Original Article

Is There a Protective Effect of Sequential Grafting in Coronary Bypass Surgery Using Bilateral Internal Thoracic Artery?

*Adel Alshamri[1], Margaux PO Jegaden[2], Salah Ashafy[3], FadiFarhat[4,5], Armand Eker[6] and Olivier JL Jegaden[5,7,8]** ID

[1]*Department of Cardiac Surgery and ICU, Saudi German Hospital, UAE*

[2]*Department of Surgery, APHP, Hopital Bicetre, France*

[3]*Department of Cardiac Surgery, Zayed Military Hospital, UAE*

[4]*Department of Cardiac Surgery, HCL, France*

[5]*UCLB University Lyon1, France*

[6]*Centre Cardio-Thoracic, Monaco, Monaco*

[7]*Department of Cardiac Surgery, Mediclinic Middle East, UAE*

[8]*MBRU University, UAE*

Abstract

Objectives: It is unclear whether the additional bypass techniques to supplement bilateral internal artery grafting (BITA) influence the patient outcome in coronary surgery. We analyzed the impact of sequential ITA grafts on late survival after BITA used on the left side.

Methods: From 1989 to 2014, 1644 patients underwent BITA surgery without any additional arterial graft. The revascularization of the left side was optimized with a sequential ITA graft in 824 patients. The revascularization of the right side was performed with an associated vein graft in 599 patients. Propensity score was calculated by logistic regression model and patients were matched 1 to 1 leading to two groups of 334 matched patients. The primary end point was overall mortality from any cause.

Results: The population was not homogenous: Greater the arterial revascularization, lower the risk profile. The 30-day mortality was 1.2% without influence of the surgical technique performed. The mean postoperative follow-up was 12.4 ± 6.7 years and 95% complete. Late mortality was significantly influenced by age, heart failure, 3-vessel disease, LV ejection fraction, number of arterial anastomoses and sequential ITA. The significant difference in patients' survival observed at 20-years in favour of sequential ITA in unmatched groups was confirmed in matched groups. In multivariable Cox model analysis, the use of sequential ITA remained predictor of long-term survival in matched groups.

Conclusions: These results confirm that higher the number of ITA anastomoses, better the long-term survival. It is a strong support of the extensive use of arterial grafting with multiple ITA bypass.

Keywords

Coronary disease, Arterial revascularization, Internal thoracic artery, Sequential graft

Introduction

Long-term advantages of multiple arterial grafting in patients undergoing coronary artery bypass surgery (CABG) has been controversial for decades despite mounting of evidence supporting the use of this technique for myocardial revascularization [1-3]. Nowadays, there is a consensus to use bilateral internal thoracic artery (BITA) to bypass the left coronary network [4] and ESC/EACTS 2018 guidelines on myocardial revascularization recommend the use of BITA grafting in patients who do not have a high risk of sternal wound infection [5]. However, the benefits of total arterial revascularization and the associated techniques to supplement BITA have remained controversial [6,7]. In this retrospective study based on our 25-year experience in arterial grafting, we have analyzed the long-term survival after *in situ* BITA grafting without additional arterial graft to test the hypothetic impact of the sequential ITAs on the

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left side, used to perform an extensive arterial myocardial revascularization.

Materials and Methods

All patients who underwent isolated CABG procedure using BITA in our department performed by the same surgeon from January 1989 to August 2014 were selected in the study. The inclusion criteria were BITA on the left side regardless if sequential ITA was used, associated or not with a vein graft on the right side. Exclusion criteria were emergency, reoperation, associated procedure, unstable situation and additional arterial graft. We retrospectively analyzed prospectively collected data from the surgical registry of the department approved by the local ethical committee and receiving individual patient consent.

Surgical technique

Our surgical techniques in CABG were previously reported in studies focused on early postoperative outcome [8]. As arterial grafting is technically more demanding, particularly in patients with left ventricular (LV) dysfunction or obesity, the main concern was no increase in mortality or morbidity. Diabetes status or severe dyslipidemia were never a limitation. CABG was done on-pump with ante grade and retrograde crystalloid cardioplegia. Patients received both left and right internal thoracic artery (LITA and RITA) to the most important coronary arteries on the left side: RITA crossing in front the aorta to the left anterior descending artery (LAD) and LITA to the circumflex artery (CX) system; sequential ITA grafts were performed according to the coronary lesions and the technical possibilities: Mainly sequential LITA to diagonal and marginal branches. A supplemental vein graft was used to bypass the right coronary artery (RCA) system, as needed. All ITA grafts were used as *in situ* grafts preferentially with thin pedicle; skeletonization was not systematic and done to increase the length of the graft when necessary; composite ITA grafts were exceptionally used. Complete myocardial revascularization was defined as bypass of all significant lesions defined as more than 70% stenosis. All patients received aspirin antiplatelet therapy postoperatively. Postoperative statin and beta-blockers became common practice over the years.

