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Citation: Fertouk M, Gordon A, Pevni D, Ziv-Baran T, Sela O, Mohr R, et al. (2021) Early and late outcomes of single versus bilateral internal thoracic artery revascularization for patients in critical condition. PLoS ONE 16(8): e0255740. https://doi.org/10.1371/journal.pone.0255740

Editor: Robert Jeenchen Chen, Ohio State University Wexner Medical Center-Department of Surgery, UNITED STATES

Received: May 23, 2021

Accepted: July 22, 2021

Published: August 5, 2021

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Data Availability Statement: Data from this study are ethically and legally restricted by the Institutional Review Board of Tel Aviv Sourasky Medical Center to prevent compromise of patient confidentiality. Any requests for data release should be addressed to Dr. Shmuel Kivity, Chairman of the Tel Aviv Sourasky Medical Center Institutional Review Board (IRB)/Ethics (Helsinki) Committee at: allergy@tlvmc.gov.il. RESEARCH ARTICLE

Early and late outcomes of single versus bilateral internal thoracic artery revascularization for patients in critical condition

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Abstract

Objective

The optimal surgical approach for critically ill patients with complex coronary disease remains uncertain. We compared outcomes of bilateral internal thoracic artery (BITA) versus single ITA (SITA) revascularization in critical patients.

Methods

We evaluated 394 consecutive critical patients with multi-vessel disease who underwent CABG during 1996–2001. Outcomes measured were early mortality, strokes, myocardialinfarctions, sternal infections, revisions for bleeding, and late survival. The critical preoperative state was acknowledged concisely by one or more of the following: preoperative ventricular tachycardia/fibrillation, aborted sudden cardiac death, or the need for mechanical ventilation or for preoperative insertion of intra-aortic-balloon counter-pulsation.

Results

During the study period, 193 of our patients who underwent SITA and 201 who underwent BITA were in critical condition. The SITA group was older (mean 68.0 vs. 63.3 years, p = 0.001) and higher proportions were females (28.5% vs. 18.9% p = 0.025), after recent-MI (69.9% vs. 57.2% p = 0.009) and with left-main disease (38.3% vs. 49.3% p = .029); the median logistic EuroSCORE was higher (0.2898 vs. 0.1597, p<0.001). No statistically significant differences were observed between the SITA and BITA groups in 30-day mortality; and in rates of early CVA, MI and sternal infections (13.0% vs. 8.5%, p = 0.148; 4.1% vs. 6.0%, p = 0.49; 6.7% vs. 4.5%, p = 0.32 and 2.1% vs. 2.5%, p>0.99, respectively). Long-term survival (median follow-up of 15 years, interquartile-range: 13.57–15) was better in the BITA group (median 14.39 vs. 9.31± 0.9 years, p = 0.001). Propensity-score matching (132

Funding: The authors received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

matched pairs) also yielded similar early outcomes and improved long-term survival (median follow-up of 15 years, interquartile-range: 13.56–15) for the BITA group (median 12.49 \pm 1.71 vs. 7.63 \pm 0.99 years, p = 0.002). In multivariable analysis, BITA revascularization was found to be a predictor for improved survival (hazard-ratio of 0.419, 95%CI 0.23–0.76, p = 0.004).

Conclusions

This study demonstrated long-term survival benefit for BITA revascularization in patients in a critical pre-operative state who presented for surgical revascularization.

Introduction

Surgical revascularization with the left internal thoracic artery (ITA) to the left anterior descending artery is an established therapeutic strategy to prolong life in patients with severe coronary artery disease [1]. Over the years, a few retrospective studies have demonstrated improved outcomes with multiple arterial grafts and most definitely with bilateral ITA (BITA) revascularization [2–6]. Moreover, two meta-analyses demonstrated a distinctive survival benefit and less reinterventions for BITA vs single ITA (SITA) revascularization strategy [7, 8]. The ART trial validated a clinical benefit for multi-arterial versus SITA revascularization [9], and a designated randomized trial assessing the true prognostic consequence of BITA vs SITA is currently ongoing [10]. All these reports focused mostly on preselected healthy and comparatively young and stable individuals with relatively protracted life expectancy. However, the data are very limited regarding the true implication of BITA revascularization in persons with multi-vessel disease who present for surgical revascularization while in critical condition.

In our center, skeletonized BITA grafting is the routine approach for most patients in need of primary coronary artery bypass grafting (CABG), even in the presence of multiple risk factors, older age and comorbidities. Patients with presumed lower life expectancy and pronounced comorbidities are not ruled out from receiving BITA revascularization procedures [11]. This is despite the predicament regarding accompanying risk factors for deep sternal wound infections (DSWI), and most particularly in regard to patients with chronic obstructive pulmonary disease (COPD) and women with obesity and diabetes mellitus [12, 13]. In this report, we investigated early and late outcomes of SITA versus BITA revascularization procedures performed in critical patients.

