

Prognostic Role of New Biomarkers in Off-Pump Coronary Artery Bypass Surgery

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The value of biomarkers of myocardial damage or inflammation in off-pump coronary artery bypass (OPCAB) surgery has not yet been established. In a prospective study of 51 consecutive patients scheduled for elective OPCAB surgery, preoperative levels of troponin T, C-reactive protein, interleukin-6, and tumor necrosis factor α were determined. The primary endpoint was the combination of cardiac death or acute myocardial infarction (AMI) within 30 days. Seven patients (14%) presented with an adverse event: 3 cardiac deaths and 6 AMIs. Univariate analysis identified the following adverse event predictors: renal failure (50% vs 11%; $P=0.028$), left ventricular ejection fraction $<50\%$ (38% vs 9%; $P=0.033$), preoperative troponin-T level >0.10 ng/dL (43% vs 9%, $P=0.016$), and EuroSCORE rating (7.6 [2.5] VS. 5.2 [2.6]; $P=0.031$). A preoperative troponin-T level >0.10 ng/dL ($P=0.03$) was the only independent adverse event predictor. No significant differences were found with biomarkers of inflammation ($P>0.05$). The presence of a preoperative troponin-T level >0.10 ng/dL is associated with a higher risk of cardiac death or AMI in patients undergoing OPCAB surgery.

Key words: Troponin T. C-reactive protein. Off-pump coronary artery bypass surgery.

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Papel pronóstico de los nuevos biomarcadores en la cirugía coronaria sin circulación extracorpórea

El papel de los marcadores de daño miocárdico e inflamación en la cirugía de revascularización coronaria (CRC) sin circulación extracorpórea (CEC) no ha sido establecido. Se realizó un estudio prospectivo de 51 pacientes consecutivos que recibieron CRC sin CEC. Se determinaron las concentraciones preoperatorias de troponina T, proteína C reactiva, interleucina-6 y factor de necrosis tumoral alfa. El evento primario fue el combinado de muerte cardíaca o infarto agudo de miocardio (IAM) a los 30 días. Un total de 7 pacientes (14%) presentaron eventos (3, muerte cardíaca y 6, IAM). En el análisis univariable fueron predictores la insuficiencia renal (el 50 frente al 11%; $p = 0,028$), la fracción de eyección del ventrículo izquierdo $< 50\%$ (el 38 frente al 9%; $p = 0,033$), la troponina T $> 0,10$ ng/dl (el 43 frente al 9%; $p = 0,016$) y el EuroSCORE (7,6 \pm 2,5 frente a 5,2 \pm 2,6; $p = 0,031$). La troponina T $> 0,10$ ng/dl preoperatoria fue el único predictor independiente de eventos ($p = 0,03$). Los marcadores de inflamación no mostraron diferencias ($p > 0,05$). La presencia de troponina T preoperatoria $> 0,10$ ng/dl se asocia con un mayor riesgo de muerte o IAM en pacientes que reciben CRC sin CEC.

Palabras clave: Troponina T. Proteína C reactiva. Cirugía coronaria sin circulación extracorpórea.

INTRODUCTION

Inflammatory markers such as C-reactive protein (CRP), interleukin 6 (IL6), and tumor necrosis factor α (TNF- α) are associated with the development of cardiovascular events in patients with acute coronary syndrome (ACS)¹ and also in healthy subjects.²

Furthermore, C-reactive protein can predict a higher incidence of cardiovascular complications after percutaneous transluminal coronary angioplasty (PTCA).³ Elevated markers of myocardial damage such as troponin T (TnT) point to a worse prognosis in patients with non-ST elevation ACS,⁴ as well as in patients undergoing PTCA⁵ or peripheral vascular surgery.⁶ The prognostic usefulness of these biomarkers in patients who undergo off-pump coronary artery bypass grafting (CABG) has not been studied. The studies published to date have only evaluated patients with extracorporeal circulation and the results have been contradictory.⁷⁻⁹ Extracorporeal circulation leads to a systemic inflammatory reaction and

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TABLE 1. Preoperative Clinical Characteristics (n=51)*