Definitions and end point

Early mortality was defined as any death within 30 days of CABG. Late death was defined as death occurring after 30 days from surgery. All causes mortality was used to assess long-term outcome. The last survival status of the patients was obtained in 2019 from the National institute of statistics and economic studies (INSEE) and a genealogy agency in case of lack of information; the common closing date for follow-up was December 1, 2019. The primary end point was overall mortality from any cause and was analyzed according to the potential risk factors and the surgical configuration.

Statistical analysis

Descriptive statistics for categorical variables are reported as number and percentage; continuous variables are reported as mean ± standard deviation. Continuous variables were compared using Student' t-test and ANOVA; categorical variables were compared using χ^2 or Fisher's exact test. Overall survival was estimated using the Kaplan-Meier method and reported as percentage (95% confidence interval). The stratified log rank test was applied to compare the equality of the survival curves; actuarial survival was reported on tables and curves. Univariable analyses of predictors of all-cause death were done with binary logistic regression. Propensity-score matching was performed to correct for the bias associated with the use of sequential ITA graft. A propensity score for each patient was calculated by logistic regression model with sequential ITA graft as the dependent variable and age, gender, NYHA status, left main stenosis, diabetes, left ventricular ejection fraction (LVEF), complete revascularization, an associated vein on the RCA system, the operative times (clamp time and cardiopulmonary time) and the year of surgery as independent variables. Patients were matched 1 to 1 on their propensity score using the greedy matching method without replacement and a fixed caliper width of 0.005. All potentially important variables were first individually tested by a log-rank test of the corresponding Kaplan-Meir survival curves and then they were included in a multivariable Cox regression analysis to identify independent predictors of survival in matched groups. Statistical analyses were based on variables documented and complete in all patients. A 2-tailed P value < 0.05 was always considered to indicate statistical significance. All statistical analyses were performed using IBM-SPSS Statistics software version 25.0 (IBM-SPSS Inv, Armonk, NY).

Results

Finally, 1644 patients were included in the study: 1045 patients had isolated BITA, 599 patients had BITA with an associated vein graft on the right side and a sequential ITA graft was performed in 824 patients (Figure 1).

In unmatched population, a sequential ITA graft was used significantly more in males, in patients with diabetes and in patients with a preserved left ventricular function. In sequential ITA group, number of distal anastomoses, number of arterial anastomoses, operative times were significantly higher, and a vein graft was less associated without difference in completeness of revascularization between both groups (Table 1). In this series, the early mortality was 1.2% and it was not significantly influenced by the surgical technique used, like postoperative complications rate (Table 2). The mean postoperative follow-up was 12.4 ± 6.7 years, and 95% complete: 805 late deaths occurred (mean delay 10.6

*Corresponding author: Olivier JEGADEN, Department of Cardiac Surgery, Mediclinic Airport Road Hospital, PO Box 48481, Abu Dhabi, UAE, Tel: +971554595891

Figure 1: CONSORT diagram of patients included in the study.