Materials and methods

Because the research was a retrospective data research that was analyzed anonymously, and with no patients involvement, the Tel Aviv Sourasky Medical Center Institutional Review Board (Helsinki Committee) granted permission to not ask for consent. This study encompassed all the critical patients with multi-vessel coronary artery disease who underwent isolated CABG in Tel-Aviv Sourasky Medical Center during 1996–2011, deploying either a single skeletonized ITA to the left anterior descending artery along with other conduits or a bilateral skeletonized ITA to the anterior and lateral walls. BITA revascularization was performed with the "composite" configuration, in which a free right ITA is attached proximally as a composite Y graft to the left ITA, or by the "in situ" configuration with an in situ right ITA supporting the LAD and an in situ left ITA to the lateral wall [11]. Importantly, for the purpose of this study,

the critical preoperative state was acknowledged in any one or more of the following: preoperative ventricular tachycardia or fibrillation, aborted sudden death, preoperative ventilation before arrival in the anesthetic room and pre-operative insertion of an intra-aortic balloon counter-pulsation (IABP). Of note, evolving myocardial infarction (MI), the need for inotropic or vasopressor therapy, and preoperative acute renal failure (anuria or oliguria < 10 ml/hr.) were not part of the study's inclusion criteria due to unavailable, unsubstantiated or insufficient data. The study was approved by the Tel Aviv Sourasky Medical Center Institutional Review Board (Helsinki Committee), and a waiver for informed consent was granted due to the retrospective study design.

The decision to perform either BITA or SITA grafting was essentially made according to each surgeon's discretion. BITA revascularization is the preferred revascularization strategy in our center also in complex and older patients [14]. All ITAs were harvested as skeletonized vessels [13]. Further technical aspects of the BITA procedures are detailed in previous publications of our group [15].

EuroSCORE clinical data standards were used to analyze patient data [16]. The definition of early mortality was mortality within the index revascularization or the first month from surgery. Cerebrovascular accident was considered as a new long-lasting neurological impairment with established evidence by computed tomography. The definition of DSWI necessitated an evident sternal or peri-sternal infection (with clinical and laboratory evidence) that required an open surgical intervention. An emergent operation was defined as an operation performed within 24h of catheterization or in patients with evident pre-operative acute or evolving MI, pulmonary edema or cardiogenic shock.

Early outcomes from the index hospitalizations were extracted from patients' medical records, discharge letters and department databases. We obtained information regarding late mortality of our patients from the Israeli National Registry database.

Statistical analysis

Categorical variables were described as frequencies and percentages. Continuous variables were evaluated for normal distribution using histograms, and reported as means and standard deviations, or medians and interquartile ranges. The Chi-square test was used to compare categorical variables between the two configurations, and the independent samples T-test and Mann-Whitney tests were applied to compare continuous variables. The length of follow-up was observed using the reverse censoring method. Kaplan Meier curve analysis was used to describe survival during the follow-up period and to report median survival time. The logrank test was used to compare survival between the two techniques. Multivariate Cox regression was applied to evaluate the association between 15-year mortality and configuration technique, while controlling for possible confounders. Each regression contained four blocks. In the first block, configuration technique, age and gender were forced into the regression. In the second and third blocks, pre-operative and operative parameters were included as potential variables for inclusion in the model using the backward method (the Wald test was used and p>0.1 was the criteria for removal). Finally, surgical era was forced into the regression in the fourth block. The two groups were matched according to the probability of a patient undergoing CABG using BITA. The probability (propensity score) was calculated using a logistic regression model. The following parameters were used to calculate the propensity score: sex, age, non-insulin dependent diabetes mellitus, insulin-dependent diabetes mellitus, diabetes mellitus end-organ damage, chronic obstructive pulmonary disease, chronic heart failure, chronic renal failure, recent MI (less than 3 weeks), old MI, unstable angina pectoris, ejection fraction <30%, the use of an IABP, emergency redo procedures, peripheral vascular disease,

number of vessel disease, left main disease and percutaneous transluminal coronary angioplasty. An absolute difference in the propensity score of up to 5% was considered acceptable for matching. Standardized differences were calculated to compare the two groups before and after matching. The matched cohorts were compared using the McNamar test for the categorical variables, and the paired T-test and Wilcoxon test for the continuous variables. Stratified Cox regression was used to compare survival between the two matched groups. All statistical tests were two sided and p<0.05 was considered statistically significant. Statistical analysis was performed with SPSS statistical software (IBM SPSS Statistics for Windows, version 27, IBM Corp., Armonk, NY, USA, 2020).

Results

Unmatched cohort

This study included 394 critically defined patients, 201 operated with BITA to the left side and 193 who were operated by SITA and additional grafts (mostly saphenous vein grafts). The preprocedural and intra-intraoperative characteristics are summarized in <u>Table 1</u>. Compared to the BITA group, the mean age of the SITA group was older, and the proportions were greater of women, and of patients after recent MIs (less than 3 weeks), acute MIs, redo procedures and left main disease. Logistic EuroSCORE levels were higher in the SITA than the BITA group.

