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Is Sequential Grafting an Added Value in Coronary Bypass Surgery Using Bilateral Internal Thoracic Artery?

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Abstract

Objectives: It is unclear whether the additional bypass technique to supplement Bilateral Internal Artery grafting (BITA) influences the patient outcome in coronary surgery. We analyzed the impact on late survival after BITA of sequential ITA grafts use on the left side and of the third associated conduit on the right side.

Methods: From 1989 to 2014, 2,477 patients underwent BITA surgery. The revascularization of the left side was optimized with a sequential ITA graft in 1,144 patients. The revascularization of the right side was performed with an associated vein graft in 599 patients and with an associated Gastroepiploic graft (GEA) in 833 patients; it was not indicated or not accessible in 1,045 patients. The primary end point was overall mortality from any cause. The mean postoperative follow-up was 13.3 ± 7.1 years and 94% complete.

Results: The population was not homogenous: greater the arterial revascularization, lower the risk profile. The 30-day mortality was 1.4% without influence of the surgical technique performed. Late mortality was significantly influenced by age, heart failure, LV ejection fraction and diabetes. In multivariate analysis with Cox model (Chi-square 624.949, df11, p=0.001), the use sequential ITA graft was the only technical significant independent prognosis factor of survival, predominant over complete revascularization. The revascularization of the right side (GEA, vein, or no graft) had no influence on long-term survival.

Conclusion: 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; Gastroepiploic artery; Sequential graft

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Introduction

It has been 20 years since Lytle and colleagues' statement "two internal thoracic artery grafts are better than one" [1], and 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 [2,3]. 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 best graft to supplement BITA has 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 and tested the hypothetic impact of the associated techniques used to perform an extensive arterial myocardial revascularization, namely sequential ITAs on the left side and Gastroepiploic Artery (GEA) as additional arterial conduit on the right side.

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. Exclusion criteria were emergency, reoperation, associated procedure, and unstable situation. We retrospectively analyzed prospectively collected data from the surgical registry of the department approved by the local ethical committee and receiving individual patient consent. Finally, 2,477 patients were included in the study: 1,045 patients had isolated BITA, 599 patients had BITA and an associated vein graft, and 833 patients had BITA and an associated gastroepiploic graft. A sequential ITA graft was performed in 1,144 patients.

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 antegrade and retrograde crystalloid cardioplegia. Patients received both Left Internal Thoracic Artery 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 or an additional GEA arterial graft was used to bypass the Right Coronary Artery (RCA) system, as needed; the choice was individually decided according to the state of the patient and the availability of GEA. The use of the GEA was conditioned to a good adequacy between the size of the GEA and the size of the target coronary vessel; a vein graft was preferred also when the GEA diameter was less than 1.5 mm. All arterial grafts (LITA, RITA, GEA) 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. The prognosis factors of long-term mortality were established in the all population of patients by univariate and multivariate analyses.

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's 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. Univariate analyses of predictors of all-cause death were done with binary logistic regression. Multivariate Cox regression analysis was used to identify independent predictors of all-cause death. 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

The data are summarized in Table 1 for all patients and according to the associated graft. In comparison with other groups and significantly, an associated vein was used in older patients, more in females, more in patients with significant heart failure defined as NYHA class ≥ 2, and more in patients with left ventricular dysfunction and impairment of ejection fraction. Interestingly in this associated vein group, the GEA graft was checked and finally not used because of an insufficient diameter, flow or length in 58% of patients; in 18% vein graft was used because GEA graft was not available easily due to previous abdominal surgery, and in 24% because of the higher risk profile of the patients. In isolated BITA group, patients had more 2-vessel disease (43%) and underwent a lower rate of complete revascularization (43%) with less distal anastomoses despite a higher use of sequential ITA graft (55%) because the RCA network was not bypassed in this group, either not indicated or not accessible. In associated GEA group, patients were mainly male with lower diabetes history and left main lesion, and they underwent a higher number of arterial anastomoses. In this series, the early mortality was 1.4% and it was not significantly influenced by the surgical technique performed. The mean postoperative follow-up was 13.3 ± 7.1 years, and 94% complete: 1,241 late deaths occurred (mean delay 11.8 ± 6.5 years), 1,044 patients were alive (mean follow-up 16.6 ± 6 years) and 157 patients were lots of follow-up (64 patients during the first postoperative year, and 93 patients after 5.1 ± 2.6 years). The long-term survival was influenced by the technique performed with a significant difference between the 3 BITA groups (Figure 1). Several preoperative and intraoperative variables were identified as significant risk factors of all causes mortality by univariate analyses: age, heart failure, diabetes history, 3-vessel disease status, LV ejection fraction, complete revascularization, number of Distal Arterial Anastomoses (DAA), sequential ITA graft; gender and RCA bypass (GEA graft, vein graft or no graft) were not significant prognosis factor of mortality (Table 2). The impact of the number of DAA on survival was found significantly discriminant from 2 to 3; after 3 there is no more significant additional effect. The 5-, 10-, 15-, 20- and 25-year survival were respectively 87 ± 2, 72 ± 3, 55 ± 4, 36 ± 4, 23 ± 5 in the 814 patients who had 2 DAA; 90 ± 2, 76 ± 3, 62 ± 3, 46 ± 3, 29 ± 4 in the 1,256 patients who had 3 DAA (p=0.001) and 91 ± 3, 77 ± 4, 63 ± 5, 46 ± 6, 31 ± 7 in the 407 patients who had 4 and more DAA (p=0.240).

