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Are three arteries better then two? Impact of using the radial artery in addition to bilateral internal thoracic artery grafting on long term survival.

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Abbreviations

AF: preoperative atrial fibrillation

BITA: Bilateral internal thoracic artery

BMI: body mass index

CABG: coronary artery bypass grafting

CCS: Canadian Cardiovascular Society

COPD: chronic obstructive pulmonary disease

CVA: cerebrovascular accident

CX: circumflex artery

DIA: Diagonal branch

DM-I: diabetes mellitus on insulin

DM-O: diabetes mellitus on oral treatment

EF: ejection fraction

IABP: need for postoperative intra-aortic balloon pump

LAD: left anterior descending artery

LMD: left main disease

LITA: left internal thoracic artery

LV: left ventricle

MI: myocardial infarction;

NYHA: New York Heart Association

OPCAB: off-pump coronary artery bypass

PCI: percutaneous coronary intervention

PSM: Propensity score matching

PVD: peripheral vascular disease

RA: radial artery

RCA: right coronary artery

RITA: right internal thoracic artery

RRT: postoperative replacement therapy

SV: saphenous vein

Central picture

Long term survival in patients receiving radial artery or saphenous vein in the context of bilateral internal thoracic artery grafting (BITA: Bilateral internal thoracic artery; RA: radial artery; SV: saphenous vein).

Central message

Long term survival in the context of bilateral internal thoracic artery grafting is not extended by using the radial artery in preference to saphenous vein **in select low risk patients.**

Perspective statement

Long term survival in the context of bilateral internal thoracic artery grafting is not extended by using the radial artery as the third arterial conduit in preference to saphenous vein also **in select low risk patients.** More data are needed before it is clear whether vein graft should be preferred as third conduit in this setting.

Abstract

Objective: Whether the use of the radial artery (RA) as third arterial conduit in addition to bilateral internal thoracic artery (BITA) is associated with better survival when compared to BITA plus saphenous vein (SV) remains to be determined. **Methods:** The study population included **a select low risk group of** 275 subjects who received BITA grafting with the RA as third arterial conduit (BITA+RA group) and 489 subjects who received BITA grafting with additional SV graft (BITA+SV). The RA was considered only in case of target stenosis ≥75%. We finally obtained 275 propensity score matched pairs for comparison.

Results: Operative mortality was 1(0.3%) and 2(0.7%) in the BITA+RA and BITA+SV groups respectively (P=0.56). After a mean follow-up time of 10.6±4.8 years the BITA+RA group the survival probability at 5, 10 and 15 years was 97.4±0.9%, 90.3±2.0% and 81.7±3.2% versus 97.0±1.0%, 94.1±1.5% and 82.1±3.4% (log-rank P=0.54, HR 1.16;95%CI 0.71-1.9). The two strategies showed comparable survival probabilities when RAs or SVs were used to graft the right coronary system only (P=0.79) or the left coronary system only (P=0.55). The lack of survival advantage in the BITA+RA group was confirmed in patients aged 60 or less (P=0.80) or aged more than 60 (P=0.53), in patients with and without diabetes mellitus (P=0.89 and P=0.54 respectively) and with or without left ventricular dysfunction (P=0.95 and P=0.65 respectively).

Conclusions: Long term survival in a select low risk group of patients receiving BITA grafting was not extended by using the RA as the third arterial conduit in preference to SV.

Word count: 248

Late survival after coronary artery bypass graft (CABG) surgery is improved when the left internal thoracic artery (LITA) is grafted to the left anterior descending (LAD) coronary artery [1]. The right internal thoracic artery (RITA) has been advocated to further improve long term revascularization outcomes [2]. Whether the use of the radial artery (RA) [3-5] as third arterial conduit in addition to bilateral internal thoracic artery (BITA) grafting is associated with better survival when compared to BITA plus saphenous vein (SV) remains to be determined with isolated small series reporting conflicting results [6,7].

Propensity score matching (PSM) based analyses are emerging as an attractive alternative in view of paucity of evidence from randomized controlled trials [8]. To investigate the impact of using the RA as third conduit instead of SV in the context of BITA grafting, we performed a single centre long term PSM comparison.