Mortality did not differ significantly (13% for the SITA vs. 8.5% for the BITA group, p = 0.148), nor did other early measurable outcomes (Table 2).

After a follow up of up to 15 years (median 15, interquartile range: 13.57–15), a significant survival advantage was observed in the BITA versus the SITA group, as depicted by the Kaplan–Meier survival curves (Fig 1). The 5, 10 and 15-year survival rates were 74.2% vs. 69.1%, 63.1% vs. 46.7% and 49.0% vs. 33.4%, respectively, p = 0.001. However, in multivariable analysis, the revascularization modality (SITA vs. BITA) was not found to affect survival in the unmatched cohort (hazard ratio [HR] = 0.87 (95%CI 0.629–1.203, p = 0.399). The following variables were significant for increased mortality: older age, non-insulin-dependent diabetes mellitus, end-organ damage following diabetes mellitus, COPD, recent MI, redo operation and the number of vessels that were revascularized. The respective HRs were 1.056 (95%CI 1.041–1.072, p<0.001), 1.375 (95%CI 1.02–1.852, p = 0.037), 1.892 (95%CI 1.238–2.891, p = 0.003), 1.984 (95%CI 1.315–2.996, p = 0.001), 1.518 (95%CI 1.118–2.06, p = 0.007), 1.787 (95%CI 1.012–3.156, p = 0.045) and 1.775 (95%CI 1.219–2.584, p = 0.003).

Matched cohort

After propensity matching, we isolated 132 pairs of comparable patients with a median followup of 15 years (interquartile range: 13.56–15). Significant differences were not found between the matched groups in any of the examined characteristics, except for a small but significantly higher proportion of patients in the SITA group with a high logistic EuroSCORE, and a higher proportion operated after the year 2000 (Table 1). As with the unmatched cohort, postoperative differences were not found between the matched BITA and SITA groups in early mortality (11.4% and 17.4%, respectively, p = 0.215) nor in other measurable outcomes such as perioperative strokes, MIs, revisions for bleeding and DSWI (Table 2).

Despite the above, a significant difference was found in long-term survival, in favor of the BITA vs. SITA group, as depicted in the Kaplan–Meier survival curves (Fig 2). The respective 5, 10 and 15-year survival rates were 68.8% vs. 62.5%, 56.5% vs. 40.8% and 43.5% vs. 31.4%, p = 0.002. In multivariable analysis of the matched groups, BITA revascularization was found to be associated with better survival, with a hazard ratio of 0.419 (95%CI 0.232–0.757, p = 0.004). As in the unmatched cohort, in the matched cohort additional variables were