Mean±SD age, years	66±9
Men	38 (75%)
Diabetes mellitus	21 (41%)
Hypertension	33 (65%)
Hyperlipidemia	31 (61%)
Smokers	12 (23%)
Mean±SD BMI	27.9±3.4
≥30	15 (30%)
LVEF<50%	8 (16%)
Recent ACS (<1 month)	38 (74%)
Prior AMI	16 (31%)
Renal failure (creatinine >1.5 mg/dL)	4 (8%)
Peripheral vascular disease	9 (18%)
Beta blockers	42 (83%)
Antiplatelet agents	46 (90%)
Mean±SD no. affected vessels per patient	2.5±0.6
Three affected vessels	31 (61%)
LMCA disease	20 (39%)
Mean±SD no. grafts per patient	1.7±0.6
Mean±SD EuroSCORE	5.6±2.7
Internal thoracic artery	42 (81%)

*LVEF indicates left ventricular ejection fraction; BMI, body mass index; ACS, acute coronary syndrome; LMCA, left main coronary artery.

TABLE 2. Preoperative Biomarker Levels (n=51)*

TnT>0.10 ng/dL	7 (15%) (0.14-1.70)
CRP, mg/dL	0.24 (0.13-0.83)
IL6, pg/mL	3.2 (1.6-12.1)
TNF-α, pg/mL	28.4 (21.4-42.9)

*IL6 indicates interleukin 6; CRP, C-reactive protein; TnT, troponin T; TNF, tumor necrosis factor. Values are expressed as number (%) and range for TnT and median (25 and 75 percentiles) for the remaining variables.

can affect hemostatic, renal, neurological, and gastrointestinal function.¹⁰ Off-pump CABG has become consolidated as an alternative that avoids inflammatory response, although it is more demanding and can affect the quality of the anastomosis.¹¹ It might therefore be more important to monitor markers of inflammation and necrosis in off-pump CABG procedures.

PATIENTS AND METHODS

Study Population

Patients scheduled for off-pump CABG in 2002 were prospectively included in this study. Patients undergoing emergency procedures, combined surgery, repeat procedures and patients with active infection, those receiving steroid treatment, and alcoholics were excluded because the markers studied may be affected in such cases.

Biomarkers

During the 24 hours prior to surgery, peripheral blood samples were taken and stored at -80°C for subsequent analysis. The patients’ treatment was not conditioned by the results of these analyses. Plasma concentrations of TnT were measured (Roche Diagnostics GmbH, Mannheim, Germany) as a marker of myocardial damage: concentrations greater than >0.10 ng/dL were considered pathological. As markers of inflammation, an ultrasensitive C-reactive protein assay (Dade-Behring Inc., Newark, USA) (normal range, 0-0.5 mg/dL) and assays for IL6 (CLB, Amsterdam, The Netherlands) (normal range, 0-1.5 pg/mL) and TNF-α (Biosource Europe S.A., Belgium) (normal range, 50-150 pg/mL) were used.

Adverse Clinical Events

Patient follow-up lasted for the first 30 days after the operation. The primary endpoint was a composite of cardiac death or acute myocardial infarction (AMI). Diagnosis of postoperative AMI was defined as concentrations of the creatine kinase-MB isoenzyme (CK-MB) more than 5 times of the normal value and more than 4% of the total CK fraction.

Statistical Analysis

Continuous variables with a normal distribution were expressed as means (SD) and those not normally distributed as medians (percentiles). Categorical variables were expressed as numbers and percentages. A logistic regression analysis was done to determine the association of the appearance of adverse events with biomarkers, as well as with all the previously described risk factors. The multivariate logistic regression analysis (forward stepwise procedure) included variables with *P* values less than <0.10 in the univariate analysis. *P* values less than <0.05 were considered statistically significant.

RESULTS

The baseline clinical characteristics are presented in Table 1. The mean postoperative EuroSCORE¹² was greater than >5. Table 2 shows the preoperative levels for the biomarkers. All patients had normal values for CK (57±30 µg/dL) and CK-MB (1.9±1.1 ng/mL), whereas 7 patients (14%) had TnT levels above >0.10 ng/dL.