Methods

The study was conducted in accordance with the principles of the Declaration of Helsinki. The local audit committee approved the study, and the requirement for individual patient consent was waived. We retrospectively analysed prospectively collected data from The National Institute for Cardiovascular Outcomes Research (NICOR) NACSA registry on 1 June 2015 for all isolated first time CABG procedures performed at the Bristol Heart Institute, Bristol United Kingdom from 1996 to April 2015. Reproducible cleaning algorithms were applied to the database, which are regularly updated as required. Briefly, duplicate records and non-adult cardiac surgery entries were removed; transcriptional discrepancies harmonized; and clinical conflicts and extreme values corrected or removed. The data are returned regularly to the local units for validation.

Further details and definition of variables are available at http://www.ucl.ac.uk/nicor/audits/adultcardiac/datasets. Among 12247 isolated first time CABG cases performed at our institution during the study period**,** we selected subjects who met the following criteria: multivessel coronary disease including left main and/or LAD disease; requiring at least 3 grafts; CABG performed by using the following strategies: BITA grafting and RA as third arterial conduit with or without additional SV grafts (BITA+RA group) or BITA grafting with additional SV grafts only (BITA+SV). In the present series, the RA was considered only in case of target stenosis ≥75% and it was used a free graft proximally connected to the ascending aorta. The internal thoracic artery was used as a pedicle graft that remained proximally connected to its respective subclavian artery (in situ) or as a free graft proximally connected to other internal thoracic artery

Experimental conduits harvesting technique

During the study period the saphenous vein was exposed by a continuous longitudinal incision, the adventitial layer was stripped and side branches ligated. The vein was removed from the leg immediately after dissection and was manually gently distended using a syringe with heparinised normal saline or by connecting it to the ascending aorta. After distension, the vein was stored in the same fluid use to distend the vein at room temperature as previously described [9]. For the RA, if the results of the Allen's test were normal in both upper extremities, the monodominant extremity was selected and the conduit was harvested with an open technique as previously described [10].

Pre-treatment variables and study end-points

The effect of adding the RA as third arterial conduit instead of SV was adjusted for the following 25 pre-treatment variables including: age, gender, body mass index (BMI);

Canadian Cardiovascular Society (CCS) grade III or IV; New York Heart Association grade III or IV; previous myocardial infarction (MI) and MI within 30 days, previous percutaneous coronary intervention (PCI); diabetes mellitus on oral treatment (DM-O) or on insulin (DM-I); chronic obstructive pulmonary disease (COPD); hypertension; current smoking; serum creatinine ≥200 mmol/l, previous cerebrovascular accident (CVA); peripheral vascular disease (PVD); preoperative atrial fibrillation (AF); left main disease (LMD); non-LAD vessel diseased including Diagonal (DIA); circumflex (CX); right coronary artery (RCA); moderate left ventricle LV dysfunction; severe LV dysfunction; non elective priority, off-pump coronary artery bypass (OPCAB) and era of surgery (1996-2004 versus 2005-1015).

The short-term outcomes investigated were: the incidence of re-exploration for bleeding, need for sternal reconstruction, postoperative CVA, postoperative renal replacement therapy (RRT), need for postoperative intra-aortic balloon pump (IABP) and in hospital mortality. Long-term outcome investigated was all-cause late mortality. All-cause death is considered the most robust and unbiased index in cardiovascular research because no adjudication is required, thus avoiding inaccurate or biased documentation and clinical assessments [11]. Information about post-discharge mortality tracking was available for all patients (100%) and was obtained by linking the institutional database with the National General Register Office.