	All		Unmatchee	d cohort n(%)	Matched cohort n(%)			
		SITA	BITA	P value	Standardized	SITA	BITA	P value	Standardized
	n = 394	n = 193	n = 201		Difference	n = 132	n = 132		Difference
Male	301(76.4%)	138(71.5%)	163(81.1%)	0.025 ^{Ch}	-0.227	95(72%)	102(77.3%)	0.41 ^{MN}	-0.122
Age(years), mean (SD)	65.65(11.53)	68.05(10.64)	63.33(11.89)	$< 0.001^{\rm IT}$	0.418	67.64(10.72)	66.24(10.88)	0.254 ^{PT}	0.13
NIDDM	128(32.5%)	70(36.3%)	58(28.9%)	0.116 ^{Ch}	0.159	39(29.5%)	46(34.8%)	0.419 ^{MN}	-0.114
IDDM	16(4.1%)	11(5.7%)	5(2.5%)	0.106 ^{Ch}	0.163	6(4.5.0%)	3(2.3%)	0.508 ^{MN}	0.125
COPD	37(9.4%)	21(10.9%)	16(8.0%)	0.32 ^{Ch}	0.1	15(11.4%)	12(9.1%)	0.648 ^{MN}	0.075
CHF	141(35.8%)	78(40.4%)	63(31.3%)	0.06 ^{Ch}	0.19	45(34.1%)	45(34.1%)	$> 0.999^{MN}$	0
CRF	40(10.2%)	24(12.4%)	16(8.0%)	0.141 ^{Ch}	0.148	17(12.9%)	12(9.1%)	0.424 ^{MN}	0.121
Recent MI	250(63.5%	135(69.9%)	115(57.2%)	0.009 ^{Ch}	0.267	84(63.6%)	83(62.9%)	$> 0.999^{MN}$	0.016
Age>70 years	154(39.1%)	83(43%)	71(35.3%)	0.118 ^{Ch}	0.158	57(43.2%)	58(43.9%)	$> 0.999^{MN}$	-0.015
Old MI	133(33.8%)	71(36.8%)	62(30.8%)	0.212 ^{Ch}	0.126	47(35.6%)	44(33.3%)	0.791 ^{MN}	0.048
Acute MI	214(54.3%)	122(63.2%)	92(45.8%)	0.001 ^{Ch}	0.356	75(56.8%)	68(51.5%)	0.45 ^{MN}	0.107
Unstable Angina	236(59.9%)	116(60.1%)	120(59.7%)	0.935 ^{Ch}	0.008	77(58.3%)	79(59.8%)	0.89 ^{MN}	-0.031
EF<30%	94(23.9%)	63(32.6%)	31(15.4%)	$< 0.001^{Ch}$	0.411	27(20.5%)	27(20.5%)	$> 0.999^{MN}$	0
IABP	326(82.7%)	154(79.8%)	172(85.6%)	0.129 ^{Ch}	-0.153	110(83.3%)	109(82.6%)	$> 0.999^{MN}$	0.02
ReDo	24(6.1%)	18(9.3%)	6(3.0%)	0.009 ^{Ch}	0.266	5(3.8%)	6(4.5%)	$> 0.999^{MN}$	-0.038
PVD	82(20.8%)	40(20.7%)	42(20.9%)	0.967 ^{Ch}	-0.004	32(24.2%)	29(22%)	0.766 ^{MN}	0.054
NOVS	291(73.9%)	139(72%)	152(75.6%)	0.416 ^{Ch}	-0.082	99(75.0%)	96(72.7%)	0.78 ^{MN}	0.052
Left Main disease	173(43.9%)	74(38.3%)	99(49.3%)	0.029 ^{Ch}	-0.221	59(44.7%)	55(41.7%)	0.699 ^{MN}	0.061
Prior PCI	80(20.3%)	47(24.4%)	33(16.4%)	0.05 ^{Ch}	0.198	28(21.2%)	27(20.5%)	$> 0.999^{MN}$	0.019
EuroSCORE, median (IQR)	11(9–14)	12(9.5–15)	10(8–12)	< 0.001 ^{MW}	0.592	12(9–14)	10(9–13)	0.052 ^{WL}	0.233
Logistic, median (IQR)	0.2023 (0.1086– 0.4082)	0.2898 (0.1454– 0.5013)	0.1597 (0.0955– 0.2885)	< 0.001 ^{MW}	0.391	0.2578 (0.1218– 0.4646)	0.181 (0.1094– 0.3602)	0.036 ^{WL}	0.275
Bypass No.≥3	254(64.5%)	116(60.1%)	138(68.7%)	0.076 ^{Ch}	-0.179	80(60.6%)	87(65.9%)	0.427 ^{MN}	-0.11
ОРСАВ	85(21.6)	41(21.2%)	44(21.9%)	0.876 ^{Ch}	-0.016	25(18.9%)	33(25%)	0.28 ^{MN}	-0.147
Patients operated after the year 2000	241(61.2%)	148(76.7%)	93(46.3%)	< 0.001 ^{Ch}	0.658	103(78%)	62(47%)	< 0.001 ^{MN}	2.242

Table 1. Preoperative and intraoperative characteristics of critical patients who underwent SITA and BITA grafting revascularizations—Unmatched and matched cohorts.

SITA: single internal thoracic artery revascularization, BITA: bilateral internal thoracic artery revascularization, SD: standard deviation, IQR: interquartile ratio, NIDDM: non-insulin-dependent diabetes mellitus, IDDM, insulin-dependent diabetes mellitus, COPD: chronic obstructive pulmonary disease, CHF: congestive heart failure, CRF: chronic renal failure, MI: myocardial infarction, EF: ejection fraction, IABP: intra-aortic balloon counter-pulsation, ReDo: redo operation, PVD: peripheral vascular disease NOVS: number of vessel disease, PCI: percutaneous coronary intervention, OPCAB: off-pump coronary artery bypass; IT-Independent samples t-test; PT-Paired t-test; Ch-Chi square test; MN-McNemar's test; MW-Mann-Whitney test; WL-Wilcoxon test

https://doi.org/10.1371/journal.pone.0255740.t001

found significant for increased mortality: end-organ damage following diabetes mellitus, old MI and the number of vessels that were revascularized. The respective HRs were 3.995 (95%CI 1.221–13.074, p = 0.022), 0.313 (95%CI 0.135–0.727, p = 0.007) and 5.95 (95%CI 2.455–14.425, p < 0.001).

