

Coronary Artery Bypass Graft Surgery with Double Internal Mammary Artery: Effect on Long-Term Survival

Cirugía coronaria con doble arteria mamarias interna: efecto en sobrevida a largo plazo

DANIEL O. NAVIA^{MTSAC, 1}, MARIANO VRANCIC^{MTSAC, 1}, FERNANDO PICCININI^{MTSAC, 1}, MARIANO CAMPOROTONDO^{†, 1}, JUAN ESPINOZA^{†, 1}, MARIANO BENZADÓN², JUAN CAMOU¹, ALBERTO DORSA³

ABSTRACT

Background: Utilization of the left internal mammary artery (IMA) in coronary artery bypass graft surgery (CABG) is associated with long-term survival free from late cardiac events; moreover, use of the right IMA as a complement of the left artery has shown favorable results. However, it is not yet clear whether double IMA revascularization is a better long-term option.

Objective: The aim of this work was to analyze long-term survival of patients with multi-vessel disease undergoing double IMA (2IMA) compared with single IMA (1IMA) CABG.

Methods: Consecutive 2IMA (n=2,098) and 1IMA (n=1,659) CABG surgeries performed between 1996 and 2014 were reviewed, comparing overall long-term survival between groups and between 485 pairs of patients matched by propensity score. Cox proportional hazard models were generated.

Results: Patients with 2IMA CABG were younger (2IMA: 63.7±9.1 years vs. 1IMA: 65.0±9.9 years; p<0.0001). Overall in-hospital mortality was lower in the 2IMA group (2IMA: 1.2% vs. 1IMA: 4.4%; p<0.0001). At 10 years, unadjusted survival was higher in the 2IMA group (2IMA: 82.6%±1.8% vs. 1IMA: 76.1%±1.3%; p=0.001). Overall Cox logistic regression analysis showed higher survival in patients with 2IMA CABG (HR 0.71, 95% CI 0.58-0.87; p<0.001). In the propensity score adjusted analysis, in-hospital mortality was similar in both groups (2IMA: 1.6% vs. 1IMA: 2.9%; p=0.196), but the 2IMA group still had higher long-term survival at 10 years (2IMA: 81.0%±4.1% vs. 1IMA: 71.8%±2.5%; p=0.039).

Conclusion: Patients with 2IMA CABG evidenced better long-term survival than patients with 1IMA plus another type of conduit.

Key words: Myocardial Revascularization - Coronary Artery Bypass, Off-Pump - Internal Mammary - Coronary Artery Anastomosis Follow-Up Studies

RESUMEN

Introducción: El uso de la arteria mamaria interna (AMI) izquierda en la cirugía de revascularización miocárdica (CRM) se asocia con mejor sobrevida alejada libre de eventos cardíacos tardíos; asimismo, el empleo de la AMI derecha como complemento de la izquierda ha mostrado resultados favorables. Sin embargo, aún no queda claro si la revascularización con doble AMI es una mejor opción para los pacientes a largo plazo.

Objetivo: Analizar la sobrevida a largo plazo de pacientes con CRM con doble arteria mamaria interna (2AMI) en comparación con pacientes con una AMI (1AMI) en la enfermedad de múltiples vasos.

Material y métodos: Se revisaron CRM consecutivas realizadas entre 1996 y 2014 de pacientes con 2AMI (n = 2.098) y con 1AMI (n = 1.659). Se comparó la sobrevida a largo plazo entre los grupos en forma global y entre 485 pares de pacientes ajustados por un puntaje de riesgo. Se generaron modelos de riesgos proporcionales de Cox.

Resultados: Los pacientes con 2AMI eran más jóvenes (63,7 ± 9,1 años 2AMI vs. 65,0 ± 9,9 años 1AMI; p < 0,0001). La mortalidad hospitalaria global fue menor en el grupo 2AMI (1,2% 2AMI vs. 4,4% 1AMI; p < 0,0001). A los 10 años, la sobrevida no ajustada fue superior en el grupo 2AMI (82,6% ± 1,8% 2AMI vs. 76,1% ± 1,3% 1AMI; p = 0,001). El análisis de regresión logística de Cox en el grupo global demostró mayor sobrevida en los pacientes con 2AMI (HR 0,71, IC 95% 0,58-0,87; p < 0,001). En el análisis ajustado por puntaje de riesgo, la mortalidad hospitalaria fue similar en ambos grupos (1,6% 2AMI vs. 2,9% 1AMI; p = 0,196). La sobrevida alejada a los 10 años fue significativamente superior en el grupo de pacientes con 2AMI que en el grupo con 1AMI (81,0% ± 4,1% vs. 71,8% ± 2,5%, respectivamente; p = 0,039).