Statistical analysis

For baseline characteristics, variables are summarized as mean for continuous variables and proportion for categorical variables. Multiple imputation was used to address missing data (http://www.jstatsoft.org/v45/i07/). Information regarding baseline creatinine level showed the higher rate of missing information (87/764, 11%) (Supplementary Figure 1 and Supplementary Table 1). To control for measured potential confounders in the data set, a propensity score (PS) was generated for each patient from a multivariable logistic regression model based on pre-treatment covariates as independent variables with treatment type (BITA+RA versus BITA+SV) as a binary dependent variable (http://CRAN.Rproject.org/package=nonrandom) [12]. The resulting propensity score represented the probability of a patient undergoing CABG with BITA+RA grafting. Pairs of patients receiving BITA+RA and BITA+SV were derived using greedy 1:1 matching with a calliper of width of 0.2 standard deviation of the logit of the PS. The quality of the match was assessed by comparing selected pre-treatment variables in propensity score– matched patient using the standardized mean difference (SMD), by which an absolute standardized difference of greater than 10% is suggested to represent meaningful covariate imbalance [13]. Analytic methods for the estimation of the treatment effect in the matched sample included McNemar's to compare proportions. Kaplan–Meier survival curves between treated and untreated subjects in the matched sample were compared using a test described by Klein and Moeschberger (http://CRAN.R-project.org/package=survival). As sensitivity analysis, to partially address the limited sample size, we performed a time-segmented Cox analysis on early (within 30 days) and late mortality (beyond 30 days) by regressing the outcome on two independent variables: the treatment assignment (BITA+RA vs BITA+SV) and the estimated propensity score [12].

Results

The study population included 275 subjects who received BITA grafting with the RA as third arterial conduit with (n=41) or without (234) additional SV grafts (BITA+RA group) and 489 subjects who received BITA grafting with additional SV graft (BITA+SV). Patients characteristics distribution before and after PS matching are summarized in Table 1. **Patients who received the RA presented a low risk profile.** In the unmatched group, BITA+SV tended to present a higher burden of comorbidities. After matching the two groups were comparable for all pre-treatment variables.

Intraoperative data

Grafts target in the unmatched and matched groups are summarized in Table 2. Mean number of graft performed were 3.26±0.5 in the BITA+RA group versus 3.33±0.5 and 3.28±0.5 in the unmatched (P=0.06) and matched (P=0.66) BITA+SV groups respectively. The radial artery was used to graft the lateral wall territory in 150 (54%) cases and the right coronary system in the remaining 125(45%) cases. Overall, the target distribution for the LITA and the RITA was comparable between the two groups.

Operative outcomes

Operative outcomes are summarized in Table 3. In hospital mortality occurred in 4 (0.5%) cases with 1(0.3%) death in the BITA+RA group and 3 (0.6%) deaths in the unmatched BITA+SV group (P=1). After matching, the two groups were comparable for all operative outcomes investigated. Of note the rate of sternal wound reconstruction was particularly low in both groups.

Long term survival

The mean follow-up time among survivors was 10.6±4.8 years [max 17.3 years], and 10.5±4.5 years and 10.5±4.9 in the BITA+RA and BITA+SV groups respectively. In the BITA+RA group the survival probability at 5, 10 and 15 years was 97.4±0.9%, 90.3±2.0% and 81.7±3.2%. In the unmatched BITA+SV group the survival probability at 5, 10 and 15 years was 96.8±0.8%, 93.6±0.1% and 83.8±2.5% (log-rank P=0.36 compared to BITA+SV group). In the matched BITA+SV group the survival probability at 5, 10 and 15 years was 97.0±1.0%, 94.1±1.5% and 82.1±3.4% (log-rank P=0.54, HR 1.16;95%CI 0.71-1.91 compared to BITA+SV group, Figure 1 left). When the analysis was restricted to BITA+RA patients receiving total arterial revascularization only by excluding cases with addition SV graft (n=41), the two strategy continued to show comparable survival (P=0.34, Figure 1 right). The two strategies showed comparable survival probabilities when RAs or SVs were used to graft the right coronary system only (P=0.79) or the left coronary system only (P=0.55) (Figure 2) or when used in the context of in-situ BITA grafting (P=0.93) or with a free RITA (P=0.30) (Figure 3). Time segmented PS adjusted Cox regression models showed that the use of the RA did not significantly impact on early (HR 0.29;95% 0.03-2.72;P=0.28) and late mortality (HR 1.27;95% 0.79-2.04;P=0.32; Figure 4).

Discussion

The main finding of the present study is that in **a select low risk group of** patients receiving BITA grafting, the addition of the RA as third arterial conduit was not associated with improved long term survival when compared to a matched group of patients receiving BITA with additional SV. The lack of survival benefit was present when the RA was used to graft both the left and the right coronary systems. In addition, when the analysis was restricted to patients receiving total arterial revascularization by using BITA and RA without additional SV graft, late survival probabilities remained comparable to those observed in subjects receiving BITA and additional SV grafts only. Furthermore, BITA+RA and BITA+SV groups showed comparable operative outcomes.