Comment

A few studies [2-6, 17-19], together with two historic meta-analyses [7, 8], exhibited better late outcome among patients with multi-vessel coronary artery disease who underwent surgical myocardial revascularization that deployed BITA rather than SITA strategy. While the

	All	Un	matched cohort n	(%)	Matched cohort n (%)			
		SITA	BITA	P value	SITA	BITA	P value	
	n = 394	n = 193	n = 201		n = 132	n = 132		
Early mortality	42 (10.7%)	25 (13%)	17 (8.5%)	0.148 ^{Ch}	23 (17.4%)	15 (11.4%)	0.215 ^{MN}	
Deep infection	9 (2.3%)	4 (2.1%)	5 (2.5%)	>0.999 ^F	3 (2.3%)	4 (3.0%)	>0.999 ^{MN}	
Perioperative CVA	20 (5.1%)	8 (4.1%)	12 (6.0%)	0.409 ^{Ch}	6 (4.5%)	7 (5.3%)	>0.999 ^{MN}	
Perioperative MI	22 (5.6%)	13 (6.7%)	9 (4.5%)	0.329 ^{Ch}	8 (6.1%)	8 (6.1%)	>0.999 ^{MN}	
Revision for bleeding	14 (3.6%)	7 (3.6%)	7 (3.5%)	0.938 ^{Ch}	5 (3.8%)	5 (3.8%)	>0.999 ^{MN}	

Table 2. Early outcomes of SITA and BITA grafting revascularizations in critical patients—Unmatched and matched cohorts.

SITA: single internal thoracic artery revascularization, BITA: bilateral internal thoracic artery revascularization CVA: cerebrovascular accident, MI: myocardial infarction; Ch-Chi square test; MN-McNemar's test; F-Fisher's exact test.

https://doi.org/10.1371/journal.pone.0255740.t002

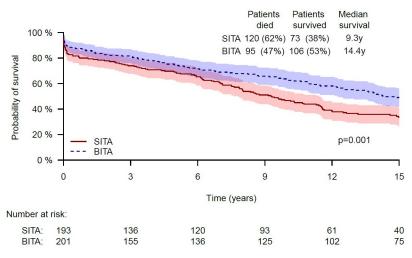
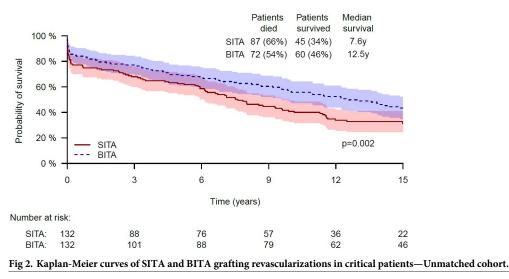


Fig 1. Kaplan-Meier curves of SITA and BITA grafting revascularizations in critical patients—Unmatched cohort.

https://doi.org/10.1371/journal.pone.0255740.g001



https://doi.org/10.1371/journal.pone.0255740.g002

recent ART trial demonstrated superiority of multiple arterial grafts over SITA revascularization [9], a randomized trial is currently evaluating the benefit of BITA revascularization [10]. However, most of these studies examined patients with anticipated prolonged life expectancy. These included most frequently young males, in a relatively healthy condition without severe comorbidities such as non-insulin-dependent diabetes mellitus, low left ventricular ejection fraction, recent MI, COPD, peripheral vascular disease and chronic renal failure. Moreover, BITA revascularization was rarely deployed in patients in need of emergent surgical intervention [2, 7].

A study by Schumer et al. [20] evaluated 212 patients who underwent emergent surgical revascularization among a total of 5,940 CABG procedures. Emergent patients were considered as those operated during an "evolving MI, shock (including the need for IABP insertion prior to surgery), ongoing ischemia, angiographic accident and other". In that study, patients classified as emergent versus non-emergent had significantly higher rates of early mortality (6.6% vs. 1.3%), postoperative need for IABP, bleeding, dialysis and prolonged length of stay. Notably, BITA revascularization was not part of the analysis, and the inclusion criteria for the emergent group were quite different from those of the current study.

A previous study from this group [21] evaluated the outcome of 215 patients, with the single inclusion criteria of preoperative insertion of an IABP between 1996 and 2001. The analysis revealed associations with reduced midterm (8 years) survival of the following: peripheral vascular disease, off-pump coronary artery bypass surgery, advanced age, prolonged cardiopulmonary bypass time, female gender and a decreased number of grafts. Although BITA revascularization was not scrutinized as part of the Cox analysis in that study, BITA demonstrated better midterm survival than SITA: 62.6% vs. 39.5%, p<0.001.

A retrospective analysis [22] of emergent or salvage coronary revascularization procedures at four northern European university hospitals included 614 patients with a preoperative state of acute coronary syndrome with ST elevation MI (38%), non-ST elevation MI (47%), and in need of inotropic drugs (14%) or a preoperative IABP insertion (13%). Eight percent of the patients endured cardiopulmonary resuscitation and 1% needed a cardiac massage during sternotomy. Hospital mortality was 13% and 41%, and five-year survival 79% and 15%, for the emergent and the salvage patients, respectively. While that study indicates the observable surgical challenge in critical patients, deducing a definite conclusion on the current analysis and revascularization strategies is difficult, for a number of reasons. For one, the heterogeneous features of that cohort were remarkable, both inherently and also compared to the current analysis. Moreover, BITA revascularization procedures were not performed in that study; 20% of the patients were operated exclusively with saphenous vein grafts and the salvage group included 53% non-ITA CABG procedures.