In multivariate analysis with Cox regression model (Chi-square: 624,949; df: 11; p=0.0001), previous preoperative clinical variables except gender and coronary status, remained independent risk factors of mortality; 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 (GEA graft, vein graft or no graft) were not identified as independent prognosis

Table 1: Comparison of preoperative clinical variables and postoperative outcome by patients groups.

Characteristic	All Patients N=2477	Both ITA alone N=1045	Both ITA + Vein N=599	Both ITA + GEA N=833	P value
Age--year	63 ± 10	63 ± 10	66 ± 9	61 ± 9	0.001
Male sex	2154 (87%)	889 (85%)	472 (79%)	793 (95%)	0.001
Heart failure NYHA ≥ 2	233 (9%)	99 (9%)	77 (13%)	57 (7%)	0.001
3-vessel disease	2013 (82%)	596 (57%)	595 (99%)	822 (99%)	0.001
Left main lesion	444 (18%)	236 (23%)	110 (19%)	98 (12%)	0.01
LV ejection fraction--%	60 ± 12	61 ± 11	59 ± 13	61 ± 12	0.001
Diabetes	280 (11%)	122 (12%)	89 (15%)	69 (8%)	0.001
Distal Anastomoses	3.1 ± 0.8	2.6 ± 0.6	3.6 ± 0.6	3.4 ± 0.6	0.001
Arterial Anastomoses	2.8 ± 0.7	2.6 ± 0.6	2.5 ± 0.6	3.4 ± 0.6	0.001
Complete Revascularization	1651 (67%)	452 (43%)	505 (84%)	694 (83%)	0.001
Clamp Time--min.	53 ± 14	47 ± 14	53 ± 14	59 ± 13	0.01
CPB time--min.	69 ± 22	61 ± 17	74 ± 15	76 ± 27	0.01
Sequential ITA	1144 (46%)	564 (55%)	260 (43%)	320 (38%)	0.001
1-month Mortality	35 (1.4%)	12 (1.1%)	12 (2%)	11 (1.3%)	0.54
Lots of follow-up at 1 year	64 (2.6%)	27 (2.6%)	11 (1.8%)	26 (3.1%)	0.26
Mean Follow-up year	13.3 ± 7.1	12.9 ± 6.9	11.5 ± 6.2	15.1 ± 7.5	0.001
Late Mortality	1241 (50%)	507 (48.5%)	294 (49%)	440 (52.8%)	0.151
Survival-- (Patients exposed)					
5 years	89 ± 1(2137)	90 ± 2(911)	87 ± 3(503)	91 ± 2(723)	0.001
10 years	75 ± 2(1669)	75 ± 3(689)	70 ± 4(369)	79 ± 3(611)	
15 years	59 ± 2(1156)	59 ± 3(443)	51 ± 5(235)	65 ± 4(478)	
20 years	42 ± 2(587)	41 ± 4(229)	33 ± 6(73)	48 ± 4(285)	
25 years	25 ± 3(165)	26 ± 5(65)	12 ± 11(4)	29 ± 4(96)	

ITA: Internal Thoracic Artery; GEA: Gastroepiploic Artery; NYHA: New York Heart Association; LV: Left Ventricular; min: minutes; CPB: Cardiopulmonary Bypass