Conclusión: Los pacientes con CRM y 2AMI presentaron mejor sobrevida alejada que los pacientes con 1AMI más otro tipo de conducto.

Palabras clave: Revascularización miocárdica - Puente de arteria coronaria off-pump- Anastomosis interna mamario-coronaria - Estudios de seguimiento

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Address for reprints: Dr. Daniel Navia - Blanco Encalada 1543 - (C1428DCO) CABA, Argentina - e-mail: donavia@icba.com.ar

Instituto Cardiovascular de Buenos Aires (ICBA). Buenos Aires, Argentina

^{MTSAC} Full Member of the Argentine Society of Cardiology

[†] To apply as Full Member of the Argentine Society of Cardiology

¹ Department of Cardiovascular Surgery

² Cardiovascular Recovery Unit

³ Division of Anesthesiology

Abbreviations

1IMA	Single internal mammary artery	LIMA	Left internal mammary artery
2IMA	Double internal mammary artery	PDA	Posterior descending artery
AMI	Acute myocardial infarction	PTCA	Percutaneous transluminal coronary angioplasty
CABG	Coronary artery bypass graft surgery	RA	Radial artery
CX	Circumflex artery	RCA	Right coronary artery
ECC	Extracorporeal circulation	RIMA	Right internal mammary artery
IQR	Interquartile range	VB	Venous bridge
LAD	Left anterior descending artery		

INTRODUCTION

Use of the left internal mammary artery (LIMA) to revascularize the left anterior descending artery (LAD) in coronary artery bypass graft surgery (CABG) is better associated with long-term survival free from late cardiac events than venous bridges (VB). (1) The right internal mammary artery (RIMA) has been used to supplement the LIMA with favorable outcomes. (2, 3) Observational cohort studies showed higher survival after revascularization with both IMA (2IMA), compared with the use of single IMA (1IMA). (4) However, it is not yet clear whether revascularization with 2IMA is a better long-term option, as the only randomized, controlled trial evaluating long-term survival (Arterial Revascularization Trial) is still ongoing. (5) Tector et al. promoted CABG using exclusively 2IMA in a T-shaped arrangement in 897 patients, with favorable outcomes after 8.5-year follow-up. (6, 7) The purpose of this retrospective study is to evaluate long-term CABG survival using exclusively 2IMA compared with 1IMA plus other types of conduits: VB with saphenous vein and/or radial artery (RA).

METHODS

A retrospective analysis was performed of prospectively obtained data from all patients undergoing CABG at the Instituto Cardiovascular de Buenos Aires during 18 years.

The set of patients represents all the myocardial revascularization experience of our Department of Cardiovascular Surgery, and includes a historical account of the different surgical techniques used over time. From November 1996 to May 2014, 3,757 patients undergoing urgent or elective CABG fulfilled the inclusion criteria. Patients were included since November 1996 when the database was implemented at our institution.

Coronary artery bypass graft surgery was exclusively performed with 2IMA on 2,098 patients (55.8%) and with 1IMA plus other types of conduit (VB and/or RA) in 1,659 (44.2%). These two groups of patients represent the study core. Data were prospectively obtained for all patients from our personalized database (Microsoft Access, Microsoft Corp, Redmond, WA) which is used on a daily basis to manage clinical data. Preoperative, intraoperative and postoperative data were acquired by retrospective review of clinical and surgical reports and from all clinical records.

Patients with two- or three-vessel disease who received at least one in situ IMA bridge were included in the analysis. In all cases complete arterial revascularization was attempted, defined as the insertion of at least one bridge (arterial or venous) in all coronary arteries with >70% stenosis. This relationship (arterial bridge/lesion >70%) was evaluated

for all coronary arteries: (LAD), circumflex artery (CX) and right coronary artery (RCA) in all patients.