There remains controversy on whether the use of the RA instead of SV in BITA grafting is associated with a further improvement in long term outcomes. To date three small series have reported on the direct comparison between the RA and SV in addition to BITA grafting with conflicting results. Di Mauro et al. [4] reported a survival rate at 8 years of 91.9±2.9% in 87 patients receiving BITA+RA compared to the 95.6±0.9% in patients receiving BITA+SV (P=0.12). More recently Grau et al. [6], recently published a series of 183 patients receiving BITA+RA. Long term survival probabilities in BITA+RA groups were comparable to those in BITA+SV groups (P=0.25) although they observed that at 10 years, the survival curves of the groups crossed and, between 10 and 14 years, the BITA+RA group demonstrated higher survival (P=0.04). However, the phenomenon of crossing survival curves is common when a treatment is associated with decreased early survival but may offer long term benefit. The observed trend of decreased early survival in patients receiving the RA instead of SV is likely to be related to selection bias. In fact the use of the RA per se does not increase operative mortality [14] and the RA patency has been demonstrated to be non-inferior to SV patency at early angiographic follow-up [15]. Mohammadi et al. [7] recently reported comparable long term survival in 249 matched pairs of patients receiving BITA+RA versus BITA+SV (P=0.44). However, the main limitation of this study is that many of the RA grafts (41.4%) were placed to noncritical coronary targets (ie, stenosis 50% to 70%). It is largely demonstrated that the degree of proximal stenosis affects RA performance [16,17] and this limitation makes it difficult to interpret this findings.

To the best of our knowledge, the present study is the largest matched series reported on the use of RA as third arterial conduit in the context of BITA grafting instead of additional SV graft where the RA has been used to graft vessels with ≥75% proximal stenosis in all cases thus fulfilling current recommendations for the use of the RA [14,15]. We found that the use of the RA did not increase operative risk although we found a trend toward a higher rate of re-exploration for bleeding in the BITA+RA groups, suggesting the need of extra-attention during haemostasis when using three arterial conduits. Of note, the incidence of sternal wound reconstruction observed in this series was particularly low thus confirming that in a low risk population (overall prevalence of diabetes on insulin ~2%) the use of BITA grafting is safe [18].

However, long term survival analysis showed that the additional of use of RA in this low risk population was not associated with a survival benefit during 15 years follow-up and this result was found when the RA was used to graft both the left and the right coronary systems. Moreover, the RA did not improve survival also in cases of total arterial revascularization without additional SV grafts.

The lack of survival benefit by using the RA as a third graft might be partially explained by the determinant role of the two internal thoracic arteries which were likely used to graft the two most important myocardial territories with the RA left to grafts the third territory in order of clinical significance [19]. In this case the choice of preferring the RA over SVG would have limited prognostic implication. Moreover, Hayward et al. [20] have previously reported on angiographic follow-up of a limited number of RAs used to graft the third and fourth targets in the Radial Artery Patency and Clinical Outcomes (RAPCO) study. These were found to have poorer patency rate than vein grafts when placed to the third and fourth position thus suggesting the hypothesis that venous conduits might be preferable for third and fourth grafts. However this analysis was largely underpowered for conclusions to be drawn. Nevertheless, it is well demonstrated that the RA patency is largely related to the magnitude of the vascular bed for run-off which is influenced not only by the target stenosis degree but also by the vessel diameter, diffuseness of disease, left or right dominance and quality of the distal arterial bed [16,17,20]. We can speculate that the angiographic superiority of the RA over SV might be lost when the RA is used to graft the third target in order of expected run-off thus eliminating any potential survival benefit. It can be argued that the present study population was highly selected with low burden of comorbidities and it does not represent the majority of patients commonly referred for CABG. However, a multiple arterial graft strategy is usually adopted in low risk patients with prolonged life expectation. In fact its beneficial impact on survival may be delayed by as much as a 7 to 10 years but persists beyond that time period; thus, it may be less appreciated in older patients with coexistent morbidities and limited life expectancy [21-24]. Of note, in the largest randomized trial investigating the impact of using a second arterial graft [25], mean age at randomization was 63 years and the prevalence of diabetes on insulin was 5.6% only.