A few reports, including from our group, have focused on patients with acute or recent MIs [23–27] while assessing the outcomes and feasibility of arterial and BITA revascularization procedures or various surgical strategies such as off-pump or beating-heart on-pump procedures. Again, all the studies that focused on patient populations during or shortly after an ischemic myocardial insult differed from the current study in inclusion criteria.

In this study we evaluated long term outcome (up to 15 years) of 394 patients who underwent isolated surgical revascularization procedures deploying either single or bilateral ITAs in the setting of a critical state. The latter was determined by preoperative ventricular dysrhythmia, aborted sudden cardiac death, resuscitation, ventilation or the need for IABP insertion. We further examined these two revascularization strategies on two matched groups of 132 patients each. The high early mortality rate presented in this study (10.7% for the whole cohort) substantiates the authenticity of these patients being critically ill and in severe condition. Nonetheless, the criteria selected for this study differ from those of previous studies that evaluated high-risk patients, and that were based mostly on myocardial ischemia or infarction [23-30]. The two most important findings of the current study are the short-term safety (equal early mortality and morbidity for the two revascularization strategies), together with the long-term survival benefit gained by deploying the BITA revascularization strategy in high-risk patients.

In general, high-risk patients are not indiscriminately designated for SITA revascularization in our center, even in the face of serious comorbidities. On the contrary, our group's predisposition has been to routinely perform left-sided BITA revascularization for most patients. Consequently, surgeons who contributed to the current study were at large highly skilled in skeletonized ITA harvesting (for extra graft length) and in all technical aspects, strategies and configurations of BITA grafting that were previously described [11–13, 15, 31]. This familiarity with BITA skeletonization and configuration techniques should be noted as a clear prerequisite for the appropriateness and safety of BITA grafting in these high-risk patients.

The single-center retrospective observational design of this study bears some characteristic limitations. First and foremost, the definition used to classify a patient as critical may differ from that of other studies. Notably, in this study the definition did not include a few key elements such as clear ischemic insult, the need for inotropic or vasopressor support, and an acute preoperative oliguric state. As such, all assumptions and conclusions might be compromised if not considered in the exact context of our definition of a critical state. Moreover, the inclusion criteria selected may have caused an inevitable disparity between the patients included in the study, as the operative risk for a post resuscitated patient can differ substantially from that of a patient in whom an IABP was inserted as a preventive measure due to a highly disturbing coronary anatomy. In addition, the late outcome analysis focused merely on survival, while important information regarding late major adverse cardiac and cerebrovascular events was not available for all patients. Another limitation results from the prolonged time span, notably, a possible calendar bias. This was addressed by the inclusion of the surgical era (operations before or after the year 2000) within the multivariable analysis, as a possible confounder. Additionally, the surgical strategy executed i.e., the use of either SITA or BITA revascularization was determined by each surgeon, subjected to personal clinical judgement, and sometimes taken with unspecified or ambiguous reasons, without strict guidelines that dictate the predilection of either strategy. This, together with the general tendency to avoid BITA revascularization in patients with increased risk for DSWI, may have led to a treatment allocation bias.

In conclusion, this study showed comparable early outcomes, and improved long-term survival, following isolated CABG with BITA compared to SITA revascularization in patients with preoperative ventricular dysrhythmias, resuscitation, in need for preoperative mechanical ventilation or preoperative insertion of an IABP. In multivariate analysis, BITA strategy was found to be an independent predictor for long-term survival. Further studies are needed to determine the exact role of BITA revascularization in these high-risk patients.

Author Contributions

Conceptualization: Dmitry Pevni, Yanai Ben-Gal. Data curation: Orr Sela, Rephael Mohr. Formal analysis: Tomer Ziv-Baran. Investigation: Michal Fertouk, Tomer Ziv-Baran, Rephael Mohr. Methodology: Dmitry Pevni, Amir Kramer, Yanai Ben-Gal. Project administration: Orr Sela, Nachum Nesher, Yanai Ben-Gal.

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Supervision: Nachum Nesher.