Endpoint analysis

In-hospital mortality, deep sternal infection (mediastinitis), postoperative acute myocardial infarction (AMI), postoperative stroke, reoperation for bleeding and renal failure requiring dialysis was assessed. A multivariate analysis was performed to identify independent predictors of in-hospital mortality.

Long-term follow-up was performed to analyze survival and presence of events through direct communication with the patient, his family and the family doctor. In addition, clinical records were reviewed. Survival, presence of symptoms, long-term medical treatment, incidence of new AMI and need for percutaneous transluminal coronary angioplasty (PTCA) were explored

Surgical technique

The indication of myocardial revascularization was based on standard clinical and angiographic criteria. All surgical procedures were performed by medial sternotomy. Internal mammary arteries were dissected as a pedicled flap using electrocautery, or more frequently, as a skeletonized conduit since 2003. The RA was harvested through a single incision in the left forearm, using electrocautery. Until 2001, most surgeries were performed with extracorporeal circulation (ECC) and intermittent antegrade or retrograde blood cardioplegia (28°C-32°C) to preserve the myocardium. Off-pump CABG started in 2002 with the availability of coronary stabilizing devices, and is currently the procedure of choice in our setting in more than 95% of cases. The surgical technique used for the 2IMA group has been previously described (8) and consists in the use of both the left and right IMA as exclusive conduits for coronary artery revascularization. The most frequent technical configuration was that of in situ LIMA with anastomosis to the LAD. The RIMA is dissected from its origin and a termino-lateral T-shaped anastomosis with the LIMA is performed; then, this is used to sequentially revascularize the CX and distal RCA (Figure 1). In the 1IMA group patients, the LIMA was used almost exclusively as graft to the LAD, while VB and/or the RA were used in the other coronary arteries. The RA was used to sequentially revascularize the CX and distal RCA territories. The RA was used as free graft combined with T-shaped anastomosis from the LIMA or as free graft from the aorta. Venous bridges were used more frequently to revascularize the RCA. In the 2IMA group, the LIMA anastomosis to the LAD was performed in 2,090 patients (98.8%) and in 198 patients (9.5%) sequential anastomosis was performed to the diagonal artery bed. The right internal mammary artery was used as T-shaped graft from the LIMA in 2,023 patients (96.4%) and in the remaining patients it was used in situ and as free graft. The RIMA

was used in 2,098 patients as part of a 2IMA revascularization strategy. A total of 4,271 anastomoses were performed, including those done sequentially, most of them to the CX (94.4%) and distal RCA (60.4%). The anastomosis quality was assessed through measurement and Doppler flow velocity (MedistimVeriQ™ system).

Statistical analysis

Preoperative characteristics of study patients were expressed as mean \pm SD, median and interquartile range (IQR), or as prevalence (in percentage), as appropriate. Differences between groups were analyzed using Student's *t* test for independent samples or the U Mann-Whitney test for continuous variables, and the chi-square test for categorical variables.

A propensity score to receive revascularization with 2AMI was calculated for each patient using a logistic regression model that included all the preoperative variables detailed in Table 1. Patients were matched by propensity score on 1:1 basis using greedy nearest neighbor matching without replacement with caliper of 0.0001. Results of interest between matched groups were compared using the *t* test for paired data for continuous variables and the McNemar test for categorical variables.

Event-free survival curves were built using the Kaplan-Meier method, with the log-rank test to analyze survival differences between both groups.

Univariate and multivariate analyses with Cox proportional risk test were used to identify significant late mor-

tality predictors. Clinical variables included in Table 1 were used for the univariate analysis. Variables which in the univariate analysis had $p < 0.2$ were included in the multivariate analysis.

Ethical considerations

The Institutional Ethics Committee approved the study and an informed consent concerning the surgical method and postoperative evaluations was obtained from each patient.