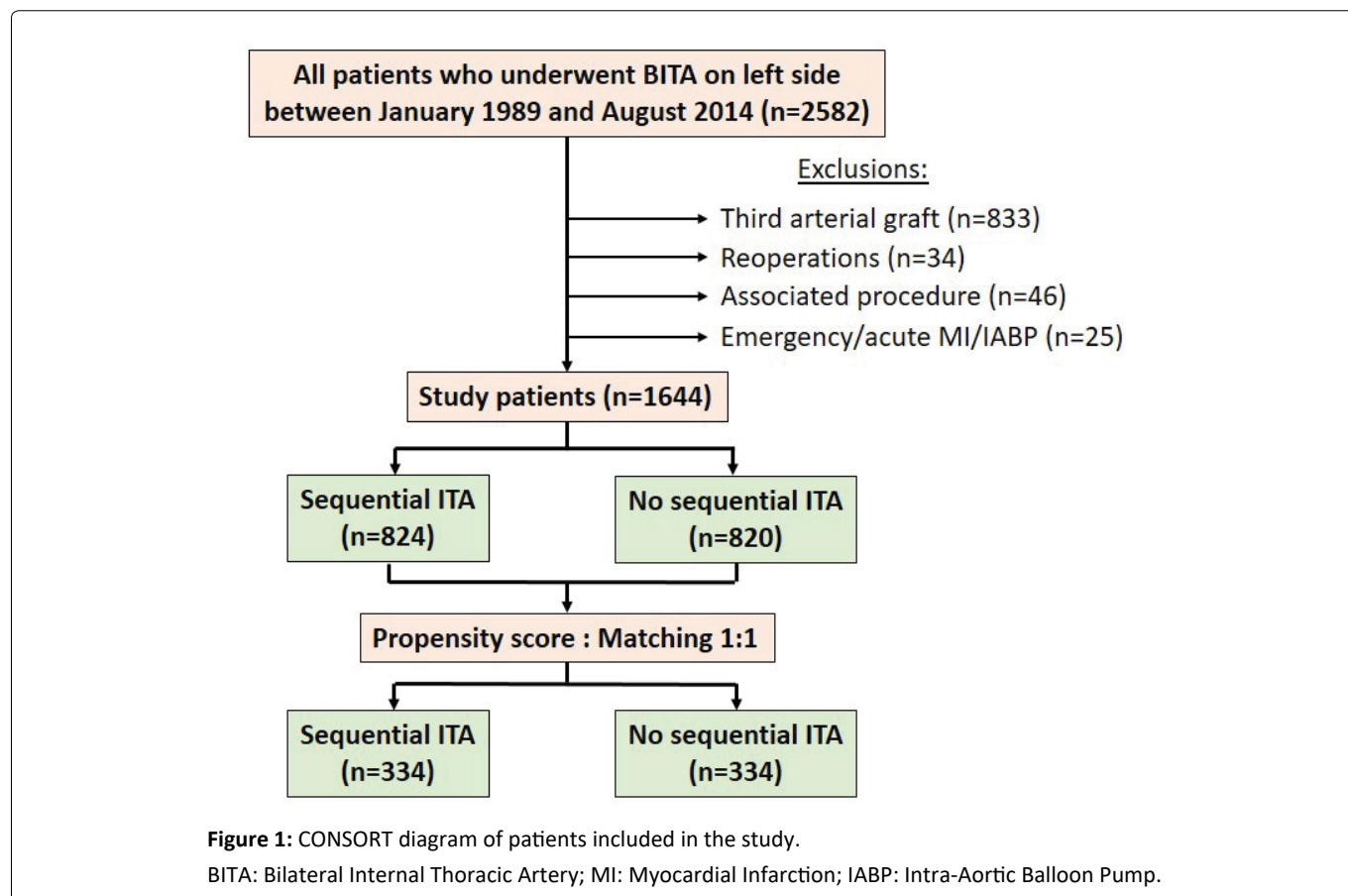BITA: Bilateral Internal Thoracic Artery; MI: Myocardial Infarction; IABP: Intra-Aortic Balloon Pump.

Table 1: Comparison of preoperative clinical variables and postoperative outcomes by groups of patients receiving bilateral internal thoracic artery.

	Unmatched groups				Matched groups			
	Sequential ITA				Sequential ITA			
	No	Yes			No	Yes		
Variable	N = 820	N = 824	SMD	P value	N = 334	N = 334	SMD	P value
Propensity score	0.35 ± 0.23	0.65 ± 0.21	-1.391	< 0.001	0.55 ± 0.21	0.55 ± 0.21	-0.004	0.996
Age-year	64 ± 9	64 ± 9	0.003	0.939	64 ± 10	64 ± 9	-0.032	0.682
Male gender	655 (80%)	706 (86%)	-0.132	0.005	285 (85%)	275 (82%)	0.081	0.293
Heart failure NYHA ≥ 2	85 (10%)	91 (11%)	-0.032	0.783	40 (12%)	40 (12%)	0	1
3-vessel disease	595 (73%)	606 (74%)	-0.023	0.653	245 (73%)	239 (72%)	0.022	0.603
Left main lesion	181 (22%)	165 (20%)	0.049	0.308	74 (22%)	74 (22%)	0	1
LV ejection fraction-%	59 ± 12	61 ± 12	-0.102	0.042	60 ± 12	60 ± 12	-0.028	0.722
Diabetes	88 (11%)	124 (15%)	-0.119	0.009	45 (13%)	47 (14%)	-0.029	0.822
Associated RCA vein graft	338 (41%)	261 (32%)	0.182	< 0.001	133 (40%)	120 (36%)	0.083	0.109
Distal Anastomoses	2.8 ± 0.6	3.4 ± 0.6	-1.632	< 0.001	2.5 ± 0.6	3.4 ± 0.5	-1.521	< 0.001
Arterial Anastomoses	2 ± 0	3.1 ± 0.4	-3.872	< 0.001	2 ± 0	3.1 ± 0.3	-3.93	< 0.001
Complete Revascularization	472 (58%)	485 (59%)	-0.02	0.594	207 (62%)	196 (59%)	0.061	0.384
Clamp Time-min.	44 ± 12	55 ± 12	-0.913	< 0.001	52 ± 12	51 ± 11	0.062	0.42
CPB time-min.	61 ± 17	70 ± 16	-0.584	< 0.001	69 ± 16	67 ± 15	0.087	0.257
1-month Mortality	14 (1.7%)	6 (0.7%)	0.092	0.07	8 (2.4%)	3 (0.9%)	0.118	0.135
Mean Follow-up-year	12.5 ± 6.8	12.4 ± 6.6	0.014	0.837	11.9 ± 6	12.4 ± 6	-0.083	0.09

ITA: Internal Thoracic Artery; SMD: Standardized Mean Difference; NYHA: New York Heart Association; LV: Left Ventricular; Min: Minutes; RCA: Right Coronary Artery; CPB: Cardiopulmonary Bypass