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References

- Loop FD, Lytle BW, Cosgrove DM, Stewart RW, Goormastic M, Williams GW, et al. Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. N Engl J Med. 1986 Jan 2; 314(1):1–6. https://doi.org/10.1056/NEJM198601023140101 PMID: 3484393
- Lytle BW, Blackstone EH, Loop FD, Houghtaling PL, Arnold JH, Akhrass R, et al. Two internal thoracic artery grafts are better than one. J Thorac Cardiovasc Surg. 1999 May; 117(5):855–72. https://doi.org/ 10.1016/S0022-5223(99)70365-X PMID: 10220677
- Buxton BF, Komeda M, Fuller JA, Gordon I. Bilateral internal thoracic artery grafting may improve outcome of coronary artery surgery. Risk-adjusted survival. Circulation. 1998 Nov 10; 98(19 Suppl):II1–6. PMID: 9852872
- Ioannidis JP, Galanos O, Katritsis D, Connery CP, Drossos GE, Swistel DG, et al. Early mortality and morbidity of bilateral versus single internal thoracic artery revascularization: propensity and risk modeling. J Am Coll Cardiol. 2001 Feb; 37(2):521–8. https://doi.org/10.1016/s0735-1097(00)01112-8 PMID: 11216973
- Berreklouw E, Rademakers PP, Koster JM, van Leur L, van der Wielen BJ, Westers P. Better ischemic event-free survival after two internal thoracic artery grafts: 13 years of follow-up. Ann Thorac Surg. 2001 Nov; 72(5):1535–41. https://doi.org/10.1016/s0003-4975(01)03040-5 PMID: 11722039
- Burfeind WR Jr, Glower DD, Wechsler AS, Tuttle RH, Shaw LK, Harrell FE Jr, et al. Single versus multiple internal mammary artery grafting for coronary artery bypass: 15-year follow-up of a clinical practice trial. Circulation. 2004 Sep 14; 110(11 Suppl 1):II27–35. https://doi.org/10.1161/01.CIR.0000138193. 51635.6f PMID: 15364834
- Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. Lancet. 2001 Sep 15; 358 (9285):870–5. https://doi.org/10.1016/S0140-6736(01)06069-X PMID: 11567701
- Rizzoli G, Schiavon L, Bellini P. Does the use of bilateral internal mammary artery (IMA) grafts provide incremental benefit relative to the use of a single IMA graft? A meta-analysis approach. Eur J Cardiothorac Surg. 2002 Nov; 22(5):781–6. https://doi.org/10.1016/s1010-7940(02)00470-0 PMID: 12414046
- Taggart DP, Gaudino MF, Gerry S, Gray A, Lees B, Dimagli A, et al. Effect of total arterial grafting in the Arterial Revascularization Trial. J Thorac Cardiovasc Surg. 2020 Mar 19:Forthcoming-S0022-5223(20) 30591-2.
- Gaudino M, Alexander JH, Bakaeen FG, Ballman K, Barili F, Calafiore AM, et al. Randomized comparison of the clinical outcome of single versus multiple arterial grafts: the ROMA trial-rationale and study protocol. Eur J Cardiothorac Surg. 2017 Dec 1; 52(6):1031–1040. https://doi.org/10.1093/ejcts/ezx358 PMID: 29059371
- Ben-Gal Y, Gordon A, Ziv-Baran T, Farkash A, Mohr R, Kramer A, et al. Late Outcomes of In Situ versus Composite Bilateral Internal Thoracic Artery Revascularization. Ann Thorac Surg. 2020 Dec 27:S0003-4975(20)32174-3. https://doi.org/10.1016/j.athoracsur.2020.11.041 PMID: 33378695
- 12. Pevni D, Uretzky G, Mohr A, Braunstein R, Kramer A, Paz Y, et al. Routine use of bilateral skeletonized internal thoracic artery grafting: long-term results. Circulation. 2008 Aug 12; 118(7):705–12. https://doi.org/10.1161/CIRCULATIONAHA.107.756676 PMID: 18663087