RESULTS

Preoperative clinical characteristics of the study population are shown in Table 1. Patients of the 2IMA group were younger (2IMA: 63.7 ± 9.1 vs. 1IMA: 65.0 ± 9.9 ; $p < 0.001$) and had greater prevalence of left ventricular dysfunction, hypertension, hypercholesterolemia, smoking habits, family history of ischemic heart disease and left main coronary artery lesion.

Off-pump surgery was less frequent in the 1IMA group ($p < 0.0001$). Table 1 shows postoperative results. Unadjusted in-hospital mortality was lower in the 2IMA group (1.2% vs. 4.4%; $p < 0.0001$). Multiple logistic regression analysis identified age (OR 1.08, 95% CI 1.05-1.11, $p < 0.0001$) and on-pump surgery (OR 2.43, 95% CI 1.47-4.01, $p < 0.001$) as predictors of in-hospital mortality. Elective surgery had a protective effect on in-hospital mortality (OR 0.42, 95% CI 0.26-0.68 $p < 0.001$).

Complete follow-up was achieved in 95% of patients who survived and were discharged ($n = 3,658$): 1,963 (94.7%) in the 2IMA group and 1,513 (95.4%) in the 1IMA group. Median follow-up was 2,016 days (IQR: 935-3,223 days) for all patients. In the 2IMA group, median follow-up was 1,464 days (IQR: 691-2,437 days). For the 1IMA group, median follow-up was 3,096 days (IQR: 1,455-4,337 days) ($p < 0.001$). There were no differences in the proportion of patients who completed follow-up: 94.7% vs. 95.4% ($p = 0.365$). Long-term mortality during follow-up was 11.1% ($n = 405$). Long-term survival at 5 and 10 years for the overall patient population was: $92.4\% \pm 0.7\%$ and $82.6\% \pm 1.8\%$, respectively, in the 2IMA group and $89.1\% \pm 0.8\%$ and $76.1\% \pm 1.3\%$, respectively, in the 1IMA group (log rank: $p = 0.001$), HR 0.71, 95% CI 0.581-0.869, $p < 0.001$ for the 2IMA group (Figure 2). In general, long-term survival was significantly better in the 2IMA than in the 1IMA group. Patients in the 2IMA group presented with higher postoperative period free from the need of PTCA than patients in the 1IMA group, [94 ± 0.5 vs. 90 ± 0.7 , $p < 0.001$ (HR 0.574, 95% CI 0.44-0.744)]. The characteristics of propensity score-matched patients are shown in Table 2. In-hospital mortality was 1.6% in the 2IMA group and 2.9% in the 1IMA group ($p = 0.19$). Overall, 139 deaths (14.3%) were recorded in the long-term follow-up: 38 patients (7.8%) with 2IMA and 101 (20.8%) with 1IMA ($p < 0.001$). Long-term survival at 5 and 10 years for the propensity score-matched group was $92.1\% \pm 1.5\%$ and $81.0\% \pm 4.1\%$, respectively, in the 2IMA group and