Table 2: Postoperative complications and early outcome by patients groups.

| Complications | Unmatched groups | | | Matched groups | | |
| | Sequential ITA | | | Sequential ITA | | |
| | YES | NO | | YES | NO | |
	N = 824	N = 820	p	N = 334	N = 334	p
Myocardial infarction	9 (1.1%)	12 (1.5%)	0.49	2 (0.6%)	6 (1.8%)	0.15
Ventricular arrhythmia	5 (0.6%)	2 (0.2%)	0.26	3 (0.9%)	1 (0.3%)	0.31
Reoperation bleeding	12 (1.5%)	8 (1%)	0.39	5 (1.5%)	4 (1.2%)	0.73
Low cardiac output	5 (0.6%)	9 (1.1%)	0.27	2 (0.6%)	3 (0.9%)	0.65
Stroke	2 (0.2%)	2 (0.2%)	0.98	0	1 (0.3%)	NA
Mediastinitis	7 (0.8%)	8 (1%)	0.79	2 (0.6%)	4 (1.2%)	0.41
All complications	40 (4.8%)	41 (5%)	0.89	14 (4.2%)	19 (5.7%)	0.37
Early mortality	6 (0.7%)	14 (1.7%)	0.07	3 (0.9%)	8 (2.4%)	0.13

ITA: Internal Thoracic Artery; P: P Value
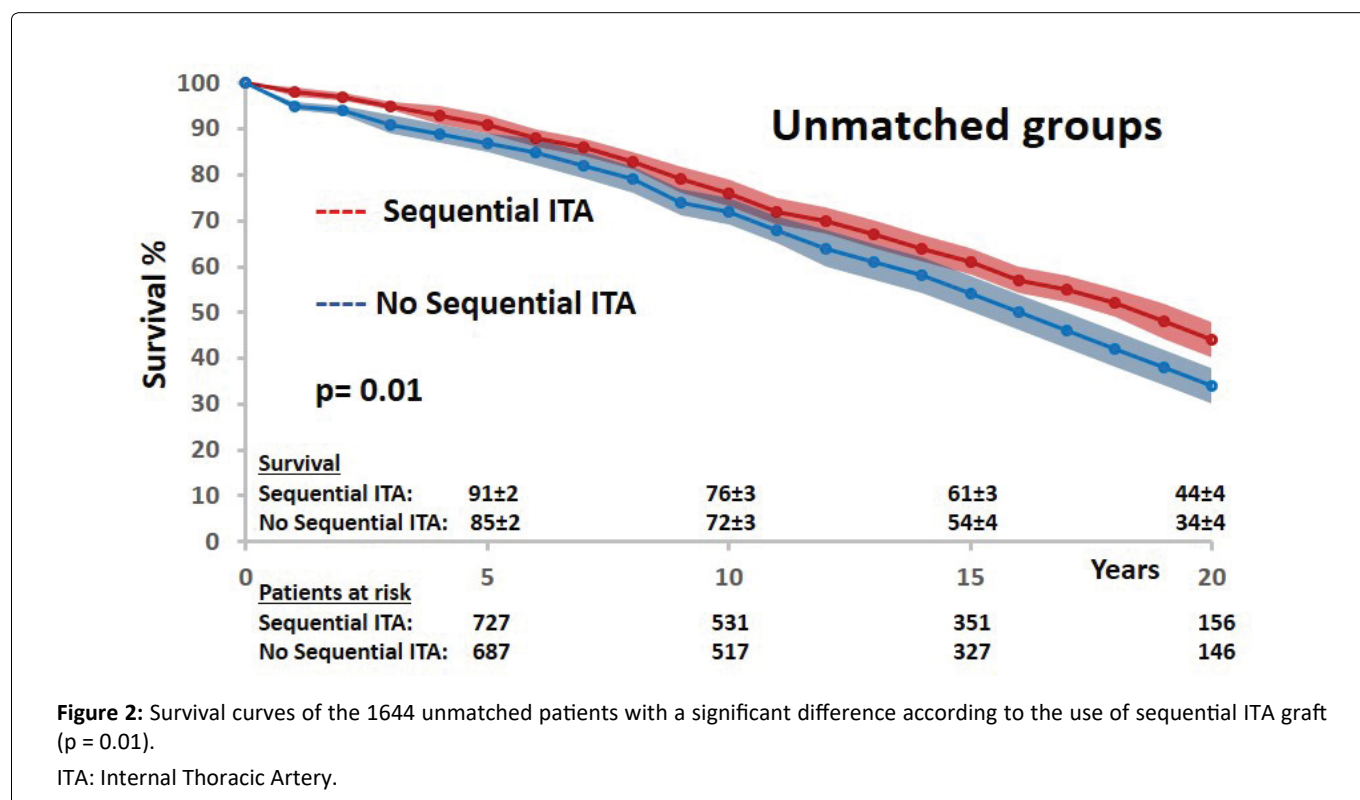
Figure 2: Survival curves of the 1644 unmatched patients with a significant difference according to the use of sequential ITA graft (p = 0.01).

