preoperative Serum Fibrinogem Level with the Occurrence of Other Impacting Endpoints in SMR Perioperative Period

Endpoint		Fibrinogen (mean ± SD – mg/dL)	p*
Stroke	Yes	440.63 ± 157.71	0.074
	No	401.75 ± 136.47	
PTE	Yes	426.05 ± 165.99	0.260
	No	402.13 ± 136.24	
Mortality	Yes	408.72 ± 162.68	0.642
	No	402.36 ± 135.01	
Composite Endpoint	Yes	411.40 ± 153.52	0.232
	No	400.31 ± 131.98	

** Analysis was carried out through Student t test.*

Discussion

The independent association between fibrinogen and MI and sudden death in UA patients had already been described; as were its straight correlation with CHD having been assessed through angiography and MI in healthy individuals and in individuals with previous MI – in the latter groups, the association with general mortality was also identified; its prognostic relevance for the outcomes when myocardial revascularization is needed; fatal and non-fatal MI, and cardiovascular death in stable angina patients, as well as a number of other associations. However, considering all evidence favoring high serum fibrinogen as predictor for clinical thrombotic events, why would this association have shown to be negative in the present study in the SMR setting? Although, at a first moment, perioperative MI was believed to be the result of vascular grafts occlusion, necropsy studies have shown that most of them were pervious in patients whose outcome was death due to perioperative MI, as the one carried out by Bulkley and Hutchins[33], which analyzed 54 autopsies of patients submitted to SMR and whose outcome was death in less than a month within 1 month after surgery. Forty-two bands of regional transmural necrosis were identified in 22 patients (38% of sample), being 34 of them in areas of vascular grafts distribution, and 30 (88%) of them reporting graft patency. Such observation supports the idea that other physiopathogenic factors may be involved in the etiology of perioperative MI. Among them, some unbalance between myocardial oxygen offer and demand in the perioperative period seems to be the key factor for MI diagnosis in postoperative SMR, which explains the null association reported in the present study.

The representative sample of a population of patients submitted to SMR, with data similar to those found in the SMR data base at the American Society of Thoracic Surgeons for patients operated on in the USA in 2000, makes the consecutive method for patient screening trustworthy. In the American sample, average age was 65 years of age, with 19% of females, 23% of LMCA lesions and 7% of REDO, and average preoperative LVEF at 49%[34]. The high number of patients included in the study – designed following pre-study calculation based on sample size – reiterates results confidence.

However, some methodology problems must be considered as possible study limitations. Data trustworthiness may be in jeopardy in retrospective studies. However, once data collection for the creation of a data base was retrospective, the chance of having incurred in such error is minimized.

Additionally, as proven by previous studies, fibrinogen serum level has circadian, circaseptan, and circanual rhythms[35-40]; therefore, some calculation bias may have occurred depending on time of day, day of the week, or

even the season when the collection was carried out.

The combination of serum CK-MB increase and the presence of a new Q wave in the ECG have been the widely accepted criteria used for diagnostic definition of perioperative MI in world literature[3,4]. However, sensitivity and specificity in such method combination are known not to be the gold standard. However, practical logistic difficulties have turned such approach unfeasible: dislocating all patients from ICU on the first days after heart surgery – some in serious condition, with pleural and mediastinal drainage or supported by other equipment such as pulmonary blood pressure monitoring catheter, systemic blood pressure catheter, pacemaker and intraortic balloon pump – and transfer them to a nuclear medicine laboratory for myocardial scintigram with technetium pyrophosphate. Despite the recent studies on troponin, as well as publications in the SMR setting[41-43], there is still no consensus in literature to define the cut-off point for the occurrence of perioperative MI.

In that sample, baseline average level for preoperative fibrinogen (403 mg/dl) was significantly higher when compared to mean values made available in the literature for random samples whose baselines ranged from 150 to 400 mg/dL[34,44]. In a study assessing the activation of SMR-related coagulation system, preoperative fibrinogen mean serum level was 359 mg/dL – closer to the upper baseline level, but still quite under the assessment in our sample[45]. The occurrence of 40.6% of UA in the sample – a clinical event known to be thrombotic and with proven association to serum fibrinogen – may have been responsible for that high baseline value[14,20,45,46].

In conclusion, preoperative serum fibrinogen level did not show any association with the occurrence of myocardial infarction in the perioperative period of surgical myocardial revascularization. Neither have stroke, pulmonary perioperative thromboembolism, intra-hospital mortality, or the composite four endpoints in the study shown any association with preoperative fibrinogen. The variables under assessment in the present study – acting as independent predictors of perioperative myocardial infarction – were female gender, left main coronary artery lesion, long period of extracorporeal circulation, and higher number of grafts.

The heart surgery data base at the UPOCC/HSL-PUCRS has been approved by the Ethics Committee at the same hospital. The study was examined and approved of by the Research Ethics Committee at HSL-PUCRS and at the Cardiology Institute / University Cardiology Foundation (IC-FUC).

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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