In the 30 days after the procedure, 3 patients (6%) died, 6 (12%) suffered an AMI, 13 (25%) had postoperative atrial fibrillation, and 7 (14%) had heart failure. The primary composite endpoint of death or AMI occurred in 7 patients (14%). In the univariate analysis (Table 3), the primary endpoint occurred significantly more often in patients with preoperative renal failure (50% vs 11%; *P*=.028), left ventricular

TABLE 3. Analysis of Predictors of Death or Acute Myocardial Infarction (n=51)*

	Univariate <i>P</i>	Multivariate <i>P</i>	With Event (n=7)	Without Event (n=44)
Renal failure	.036	.18	29%	4%
LVEF<50%	.049	.18	43%	11%
LMCA disease	.067	.17	71%	34%
EuroSCORE	.03	.08	7.57±2.50	5.25±2.58
TnT>0.1 ng/dL	.016	.03	43%	9%
CRP>0.3 mg/dL	.080	.12	71%	36%

*LVEF indicates left ventricular ejection fraction; CRP, C-reactive protein; LMCA, left main coronary artery; TnT, troponin T.

ejection fraction below < 50% (38% vs 9%; $P=.033$), and preoperative TnT greater than > 0.10 ng/dL (43% vs 9%; $P=.016$). The EuroSCORE was significantly higher in patients with the primary endpoint (7.6±2.5 vs 5.2±2.6; $P=.031$). Of the inflammatory markers, only CRP showed a nonsignificant tendency for the cutoff point of 0.30 mg/dL (24% vs 7%; $P=.08$). A history of ACS was not associated with a higher mortality or incidence of AMI (18.8% vs 14.4%; $P=.24$). According to the multivariate analysis (Table 3), TnT greater than > 0.10 ng/dL was the only independent predictor of the primary endpoint ($P=.03$).

DISCUSSION

A number of studies have shown that patients with clinical suspicion of ACS and TnT concentrations greater than > 0.10 µg/L at the time of admission have a higher rate of cardiac events in both the short and long term.^{5,13} Preoperative concentrations of TnT have only been assessed for surgery with extracorporeal circulation. Mächler et al⁷ studied patients with unstable angina and normal CK-MB levels and found that preoperative TnT was of no prognostic value, whereas Carrier et al⁸ reported that TnT concentrations greater than > 0.02 µg/L were associated with a higher risk of perioperative AMI, and Lyon et al⁹ found that TnT greater than or equal to ≥ 0.20 ng/mL was associated with higher early and late postoperative mortality.

In our study, the presence of preoperative concentrations of TnT greater than > 0.10 ng/dL was predictive of early cardiac complications. No other studies have been published that assessed the usefulness of preoperative TnT or other markers of myocardial damage in off-pump CABG. The population assessed in our study of off-pump surgery was representative of those undergoing surgery in Spain, and our findings were comparable to previously published studies.¹⁴ Off-pump of surgery is technically more demanding, and so increased TnT might identify a subgroup of higher risk, with worse tolerance of surgical manipulation and perioperative ischemia. Normal values for TnT are very low, below the limit of sensitivity of the assays used, and so small elevations point to ischemia and myocardial

damage.¹⁵ Our patients had low values of TnT, with a range between 0.14 ng/dL and 1.70 ng/dL, and normal concentrations of CK-MB. These small elevations generally indicate thrombus formation and complex coronary lesions, associated with a high risk of recurrence.¹⁶ Thus, preoperative elevation of TnT could identify an unstable coronary process which, although subclinical, might lead to a higher risk of perioperative complications. The prognostic value of TnT was independent of other baseline variables, suggesting that it can be included in risk stratification and that it would add to information provided by traditional risk markers. Troponin T was of greater prognostic value than history of recent ACS, which was not significant as a risk marker in this population.

Only a few studies have assessed the usefulness of preoperative CRP in CABG and these studies were done exclusively with CABG with extracorporeal circulation. Gaudino et al¹⁷ did not find that patients with high preoperative CRP were at greater risk, whereas Milazzo et al¹⁸ reported worse long-term prognosis in patients with CRP greater than or equal to ≥ 0.30 mg/dL, and Biancari et al¹⁹ found a higher risk of early complications in patients with CRP greater than or equal to ≥ 1 mg/dL. Unlike these studies, we assessed patients undergoing off-pump surgery, which avoids the inflammatory response induced by extracorporeal circulation. In our population, the preoperative concentrations of CRP, IL6, and TNF-α did not show any significant association with mortality or the incidence of AMI in the immediate postoperative period, indicating that inflammatory status was not a significant determinant.

Limitations

Because of the low number of events, the multivariate analysis lacked sufficient statistical power to allow definitive conclusions to be drawn. Study designs would therefore be needed with larger populations. However, our findings are in line with those obtained in studies done in other populations and suggest that current surgical risk models could be refined through the incorporation of new biomarkers of risk, such as TnT, into the individual assessment.