The main limitation of the present study is that no follow-up data were available on the cause of death (cardiac versus non-cardiac), recurrence of angina, need for repeat revascularization and graft patency to compare the two groups. All-cause mortality might not be an adequate outcome to assess clinical difference in the present highly select low risk patient population.

As a consequence, the conflicting findings in the literature might be partially explained by different patient selection. Moreover, the relatively small sample size can partially account for lack of survival benefit by using the RA. However, the non-significant trend towards lower survival probabilities in the BITA+RA group, also reported by others [4,5] limits the potential role of type beta error in rejecting the hypothesis of the superiority of the RA. Finally, the study was observational on prospectively collected data and selection bias cannot be excluded despite propensity score adjustment.

In conclusion**, we found that long term survival in a highly select group of patients receiving BITA grafting was not extended by using the RA as the third arterial conduit in preference to SV in patients undergoing first time coronary revascularization.**

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Table 1. Pre-treatment variable distribution in the BITA+RA group and in the unmatched and matched BITA+SV groups

	BITA+RA		Unmatched BITA+SV		SMD	P	Matched BITA+SV		SMD	P
	N=275		N=489				N=275			
	N	%	n	%			n	%		
Age (years)					8	0.3			7	0.4
<60	176	64.0	317	64.8			181	65.8		
60-69	70	25.5	142	29.0			78	28.4		
70-79	28	10.2	26	5.3			12	4.4		
≥80	1	0.4	4	0.8			4	1.5		
Female	18	6.5	29	5.9	3	0.8	16	5.8	3	0.8
BMI≥30	59	21.5	110	22.5	13	0.08	49	17.8	2	0.8
CCS III/IV	114	41.5	224	45.8	8	0.3	114	41.5	0	1
NYHA III/IV	70	25.5	87	17.8	19	0.01	66	24.0	3	0.7
Past MI	115	41.8	220	45.0	6	0.44	115	41.8	0	1
MI within 30 days	34	12.4	89	18.2	16	0.04	36	13.1	2	0.9
Past PCI	6	2.2	23	4.7	14	0.1	5	1.8	3	1
DM-O	13	4.7	12	2.5	12	0.13	11	4.0	4	0.83
DM-I	5	1.8	12	2.5	4	0.75	4	1.5	3	1
Hypertension	171	62.2	317	64.8	5	0.51	177	64.4	5	0.65
Smoking	47	17.1	77	15.7	4	0.70	49	17.8	2	0.91
Creatinine≥200mmol	1	0.4	2	0.4	1	1	2	0.7	5	1
COPD	8	2.9	22	4.5	8	0.37	7	2.5	2	1

CVA	10	3.6	17	3.5	1	1	11	4.0	2	1
PVD	17	6.2	24	4.9	6	0.56	16	5.8	2	1
AF	5	1.8	4	0.8	8	0.38	4	1.5	3	1
LMD	52	18.9	96	19.6	2	0.8	57	20.7	6	0.7
Vessel diseased										
CX	262	95.3	460	94.1	5	0.6	265	96.4	4	0.7
DIA	57	20.7	152	31.1	23	0.003	57	20.7	0	1
RCA	248	90.2	430	87.9	7	0.4	250	90.9	2	0.9
LV function										
EF 0.30-0.49	30	10.9	74	15.1	13	0.13	24	8.7	7	0.47
EF <0.30	3	1.1	6	1.2	1	1	4	1.5	3	1
Non elective	112	40.7	210	42.9	5	0.6	110	40.0	1	0.9
Performed by trainee	93	33.8	207	42.3	17	0.02	93	33.8	1	1
OPCAB	103	37.5	209	42.7	11	0.2	110	40.0	5	0.6
Year 1996-2005	176	64.0	296	60.5	6	0.3	167	60.7	2	0.7
2006-2015	99	36.0	193	39.5			108	39.3		