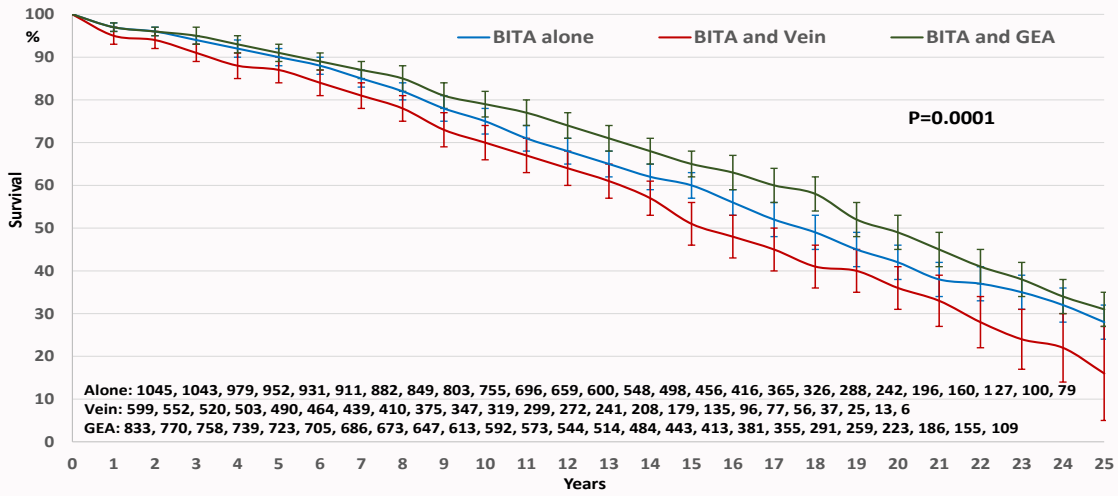

Figure 1: Survival curves of the 2477 BITA patients according to the additional graft.
BITA: Bilateral Internal Thoracic Artery; GEA: Gastroepiploic Artery

factors (Table 3). According to these results, the impact of the number of DAA on survival was directly related to sequential ITA graft use with a limited but significant effect on long-term survival (Figure 2). There was no benefit effect of GEA as additional arterial graft to bypass the RCA network, in comparison with vein graft. 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 the significant positive impact on survival of sequential ITA was independent of the RCA revascularization (GEA graft, vein graft or no graft): Adjusted survival, Log rank Mantel-Cox, Chi-square 3.899, p=0.048.

Discussion

Multiple graft configurations have been described to use both ITA, including in situ and free grafts, and patency rates for both LITA

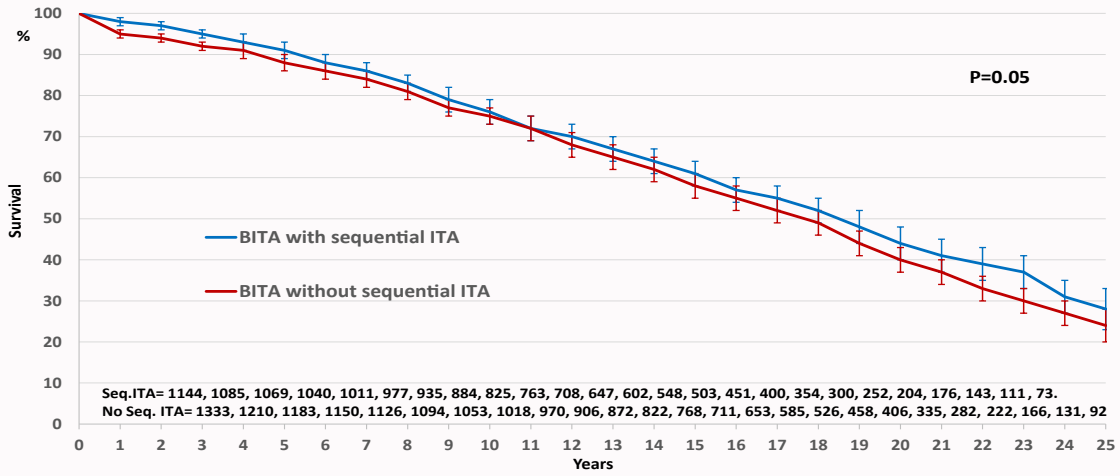

Figure 2: Survival curves of the 2477 BITA patients according to sequential ITA grafting.
BITA: Bilateral Internal Thoracic Artery; ITA: Internal Thoracic Artery

Table 2: Univariate binary logistic regression analysis of variables influencing mortality in the entire cohort of patients.