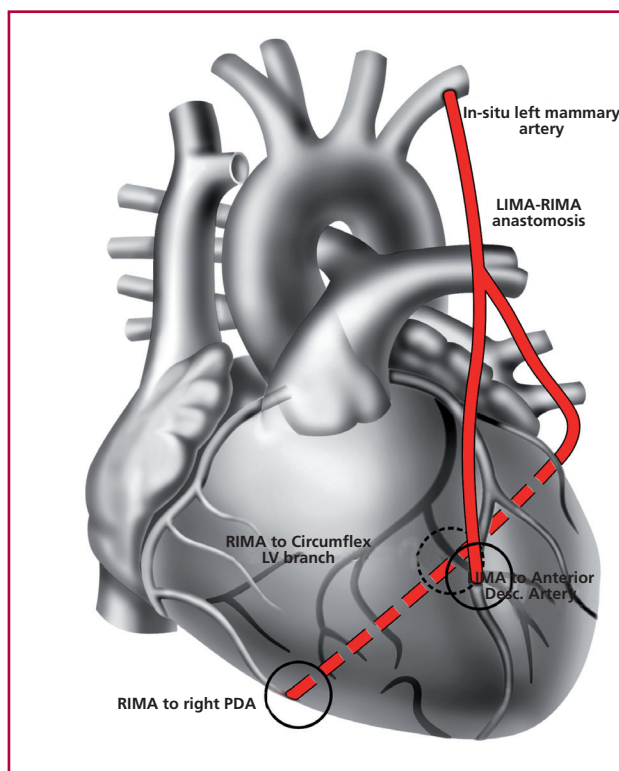


Fig. 1. Surgical technique used in patients with double internal mammary artery: the left internal mammary artery (LIMA) is anastomosed to the anterior descending artery. The right internal mammary artery (RIMA) is anastomosed to LIMA in a T-shaped arrangement. Then RIMA is used to sequentially revascularize the circumflex and distal right coronary arteries. PDA: Posterior descending artery. LV: Lateral ventricular

Unadjusted risk	2IMA (n=2,098)	1IMA (n=1,659)	p
Age (years±SD)	63.7 ± 9.1	65 ± 9.9	0.000
	n (%)	n (%)	
Female gender	205 (9.8)	261(15)	0.000
Diabetes	544 (25.9)	434 (26)	0.873
Hypertension	1,605 (76.5)	1,157 (69)	0.000
Dyslipidemia	1,668 (79.5%)	1,085 (65)	0.000
Smoking	1,363(65)	868(52)	0.000
Family history	592 (28.2%)	153 (9)	0.000
Elective surgery	1,385 (66)	1,064 (64)	0.230
On-pump surgery	8 (0,4)	1,014 (61)	0.000
LV dysfunction (moderate/severe)	313 (15)	126 (8)	0.000
Main LCA disease	472 (22)	325 (19)	0.030
Three-vessel disease (%)	1,721 (82)	1,293(77,9)	0.002
Reoperation	13 (0,6)	103 (6,2)	0.000
Prior AMI	605 (28)	490 (29)	0.640
Prior angioplasty	444 (21)	306 (18)	0.038
Peripheral artery disease	62 (3)	83 (5)	0.001
Carotid disease	102 (4.9)	48 (2.9)	0.002
Abdominal aortic aneurysm	20 (1)	21 (1.3)	0.360
COPD	88 (4.2)	72 (4.3)	0.826
Cerebrovascular disease	80 (3.8)	50 (3)	0.183
Prior renal failure	88(4.2)	49 (3)	0.130
In-hospital results	2IMA (n=2,098)	1IMA (n=1,659)	p
In-hospital mortality, %	1.2	4.4	0.000
Mediastinitis, %	1.9	1.6	0.521
Postoperative AMI, %	1.0	3.2	0.000
Postoperative stroke, %	0.5	0.7	0.325
Reoperation for bleeding, %	2.1	2.4	0.586
Renal failure with dialysis, %	0.7	1.3	0.06

2IMA: Double internal mammary artery. 1IMA: Single internal mammary artery. SD: Standard deviation. LV: Left ventricular. LCA: Left coronary artery. AMI: Acute myocardial infarction. COPD: Chronic obstructive pulmonary disease.

Table 1. Preoperative clinical profile and immediate post-operative results in the unadjusted group of patients