CONCLUSION

The presence of increased preoperative concentrations of TnT was associated with a higher risk of a poor outcome in off-pump revascularization surgery, independently of other traditional risk factors. The markers of systemic inflammation did not provide any additional prognostic information.

REFERENCES

- Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L, for the Frisc study Group. Markers of myocardial damage and inflammation in relation to long term mortality in unstable coronary disease. *N Engl J Med.* 2000;343:1139-47.
- Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation.* 2000;101:1767-72.
- Liuzzo G, Buffon A, Bissacchi LM, Gallimori JR, Caligiuri G, Vitelli A, et al. Enhanced inflammatory response to coronary angioplasty in patients with severe angina. *Circulation.* 1998;98:2370-6.
- Stubbs P, Collinson P, Moseley D, Greenwood T, Noble M. The prognostic significance of admission troponin T concentrations in myocardial infarction. *Circulation.* 1996;94:1291-7.
- Kurowski V, Killerman D, Frey N. A positive troponin T test on admission independently predicts an adverse prognosis in patients with acute myocardial infarction and direct PTCA. *Circulation.* 1999;100 Suppl:373.
- Kim LJ, Martinez EA, Faraday N, Dorman T, Fleisher L, Perler B, et al. Cardiac troponin I predicts short-term mortality in vascular surgery patients. *Circulation.* 2002;106:2366-71.
- Mächler H, Metzler H, Sabin K, Anelli-Monti M, Rehak P, Rigler B, et al. Preoperative myocardial cell damage in patients with unstable angina undergoing coronary artery bypass graft surgery. *Anesthesiology.* 1994;81:1324-31.
- Carrier M, Pelletier LC, Martinau R, Pellerin M, Solymoss B. In elective coronary artery bypass grafting, preoperative troponin T level predicts the risk of myocardial infarction. *J Thorac Cardiovasc Surg.* 1998;115:1328-34.
- Lyon WJ, Baker RA, Andrew MJ, Tirimacco R, White G, Knight J. Relationship between elevated preoperative troponin T and adverse outcomes following cardiac surgery. *ANZ J Surg.* 2003;73:40-4.
- Westaby S. Organ dysfunction after cardiopulmonary bypass: a systematic inflammatory reaction initiated by the extracorporeal circuit. *Intensive Care Med.* 1987;13:89-95.
- Mack M, Bachand D, Acuff T, Edgerton J, Prince Syma, Dewey T, et al. Improved outcomes in coronary artery bypass grafting with beating-heart techniques. *J Thorac Cardiovasc Surg.* 2002;124:598-607.
- Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg.* 1999;16:9-13.
- Lindahl B, Venge P, Wallentin L, for the FRISC study group. Troponin T identifies patients with unstable coronary artery disease who benefit from long-term antithrombotic protection. Frisc study group. *J Am Coll Cardiol.* 1997;29:43-8.
- Palma-Ruiz M, García de Dueñas L, Rodríguez-González A, Sarría-Santamera A. Análisis de la mortalidad intrahospitalaria de la cirugía de revascularización coronaria. *Rev Esp Cardiol.* 2003;56:687-94.
- Katus Ha, Remppis A, Scheffold T, Diederich KW, Kuebler W. Intracellular compartmentation of cardiac troponin T and its release kinetics in patients with reperfused and non reperfused myocardial infarction. *Am J Cardiol.* 1991;67:1360-7.
- Heeschen C, van den Brand MJ, Hamm CW, Simoons ML. Angiographic findings in patients with refractory unstable angina according to troponin T status. *Circulation.* 1999;100:1509-14.
- Gaudino M, Nasso G, Andreotti F, Minniti G, Iacoviello L, Donatti MB, et al. Preoperative C-reactive protein and outcome following coronary surgery. *Eur J Cardiothorac Surg.* 2002;22:521-6.
- Milazzo D, Biasucci LM, Luciani N, Martinelli L, Canosa C, Schiavello R, et al. Elevated levels of C-reactive protein before coronary artery bypass grafting predict recurrence of ischemic events. *Am J Cardiol.* 1999;84:459-61.
- Biancari F, Lahtinen J, Lepojärvi S, Rainio P, Salmela S, Pokela R, et al. Preoperative C-reactive protein level and outcome after coronary bypass surgery. *Ann Thorac Surg.* 2003;76:2007-12.