ITA: Internal Thoracic Artery.

± 6.2-years), 734 patients were alive (mean follow-up 14.4 ± 6.6-years) and 85 patients were lost of follow-up (37 patients during the first postoperative year, and 48 patients after 5.8 ± 2.6-years).

The long-term survival after BITA grafting was significantly influenced by the technical configuration with a 10% difference at 20-years in favor of sequential ITA use (Figure 2). Several preoperative and intraoperative variables were identified as significant predictors of all causes mortality by univariable analysis: Age, heart failure, 3-vessel disease status, LV ejection fraction, number of arterial anastomoses, and sequential ITA graft. Gender, diabetes status, left main lesion, completeness of revascularization and operative times were not significant prognosis factors of mortality (Table 3).

In matched groups, there was no more difference in preoperative characteristics between both groups, confirming an optimal matching model according to propensity score distributions (Figure 3) and standardized median differences (Table 1). Obviously, the two groups were not matched according to the number of distal and arterial anastomoses. The early postoperative outcome was similar in both groups (Table 2). The late survival was significantly influenced by age, heart failure, diabetes status, 3-vessel disease status and LV ejection fraction (Table 4). Regarding the technical configuration, the late survival was significantly different among matched groups in favor of sequential grafting (Mantel-Cox chi-square: 5.069, p = 0.03; Figure 4). In multivariable analysis with Cox regression model (Chi-square: 204,030; df:

Table 3: Univariate binary logistic regression analysis of variables influencing mortality in the entire cohort of patients.

Predictor	RC	HR (95 % CI)	P Value
Preoperative			
Age	1.069	1.057-1.081	< 0.001
Male gender	1.123	0.871-1.454	0.368
Heart Failure NYHA ≥ 2	1.346	1.172-1.545	< 0.001
Diabetes	1.206	0.903-1.610	0.205
3-vessel disease	1.403	1.127-1.747	0.002
Left Main	0.934	0.737-1.185	0.575
LV ejection fraction	0.987	0.979-0.995	0.001
Intraoperative			
Complete revascularization	0.78	0.565-1.076	0.13
Clamp time	0.993	0.986-1.000	0.052
CPB time	1.001	0.995-1.006	0.858
Number of distal anastomoses	1.18	0.715-1.948	0.517
Number of arterial anastomoses	0.774	0.660-0.908	0.002
Sequential ITA	0.687	0.565-0.834	< 0.001
Associated vein	1.058	0.866-1.294	0.579

RC: Regression Coefficient; HR: Hhazard Ratio; CI: Confidence Interval; NYHA: New York Heart Association; LV: Left Ventricular; CPB: Cardiopulmonary Bypass; ITA: Internal Thoracic Artery

Table 4: Variables potentially influencing the survival in matched cohort of patients. Comparison of Kaplan-Meir survival curves with log-rang test.

Variable	Chi-square (Mantel-Cox)	df	P Value
Preoperative			
Age	195.047	48	< 0.001
Male gender	1.049	1	0.306
Heart Failure NYHA class	30.056	4	< 0.001
Diabetes	9.761	1	0.002
Left Main	0.689	1	0.407
3-vessel disease	15.991	1	< 0.001
LV ejection fraction	184.789	60	< 0.001
Intraoperative			
Number distal anastomoses	5.659	3	0.129
Complete revascularization	1.406	1	0.236
Associated vein	1.604	1	0.205
Sequential ITA	5.069	1	0.03

Df: Degree Of Freedom; NYHA: New York Heart Association; LV: Left Ventricular; ITA: Internal Thoracic Artery

Table 5: Multivariate Cox regression analysis of variables influencing survival in the 668 matched patients (Chi-square 204,030; df 11; p = 0.0001).

Predictor	RC	HR (95 % CI)	P Value
Preoperative			
Age	1.077	1.063-1.091	0.001
Male gender	0.912	0.683-1.219	0.536
Heart Failure NYHA ≥ 2	1.157	1.002-1.335	0.047
Diabetes	1.315	0.975-1.775	0.073
3-vessel disease	1.306	0.887-1.923	0.177
Left Main	1.196	0.905-1.580	0.208
LV ejection fraction	0.977	0.967-0.986	0.001
Intraoperative			
Complete revascularization	0.83	0.589-1.170	0.287
Sequential ITA	0.628	0.424-0.931	0.021
Associated vein	0.683	0.417-1.118	0.129
Number of distal anastomoses	1.236	0.779-1959	0.369

RC: Regression Coefficient; HR: Hazard Ratio; CI: Confidence Interval; NYHA: New York Heart Association; LV: Left Ventricular; ITA: Internal Thoracic Artery

11; p = 0.0001), age, heart failure and LV ejection remained independent risk factors of survival; regarding operative and technical criteria, only the use of sequential ITA graft was a significant independent prognosis factor of survival; complete revascularization and RCA bypass (vein graft or no graft) were not identified as independent prognosis factors (Table 5). According to these results, only the revascularization of the left coronary network by multiple ITA anastomoses with sequential technique had an impact on long-term survival, predominant over complete revascularization and independently of the RCA revascularization (vein graft or no graft).