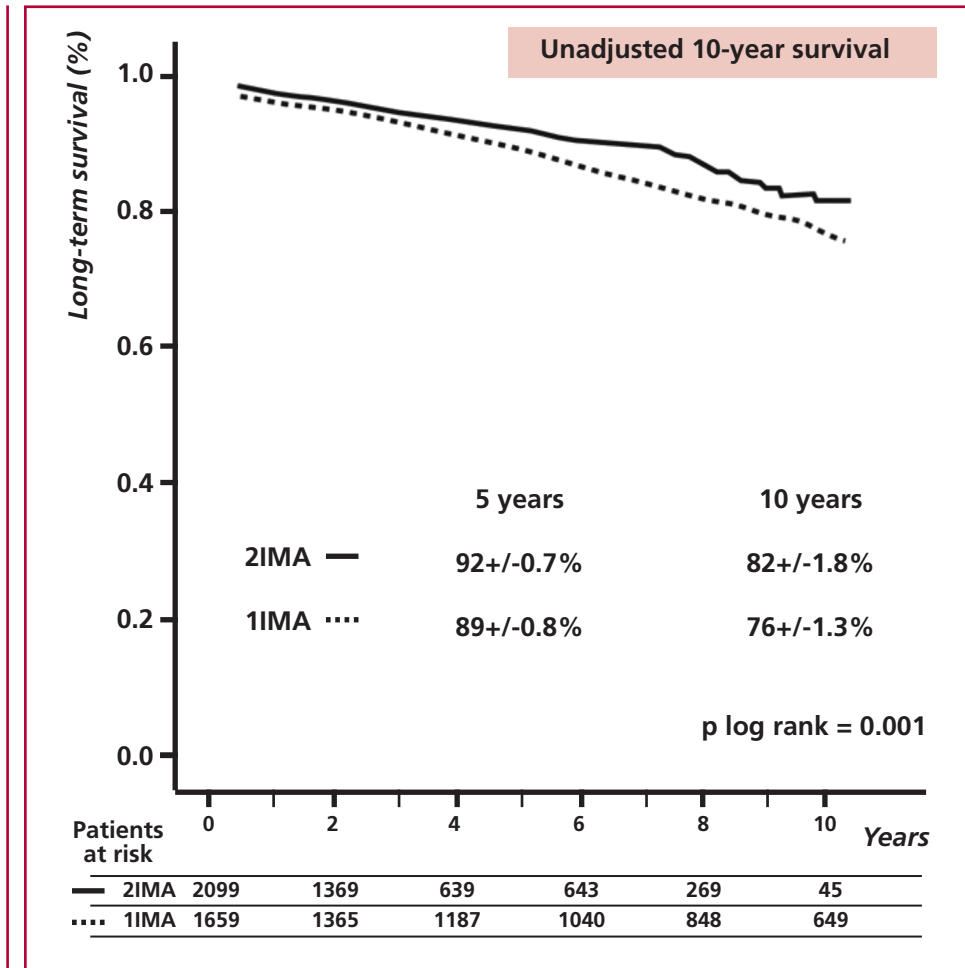
87.9%±1.6% and 71.8%±2.5%, respectively, in the 1IMA group (log-rank: p=0.039) (Figure 3). In general, long-term results for the propensity score-matched population were significantly better in the 2IMA than in the 1IMA group.

DISCUSSION

In this study, patients with CABG in whom 2IMA was exclusively used presented with higher long-term survival than patients with 1IMA plus another type of conduit. This result was observed both for the overall group as for patients selected by propensity score. Coronary artery bypass graft surgery with 2IMA has been associated with better long-term survival and

absence of late cardiac events. In a meta-analysis including 15,962 patients (11,269 using 1IMA and 4,693 with 2IMA), Taggart et al. (9) found that patients with 2IMA had significantly longer survival than patients with 1IMA (HR 0.81, 95% CI 0.70-0.94). Similar results were reported by Weiss et al. in another recent meta-analysis. (10) Off-pump CABG was performed in 95% of patients with 2IMA with lower overall in-hospital mortality than the 1IMA group. Although off-pump CABG exclusively with 2IMA is technically more demanding, this strategy is more beneficial for patients: 88% of patients were extubated in the operating room, (11) elimination of aortic clamping in CABG is a predictor of lower postoperative stroke incidence,

Fig. 2. Unadjusted 10-year survival. 2IMA: Double internal mammary arteries. 1IMA: Single internal mammary artery.



(12) it is not necessary to perform surgical incisions in the arms and lower limbs, which are a major source of postoperative discomfort and lastly, a lower inflammatory postoperative response allows shorter in-hospital stay. Greater incidence of mediastinitis (MED) has discouraged the use of 2IMA in the general population, especially in diabetic patients. The present study showed no difference in mediastinitis between both groups. It has been suggested that the skeletonized IMA harvesting method and strict glycemic control during the whole procedure influence the incidence of this complication. (13) Ten-year survival, both for the overall group as for patients grouped by propensity score, was higher in patients receiving 2IMA than in the 1IMA group. Paterson et al. have also reported excellent long-term results using off-pump CABG with 2IMA. (14) Long-term survival following CABG is usually associated with the permeability of the conduits used. It is known that IMA is more resistant to atherosclerosis due to the ability of its endothelium to produce nitric oxide. Another advantage is its reduced diameter, with lower discordance with coronary artery diameter, facilitating the coronary artery revascularization technique. (15, 16) Buxton et al. demonstrate

better long-term survival in a series of patients with multiple RA bridges compared with VB. (17) However, there is evidence showing the superiority of RIMA over RA as second conduit for CABG with multiple arterial bridges. (18)