Predictor	RC	HR (95% CI)	P Value
Preoperative			
Age	0.066	1.068 (1.058-1.078)	0.0001
Male gender	0.051	1.052 (0.832-1.329)	0.672
Heart Failure NYHA ≥ 2	0.338	1.401 (1.241-1.582)	0.0001
Diabetes	0.256	1.292 (1.005-1.660)	0.046
3-vessel disease	0.394	1.484 (1.211-1.818)	0.0001
LV ejection fraction	-0.016	0.984 (0.978-0.991)	0.0001
Intraoperative			
Complete revascularization	-0.325	0.722 (0.611-0.855)	0.0001
Number of arterial anastomoses	-0.11	0.896 (0.805-0.998)	0.045
Sequential ITA	-0.347	0.706 (0.603-0.828)	0.0001
Associated GEA	0.159	1.172 (0.992-1.385)	0.063
Associated vein	-0.032	0.969 (0.806-1.164)	0.734
No associated graft	-0.128	0.880 (0.750-1.032)	0.116

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

Table 3: Multivariate Cox regression analysis of variables influencing mortality in the entire cohort of patients (Chi-square 624,949; df 11; p=0.0001).

Predictor	RC	HR (95% CI)	P Value
Preoperative			
Age	0.074	1.077 (1.069-1.085)	0.0001
Male gender	-0.138	0.871 (0.736-1.031)	0.109
Heart Failure NYHA ≥ 2	0.154	1.166 (1.078-1.261)	0.0001
Diabetes	0.484	1.623 (1.369-1.923)	0.0001
3-vessel disease	0.031	1.032 (0.833-1.278)	0.774
LV ejection fraction	-0.023	0.978 (0.973-0.983)	0.0001
Intraoperative			
Complete revascularization	-0.069	0.933 (0.797-1.093)	0.391
Sequential ITA	-0.163	0.850 (0.757-0.955)	0.006
Associated GEA	-0.907	0.404 (0.057-2.881)	0.366
Associated vein	-0.859	0.424 (0.059-3.019)	0.391
No associated graft	-0.903	0.405 (0.056-2.916)	0.37

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

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 graft or pedicled GEA 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 patient 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 13 years.

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, only the use of sequential ITA graft was identified as an independent prognosis factor of survival, predominant over complete revascularization. In this study based on a large population of patients who underwent BITA grafting, the revascularization of the RCA territory and the technique of bypass used for it (vein or GEA) had no influence on the late mortality, and the bypassing of multiple target coronary vessels of the left territory with sequential ITA grafts was a significant independent predictor of late survival.

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 and coll [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 and coll [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 and coll [15] showed that in BITA grafting, bypassing multiple targets to maximize myocardium mass supplied by ITAs, improved long-term survival.

The impact of a third arterial graft in addition to the bilateral mammary arteries has not been clearly defined and remained controversial [7,16]. GEA graft has been identified as a good option to supplement BITA grafts to achieve total arterial revascularization in patients with 3-vessel disease [17]. This third arterial conduit has potential advantages over the BITA Y-graft strategy or the use of the radial artery because it is a third *in situ* graft. Di Mauro and coll [18] in a meta-analysis comparing the saphenous vein to the radial artery and the right gastroepiploic artery for the right coronary artery grafting in patients receiving a bilateral internal thoracic artery to the left coronary arteries, showed that the choice of a third arterial conduit seems to be preferable in order to achieve better long-term survival. In our series, the significant differences in preoperative data between patients who underwent additional GEA graft or vein graft to RCA network illustrate some reasons the patients who had BITA grafting did not get a third arterial graft: Older patient, more female gender, LV dysfunction, heart failure symptoms; however, despite its use in lower risk patients, our results regarding GEA graft were disappointing and they have not confirmed the positive impact on long-term survival of GEA grafting to the right coronary network in comparison with a vein graft as reported by Gaudino et coll in a meta-analysis [19]. Better patency of GEA graft over vein graft has been reported correlated to a large inner diameter of GEA, a severely stenosed RCA and possibly a skeletonized graft [17]. However in our experience we did not change our technique of GEA grafting more focused on the adequacy in size of the vessels. The alternative of a radial artery conduit could have provided better results possibly but we had no experience with and it was never used in this series [16]. However, in a previous study, Pevni et coll [20] showed 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.

Interestingly, despite significant differences in risk factors, there was no difference in early mortality 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.

Despite its inherent limitations, our study has 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. However the GEA as additional arterial graft to bypass the RCA has no impact on late survival, probably because RCA revascularization has 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. Regression adjustment method was used to identify independent predictors of late outcomes; it was the most appropriate method to integrate the bias associated with extensive arterial revascularization and to analyze the impact of all graft configurations. Matched-group analyses could be focused on one graft configuration only (RCA bypass or Sequential ITA) with the loss of half information; more the artificial matched population would have been unrealistic because only RCA bypass with GEA or vein graft was a possible alternative; other configurations were dictated by coronary lesions and not open to a hypothetic randomization.

Conclusion

According to the results of this study, sequential ITA graft is an independent predictor of late survival after BITA grafting on the left side without significant impact of the third conduit used to bypass the right side, vein or GEA graft. This finding 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.

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