Discussion

Multiple graft configurations have been described to use both ITA, including *in situ* and free grafts, and patency rates
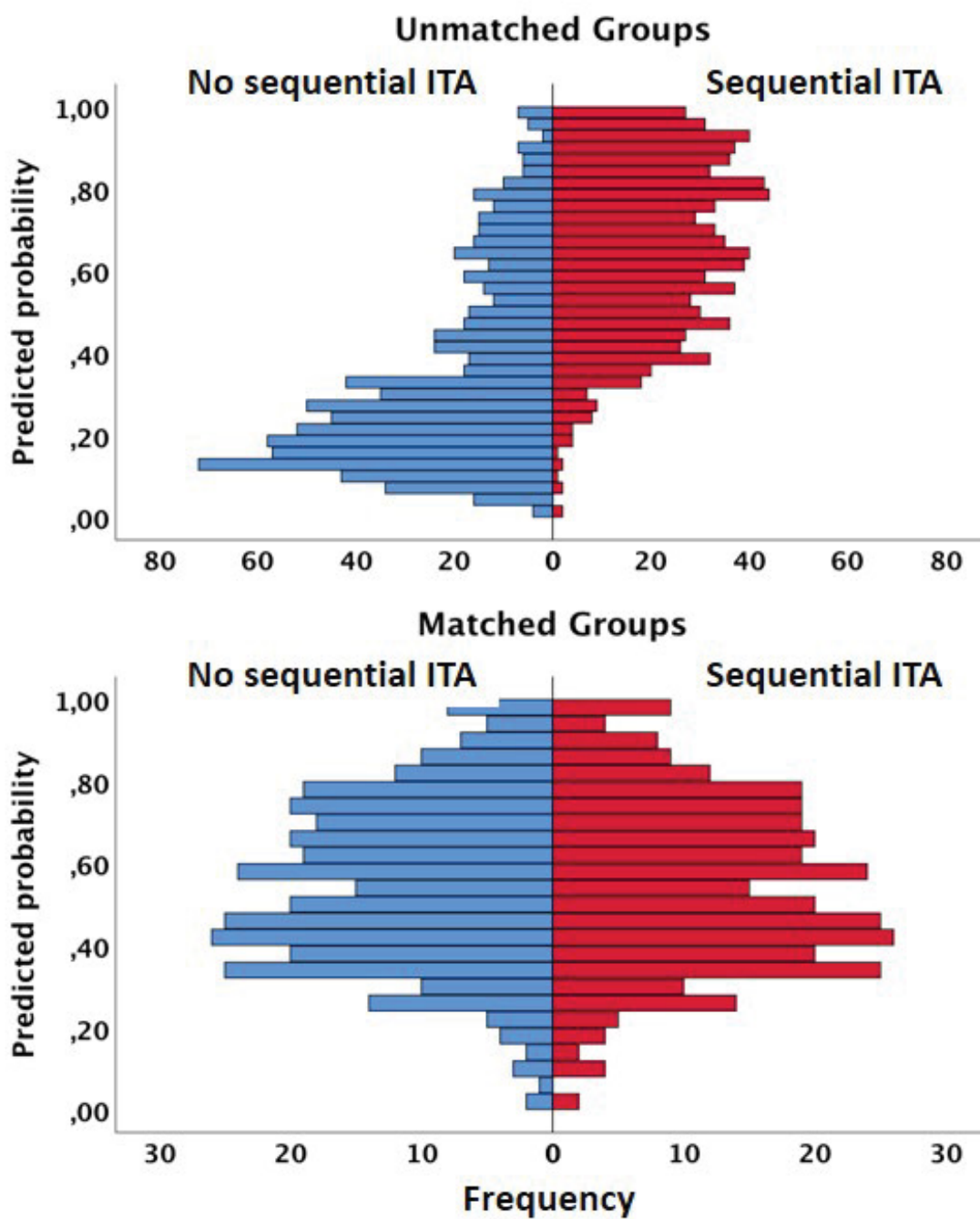
Figure 3: Propensity score-matched study of BITA grafting on the left side according to the use of sequential ITA: Mirrored histograms of propensity score in unmatched and matched groups.