The effect of arterial conduits on the native circulation may explain their superiority compared with VB. Venous grafts provide higher than physiological flow, which might elicit turbulence leading to the progression of the atherosclerotic disease. (19) Use of 2IMA as T-shaped grafts from LIMA allows multiple sequential anastomoses on the lateral and inferior wall using the best available arterial conduit (Figure 1). (20) With this surgical strategy, total coronary flow depends on RIMA anastomosis with the proximal LIMA, which led to contemplate whether LIMA flow reserve was sufficient to maintain flow in more than one coronary anastomosis. Several reports have concluded that 2IMA T-shaped grafts allow complete coronary artery revascularization with an adequate coronary flow reserve from the proximal LIMA. (21) Regarding T-grafting and risk of competitive flow, Glineur et al. showed that both grafted branches have similar resistance, excluding the possibility of steal

Data of patients matched by propensity score	2AMI n=485	1AMI n=485	p
Age (years±SD)	65.4 (8.9)	65.5 (9.5)	0.948
[n (%)]	66 (13)	67 (14)	0.926
	n (%)	n (%)	
Diabetes	131 (27)	141(29)	0.475
Hypertension	369 (76)	370 (76)	0.940
Dyslipidemia	355 (73)	347(71)	0.566
Current or ex-smoker	291(60)	280 (57)	0.473
Family history	122 (25)	115 (23)	0.601
Elective surgery	301 (62)	303(62)	0.895
On-pump surgery	8 (1.6)	8 (1.6)	1.000
LV dysfunction (moderate/severe)	74 (15)	76 (15.7)	0.859
Main LCA disease	102 (21)	101(20.8)	0.937
Three-vessel disease (%)	389 (80.2)	395 (81.4)	0.625
Reoperation	2(0.4)	2 (0.4)	1.000
Prior AMI	126 (26)	125(25.8)	0.942
Prior angioplasty	82 (16.5)	85 (17.5)	0.799
Peripheral artery disease	22(4.5)	11(2.3)	0.051
Carotid disease	13 (2.7)	15 (3.1)	0.701
Abdominal aortic aneurysm	6 (1.2)	5 (1.0)	0.762
COPD	23 (4.7)	22 (4.5)	0.879
Cerebrovascular disease	11(2.3)	15 (3.1)	0.427
Prior renal failure	17(3.5)	23(4.7)	0.382
Adjusted data	2AMI	1AMI	p
Immediate results	(n=485)	(n=485)	
In-hospital mortality, %	1.6	2.9	0.196
Mediastinitis, %	2.3	1.4	0.341
Postoperative AMI, %	1.4	1.9	0.614
Postoperative stroke, %	0.6	1.0	0.478
Reoperation for bleeding, %	2.9	1.6	0.196
Renal failure requiring dialysis, %	0.8	0.8	1.000

2IMA: Double internal mammary artery. 1IMA: Single internal mammary artery. SD: Standard deviation. LV: Left ventricular. LCA: Left coronary artery. AMI: Acute myocardial infarction. COPD: Chronic obstructive pulmonary disease.