- Matsa M, Paz Y, Gurevitch J, Shapira I, Kramer A, Pevny D, et al. Bilateral skeletonized internal thoracic artery grafts in patients with diabetes mellitus. J Thorac Cardiovasc Surg. 2001 Apr; 121(4):668–74. https://doi.org/10.1067/mtc.2001.112824 PMID: 11279406
- Pevni D, Mohr R, Kramer A, Paz Y, Nesher N, Ben-Gal Y. Are two internal thoracic grafts better than one? An analysis of 5301 cases. Eur J Cardiothorac Surg. 2019 Nov 1; 56(5):935–941. <u>https://doi.org/ 10.1093/ejcts/ezz094 PMID: 30957860</u>
- Gurevitch J, Kramer A, Locker C, Shapira I, Paz Y, Matsa M, et al. Technical aspects of double-skeletonized internal mammary artery grafting. Ann Thorac Surg. 2000 Mar; 69(3):841–6. https://doi.org/10. 1016/s0003-4975(99)01407-1 PMID: 10750770
- Roques F, Nashef SA, Michel P, Gauducheau E, de Vincentiis C, Baudet E, et al. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. Eur J Cardiothorac Surg. 1999 Jun; 15(6):816–22; discussion 822–3. https://doi.org/10.1016/ s1010-7940(99)00106-2 PMID: 10431864
- Yi G, Shine B, Rehman SM, Altman DG, Taggart DP. Effect of bilateral internal mammary artery grafts on long-term survival: a meta-analysis approach. Circulation. 2014 Aug 12; 130(7):539–45. <u>https://doi.org/10.1161/CIRCULATIONAHA.113.004255 PMID: 24916209</u>
- Lytle BW, Blackstone EH, Sabik JF, Houghtaling P, Loop FD, Cosgrove DM. The effect of bilateral internal thoracic artery grafting on survival during 20 postoperative years. Ann Thorac Surg. 2004 Dec; 78(6):2005–12; discussion 2012–4. https://doi.org/10.1016/j.athoracsur.2004.05.070 PMID: 15561021
- Ruttmann E, Fischler N, Sakic A, Chevtchik O, Alber H, Schistek R, et al. Second internal thoracic artery versus radial artery in coronary artery bypass grafting: a long-term, propensity score-matched follow-up study. Circulation. 2011 Sep 20; 124(12):1321–9. <u>https://doi.org/10.1161/CIRCULATIONAHA.111</u>. 030536 PMID: 21900082
- Schumer EM, Chaney JH, Trivedi JR, Linsky PL, Williams ML, Slaughter MS. Emergency Coronary Artery Bypass Grafting: Indications and Outcomes from 2003 through 2013. Tex Heart Inst J. 2016 Jun 1; 43(3):214–9. https://doi.org/10.14503/THIJ-14-4978 PMID: 27303236
- Hemo E, Medalion B, Mohr R, Paz Y, Kramer A, Uretzky G, et al. Long-term outcomes of coronary artery bypass grafting patients supported preoperatively with an intra-aortic balloon pump. J Thorac Cardiovasc Surg. 2014 Nov; 148(5):1869–75. <u>https://doi.org/10.1016/j.jtcvs.2013.12.063</u> PMID: 24521970
- Axelsson TA, Mennander A, Malmberg M, Gunn J, Jeppsson A, Gudbjartsson T. Is emergency and salvage coronary artery bypass grafting justified? The Nordic Emergency/Salvage coronary artery bypass grafting study. Eur J Cardiothorac Surg. 2016 May; 49(5):1451–6. https://doi.org/10.1093/ejcts/ezv388 PMID: 26582345
- Gaudino M, Glineur D, Mazza A, Papadatos S, Farina P, Etienne PY, et al. Long-Term Survival and Quality of Life of Patients Undergoing Emergency Coronary Artery Bypass Grafting for Postinfarction Cardiogenic Shock. Ann Thorac Surg. 2016 Mar; 101(3):960–6. https://doi.org/10.1016/j.athoracsur. 2015.08.066 PMID: 26518374
- 24. Santarpino G, Ruggieri VG, Mariscalco G, Bounader K, Beghi C, Fischlein T, et al. Outcome in Patients Having Salvage Coronary Artery Bypass Grafting. Am J Cardiol. 2015 Oct 15; 116(8):1193–8. https:// doi.org/10.1016/j.amjcard.2015.07.034 PMID: 26303635
- Loberman D, Pevni D, Mohr R, Paz Y, Nesher N, Midlij MK, et al. Should Bilateral Internal Thoracic Artery Grafting Be Used in Patients After Recent Myocardial Infarction? J Am Heart Assoc. 2017 Jul 21; 6(7):e005951. https://doi.org/10.1161/JAHA.117.005951 PMID: 28733432
- 26. Nesher N, Mohr R, Raviv Z, Ganiel A, Ben-Gal Y, Paz Y, et al. Similar long-term outcome for arterial myocardial revascularization performed after or within the first seven day of acute myocardial infarction. Health. 2013 Sep 29.
- Dominici C, Salsano A, Nenna A, Spadaccio C, Mariscalco G, Santini F, et al. On-pump beating-heart coronary artery bypass grafting in high-risk patients: A systematic review and meta-analysis. J Card Surg. 2020 Aug; 35(8):1958–1978. https://doi.org/10.1111/jocs.14780 PMID: 32643847
- Khaladj N, Bobylev D, Peterss S, Guenther S, Pichlmaier M, Bagaev E, et al. Immediate surgical coronary revascularisation in patients presenting with acute myocardial infarction. J Cardiothorac Surg. 2013 Jul 3; 8:167. https://doi.org/10.1186/1749-8090-8-167 PMID: 23819483
- 29. Rastan AJ, Eckenstein JI, Hentschel B, Funkat AK, Gummert JF, Doll N, et al. Emergency coronary artery bypass graft surgery for acute coronary syndrome: beating heart versus conventional cardioplegic cardiac arrest strategies. Circulation. 2006 Jul 4; 114(1 Suppl):I477–85. <u>https://doi.org/10.1161/</u> CIRCULATIONAHA.105.001545 PMID: 16820622

- Hagl C, Khaladj N, Peterss S, Martens A, Kutschka I, Goerler H, et al. Acute treatment of ST-segmentelevation myocardial infarction: is there a role for the cardiac surgeon? Ann Thorac Surg. 2009 Dec; 88(6):1786–92. https://doi.org/10.1016/j.athoracsur.2009.07.050 PMID: 19932235
- Pevni D, Mohr R, Lev-Ran O, Paz Y, Kramer A, Frolkis I, et al. Technical aspects of composite arterial grafting with double skeletonized internal thoracic arteries. Chest. 2003 May; 123(5):1348–54. <u>https:// doi.org/10.1378/chest.123.5.1348</u> PMID: 12740246