ITA: Internal Thoracic Artery.

for both LITA and RITA have been shown to be equivalent for specific myocardial territories, and better than radial or saphenous vein grafts [7,9]. Because the additional risk has been sufficiently low and the potential benefit could be a life expectancy improvement, in 1989 we estimated that our patients have deserved a shift in our practice of coronary revascularization and we decided to perform BITA grafting and multiple arterial revascularization as often as possible. Our strategy was to tailor the operation to the patient according to the coronary network and the estimated operative risk to avoid an increase of early mortality. Our preference has been

pedicled ITA grafts to bypass the left coronary artery system with wide use of sequential ITA graft, and an additional vein or arterial graft to the right side. Our previous reports focused on short-term and mid-term results, demonstrated that this strategy was safe even in diabetes patients with a low rate of sternal wound infection [8]. The primary endpoint of this retrospective observational study conducted in one institution and based on a single surgeon experience, was focused on the overall mortality with a mean postoperative follow-up of 12-years. The aim of the study was focused on the impact of sequential ITA and patients who underwent
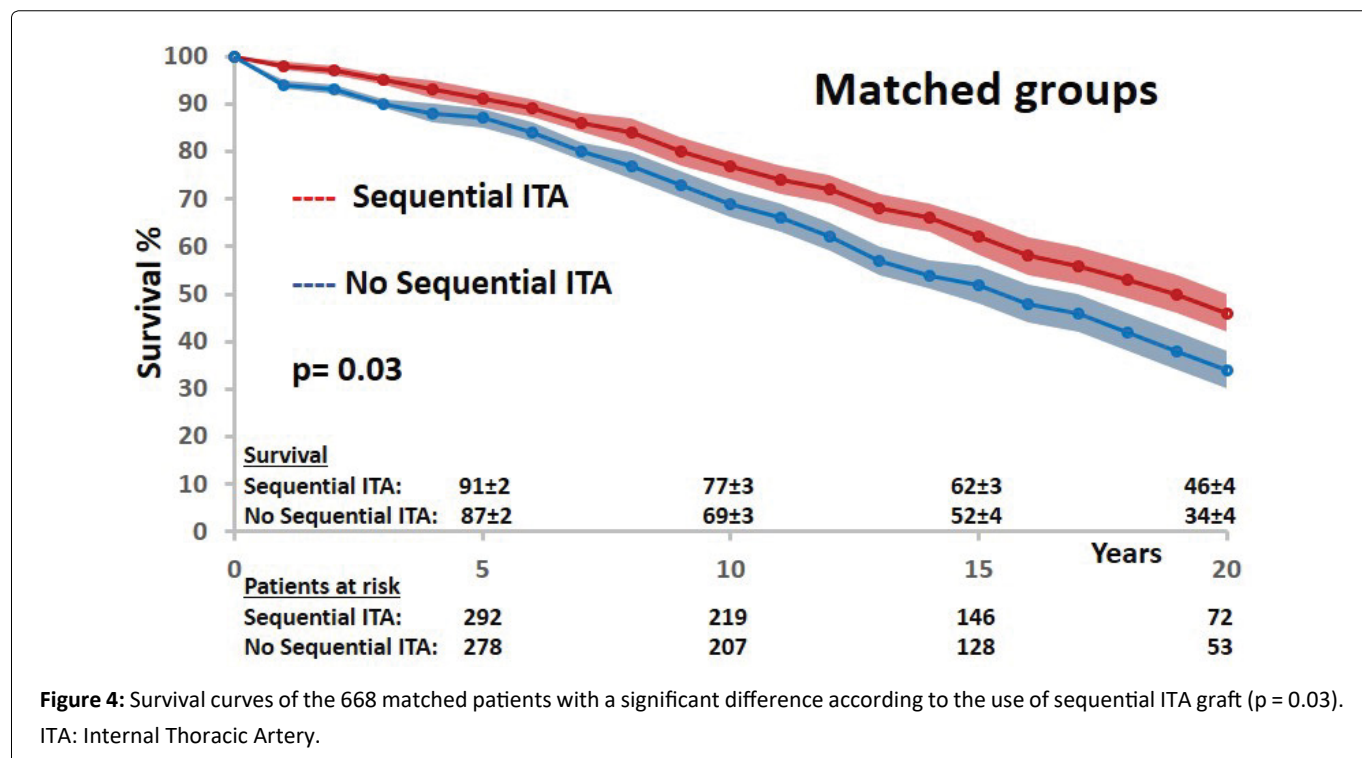
Figure 4: Survival curves of the 668 matched patients with a significant difference according to the use of sequential ITA graft (p = 0.03). ITA: Internal Thoracic Artery.

an additional arterial graft to BITA were excluded to avoid an additional bias. In unmatched and matched groups, univariate and multivariate analyses have confirmed the traditional prognosis factors of mortality after CABG [10,11]. Regarding the arterial grafting configuration and the technical strategy, the bypassing of multiple target coronary vessels of the left territory with sequential ITA grafts was a significant independent predictor of late survival, predominant over complete revascularization and the revascularization of the RCA territory, with a 12% difference at 20-years between the matched groups, in favor of sequential ITA graft . However, the interpretation of the results remains tricky because there was no alternative to sequential ITA bypass, and it is difficult to know if the impact we have observed is related to an obvious additional revascularization or to its ITA origin. Interestingly, there was no difference in early mortality and morbidity after CABG according to the surgical technique performed, confirming a posteriori the efficiency of the strategy of revascularization we adopted and that judicious patient selection for a given grafting strategy is important for optimal outcomes.