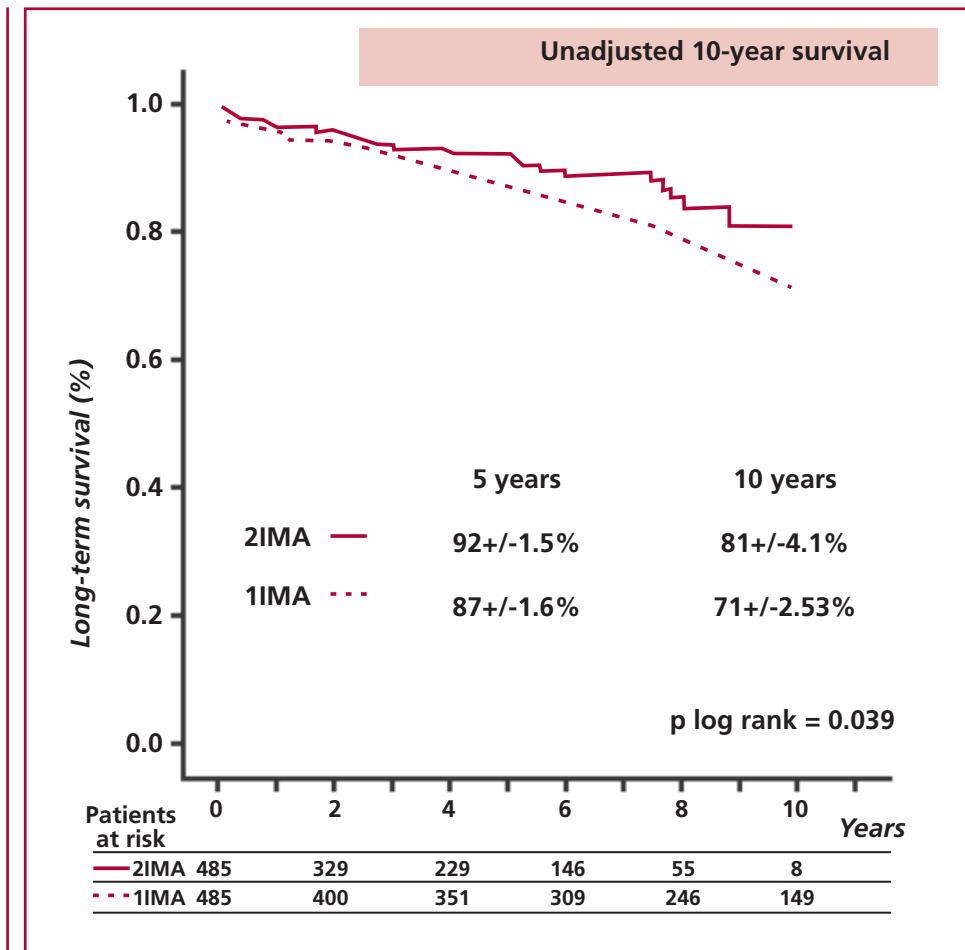
Table 2. Preoperative clinical profile and immediate post-operative results in the group of patients matched by propensity score

from one branch to the other during the periods of high myocardial blood flow demand. However, the greater the number of sequential anastomoses the lower the distal anastomosis perfusion pressure. (22, 23) In our series of postoperative angiographies, the rate of distal graft permeability to the RCA/PDA) was 91%, and only 8 patients presented competitive flow in the anastomosis from the RIMA to the RCA/PDA. In these patients, the opacification of native coronary arteries through retrograde flow evidenced perfect RIMA graft permeability, with optimal diameter. This scenario was more frequent in the case of dominant RCA. Nevertheless, these angiographic anomalies did not have postoperative consequences in our group of patients. (8)

Limitations

The limitations of the study were: a) the retrospective nature of the study which, despite the propensity score selection of a group of patients, was not a randomized study and hence, interaction with other covariates cannot be discarded, and b) the extension of the study over a long CABG period, where most patients received 1IMA (60%) with on-pump surgery in the initial stage of our experience, whereas the off-pump CABG technique was implemented since 2002. This could have been a factor influencing the final results in the unadjusted overall group. However, in the adjusted selection of comparable patients by propensity score, the potential ECC effect on early and long-term mortality was counterbalanced when a majority of off-

Fig. 3. Adjusted 10-year survival in the 485 pairs of patients matched by propensity score. 2IMA: Double internal mammary arteries. 1IMA: Single internal mammary artery.



pump patients was included in both groups.

CONCLUSION

In this study, the exclusive use of 2IMA in CABG is a safe technique, with low in-hospital morbidity and mortality, and can be associated with improved long-term survival compared with 1IMA revascularization plus other types of conduits.

Conflicts of interest

None declared
(See author’s conflicts of interest forms in the web / Supplementary Material)

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