BITA: Bilateral internal thoracic artery; RA: radial artery; SV: saphenous vein; BMI: body mass index; CCS: Canadian Cardiovascular Society; NYHA: New York Heart Association; MI: previous myocardial infarction; PCI: percutaneous coronary intervention; DM-O: diabetes mellitus on oral treatment; DM-I: diabetes mellitus on insulin; COPD: chronic obstructive pulmonary disease; CVA: previous cerebrovascular accident; PVD: peripheral vascular disease; AF: preoperative atrial fibrillation; LMD: left main disease; DIA: Diagonal; CX: circumflex; RCA: right coronary artery; LV: left ventricle; EF: ejection fraction; OPCAB: off-pump coronary artery bypass

Table 2. Grafts target in the BITA+RA group and in the unmatched and matched BITA+SV groups

	BITA+RA N=275	**Unmatched BITA+SV N=489**	**Matched BITA+SV N=275**
RA target	CX/DIA = 150 (54%) RCA=125(45%)	-	-
SV target	CX/DIA=29 (10%) RCA=12(4%)	CX/DIA=293 (60%) RCA=217(44%) CX+RCA=70 (14%)	CX/DIA=117 (43%) RCA=129(47%) CX+RCA=26(9%)
LITA target	LAD in situ=199(72%) CX/DIA in situ=76(28%)	LAD in situ=345(71%) CX/DIA in situ=144(29%)	LAD in situ=203(74%) CX/DIA=72(26%)
RITA target	LAD in situ=70(25%) CX/DIA in situ=54 (20%) CX/DIA free=38(14%) RCA in situ=98(36%) RCA free=15(5%)	LAD in situ=128(26%) LAD free=8(2%) CX/DIA in situ=162(33%) CX/DIA free=66(13%) RCA in situ=103(21%) RCA free=22(0.5%)	LAD in situ=64(23%) LAD free=3(1%) CX/DIA in situ=95(35%) CX/DIA free=32(11%) RCA in situ=67(24%) RCA free=14(6%)

BITA: Bilateral internal thoracic artery; RA: radial artery; SV: saphenous vein; LITA: left internal thoracic artery; RITA: right internal thoracic artery; LAD: left anterior descending; CX: circumflex artery; DIA: Diagonal; CX: circumflex; RCA: right coronary artery

Table 3. Operative outcomes in the BITA+RA group and in the unmatched and matched BITA+SV groups

	BITA+RA	Unmatched BITA+SV	P	Matched BITA+SV	P
	N=275	N=489		N=275	
In hospital mortality	1(0.3%)	3(0.6%)	0.64	2(0.7%)	0.56
Re-exploration for bleeding	12(4.4%)	18(3.7%)	0.64	6(2.2%)	0.15
Sternal wound reconstruction	1(0.3%)	6(1.2%)	0.22	1(0.4%)	1
Postoperative cerebrovascular accident	1(0.3%)	8(1.9%)	0.11	6(2.2%)	0.057
Need for renal replacement therapy	3(1.1%)	7(1.4%)	0.69	4(1.4%)	0.70
Need for postoperative IABP	3(1.1%)	10(2.0%)	0.32	4(1.4%)	0.70

BITA: Bilateral internal thoracic artery; RA: radial artery; SV: saphenous vein; IABP: intra-aortic balloon pump

Figure Legend

Figure 1. Survival curve probabilities comparison between BITA+RA and BITA+SV groups in the overall matched samples (left) and using BITA+RA subgroup with total arterial revascularization (right) (BITA: Bilateral internal thoracic artery; RA: radial artery; SV: saphenous vein)

Figure 2. Survival curve probabilities comparison between BITA+RA and BITA+SV groups according to the third conduit target (BITA: Bilateral internal thoracic artery; RA: radial artery; SV: saphenous vein)

Figure 3. Survival curve probabilities comparison between BITA+RA and BITA+SV groups according to BITA configuration (BITA: Bilateral internal thoracic artery; RITA: right internal thoracic artery; RA: radial artery; SV: saphenous vein)

Figure 4. Survival probabilities comparison between BITA+RA and BITA+SV groups in a time segmented propensity score adjusted analysis (BITA: Bilateral internal thoracic artery; RA: radial artery; SV: saphenous vein)