In many studies focused on both ITA grafting, the impact of sequential ITA graft is not clear, the non-LAD target vessels bypassed by additional arterial graft are variable, *in situ* or free arterial graft are mixed and the number of distal arterial anastomoses are not mentioned; so finally the unicity of the surgical technique is not enough to determine a consistent impact. In our experience, sequential ITA grafts were used to increase the number of distal arterial anastomoses and to perform extensive arterial grafting on the left side. Benefits of sequential ITA are well established [11,12]. Kieser, et al. [13] have reported that a strategy of multiple ITA grafts may balance survival between complete and incomplete revascularization that is one of our result as well. Yanagawa,

et al. [2] have reported a meta-analysis showing that total arterial revascularization may improve long-term survival even when compared with two arterial grafts, suggesting that higher the number of arterial anastomoses better the survival. The better patency of ITA grafts has been involved to explain such positive impact [12]. The hypothesis that arterial grafts has a strong protective effect against progression of native coronary artery disease in previously grafted vessels has been proposed and multiple arterial grafting may improve long-term survival by preventing progression of atherosclerosis in the native coronary vessels with a possible NO mediation [14]. More recently, Bakaeen, et al. [15] showed that in BITA grafting, bypassing multiple targets to maximize myocardium mass supplied by ITAs, improved long-term survival. According to our results and the preceding studies, we can speculate that an extended ITA revascularization of the left coronary network with sequential BITA may have a protective effect on the long-term outcome related to preventing the progression of the atherosclerosis of bypassed vessels and related to a bigger myocardium mass supplied by ITAs, despite the fact that patient who underwent sequential ITA had initially more severe coronary lesions. This hypothesis is consistent with our principal finding in the matched group analysis, that the impact of sequential ITA is predominant over complete revascularization and the RCA grafting options; patients without sequential ITA had additional lateral vessels either no sick and exposed to a progression of the disease or too sick to be bypassed and exposed to an incomplete revascularization, that was balanced in the propensity score matching. Pevni, et al. [16] have already shown that the revascularization of the RCA independently of the graft used had no impact on the late survival of patients who underwent BITA grafting on the left side, which is consistent with our results as well.

Despite its inherent limitations, our study has

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demonstrated that BITA grafting is not an end in itself: Higher the number of ITA anastomoses with the use of sequential ITA, greater the myocardial mass perfused by ITA grafts, better the long-term survival. RCA revascularization seems having no impact on survival after BITA grafting, without prejudging a possible impact on late cardiac events.

Limitations

The present study has several limitations, inherent to its design and objectives. This is a retrospective observational nonrandomized study based on a 25-year single center, single surgeon and single technical configuration operative experience. Only solid preoperative characteristic and documented for all patients were integrated in the risk factors analysis: For example Euroscore or STS score were missing before 2000, obesity status was not defined properly according to BMI, and they were not included. Nevertheless, the preoperative characteristic included are recognized as the main risk factors of CABG, defining well our CABG population and discriminant in comparisons between the multiple arterial grafting strategies performed in patients. The operative parameters were more exhaustive, more precise, allowing a robust analysis of the operative configuration and its impact. Only long-term survival and all-cause mortality were defined as primary end-point of the study. It was not the intent of the study to report on other major adverse events as myocardial infarction, repeat revascularization, cause of death, or on graft patency, and the collection of these information was not realistic in this retrospective study over 30-years. Propensity-score matching was performed to correct for the bias associated with the use of sequential ITA graft. The residual bias related to the absence of alternative to sequential ITA graft in our strategy, was probably mitigated by the balance in complete revascularization and RCA bypass in the two matched groups; however it makes the interpretation of the results questionable. Therefore, we expect confirmation from the ROMA (Randomized Comparison of the Clinical Outcome of Single versus Multiple Arterial Grafts) trial under way [17]. Nevertheless, we can distill our finding to practical recommendations. In patients who are selected for BITA grafting, use the ITAs to revascularize the greatest total myocardium with the added-value of sequential technique; the more myocardium supplied by ITAs, the better the survival.

Conclusions

According to the results of this study, sequential ITA graft is an independent predictor of late survival after BITA grafting on the left side, predominant over the completeness of the revascularization. These findings support the concept that extensive use of ITA grafts should be the cornerstone of modern coronary artery surgery. However they have to be confirmed in further studies.

Acknowledgement

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Conflict of Interest

None declared.

Funding Statement

None declared.

Data Availability

The data that support the finding of this study are available from the corresponding author, upon reasonable request.

Ethics Approval and Consent to Participate

Ethics approval and consent to participate are mentioned in Methods.

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