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Age cut-off for the loss of benefit from bilateral internal thoracic artery grafting☆

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Abstract

Objectives: To identify the age-related benefit of single and bilateral internal thoracic artery (ITA) grafting on long-term cardiac-related survival in patients who survived from primary isolated coronary artery bypass grafting (CABG). **Methods:** A unicenter study was conducted on 12,231 consecutive survivors from primary isolated CABG who received single (n = 9566 patients) or bilateral (n = 1388 patients) ITA grafts, or vein grafts only (n = 1277 patients) between 1992 and 2005. Data was collected prospectively. The Cox regression model estimates the hazard ratio of each independent variable on cardiac-specific survival over the entire length of follow-up. Age was a significant covariate into the statistical model. The mean follow-up was 5.7 ± 3.7 years and 100% complete as of December 2005. The date and cause of death were obtained from the regional statistical institute. **Results:** After adjustments for different risk factors, the cardiac-related survival benefit in patients undergoing CABG with two ITAs was superior to that of single ITA grafting up to 60 years of age, displaying a constant decrease over time. The use of a single ITA was beneficial on cardiac-related survival in all age groups, including octogenarians, compared to patients receiving only vein grafts. **Conclusions:** The use of at least one ITA is associated with increased long-term cardiac-specific survival in all age groups compared to venous-only CABG, even in octogenarians. The additional survival benefit of using a second ITA decreases gradually with age, and is lost after 60 years of age.

Keywords: Coronary artery bypass; Bilateral internal thoracic arteries; Long-term survival

1. Introduction

The superiority of the single internal thoracic artery (ITA) as a graft in coronary artery bypass grafting (CABG) is widely accepted with documented excellent long-term results. Bilateral ITA grafting is associated with an even greater long-term survival advantage [1—4]. Several studies have revealed that the use of either ITAs or multiple ITA grafting was also associated with a reduction of myocardial infarction, re-operation, and need for future percutaneous coronary interventions [5,6]. However, bilateral ITA grafting has traditionally been performed in the younger patients presenting with coronary artery disease, although no studies have thus far specified the age range where this benefit could be lost. In the present study, we sought to identify the age-related benefit of single and bilateral (ITA) grafting on long-term cardiac-related survival in a large number of survivors from primary isolated CABG.

2. Materials and methods

2.1. Patients

Patient and operative information was reviewed from the computerized cardiac surgical database that was collected prospectively for all patients. We retrospectively analyzed data for all 12,231 consecutive patients who survived from their primary isolated CABG surgery and were discharged from hospital between January 1992 and December 2005 at the Quebec Heart Institute, Quebec City, Canada. Three subgroups were identified on the basis of the number of ITAs used (none (n = 1277 patients), one (n = 9566 patients), or two (n = 1388 patients)) during CABG surgery to evaluate and compare cardiac-specific survival in each group. Cardiac-specific survival and Cox regression analyses were performed to assess long-term survival and overall impact of ITA use on cardiac-related death. Cardiac death was defined as any cardiac-related, sudden, or unknown death. Stroke was considered as cardiac death. The date and cause of death were obtained from the Quebec statistical institute. All patients without a Quebec provincial health insurance number, for whom the long-term follow-up data might have

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been incomplete, were excluded from the study. Follow-up for 12,231 patients enrolled was 100% complete as of December 2005 (i.e. 5.7 ± 3.7 years).

2.2. Statistical analysis

Results are expressed as mean ± SD or percentage for continuous and categorical variables, respectively. Patients were censored at the time of last complete information collection (December 2005). Patients with non-cardiac death were censored at the time of death. Continuous and dichotomous variables were analyzed using one-way ANOVA or chi-square test, respectively. Survival function was obtained from the Nelson–Aalen estimator of the cumulative hazard rate. The Cox regression model estimates the hazard ratio of each independent variable on cardiac-specific survival over the entire length of follow-up. These independent variables were age, gender, non-insulin dependent diabetes, insulin dependent diabetes, chronic renal failure (serum creatinine $\geq$150 μmol/l), peripheral vascular disease, low ejection fraction (ejection fraction of 35% or less), chronic obstructive pulmonary disease, previous myocardial infarction, triple vessel disease, hypercholesterolemia, previous cerebro-vascular accident, hypertension, use of internal thoracic artery (none, one, or both), and obesity (body mass index $\geq$30 kg m^2). All parameters were initially analyzed using univariate Cox regression models. Variables with a probability value $<$0.25 were candidates for the multivariate Cox regression model building. Selection variables with interaction terms were performed using a forward approach. Akaike's information criteria and Schwarz's Bayesian criteria were used to compare candidate models. The same approach was performed to include interaction terms in the Cox model. Martingale residuals were used to examine the functional form of the continuous variable age and to determine that no transformation was necessary. After model building, adequacy of the proportional hazards assumption was checked. To check the proportionality assumption, first the graphical representation of the logarithm cumulative hazard rates vs time was used to assess parallelism and constant separation among the different values of nominal variables, whereas the continuous variable age was stratified into four disjointed strata. Second, an artificially time-dependent covariate was added to the model to test the proportionality assumption. For all variables in the final model, proportional hazards assumptions were not rejected, since local tests linked to the time-dependent covariates were not significant and scatter plots were roughly constant over time. The graphical representations of martingale and deviance residuals vs risk scores did not suggest any potential outliers. Significance was ascribed with p values $<$0.05. Log-rank tests were performed at these identified intervals, for accordingly censored data, to obtain specific respective p values. Analyses were performed using the statistical software version package of SAS 9.1.3 (SAS Institute Inc., Cary, NC).

3. Results

Three subgroups were identified on the basis of none (n = 1277 patients), one (n = 9566 patients), or two (n = 1388 patients) ITAs used during surgery. Among study patients (n = 12,231) who underwent isolated primary CABG surgery and survived to hospital discharge at our institution between 1992 and 2005, 9566 (78.2%) had one ITA, and 1388 (11.3%) had both ITAs used, while CABG was performed without ITA grafting in 1277 (10.5%) patients. Perioperative characteristics for patients in the three study groups are listed in Table 1. Overall mean duration of follow-up was 5.7 ± 3.7 years. It was 5.9 ± 3.0 years for patients with single ITA use, 6.6 ± 4.0 years for patients with bilateral ITA use, and 5.5 ± 3.7 years for patients without ITA use. During follow-up, there were a total of 733 cardiac-related deaths in our cohort of patients; 529 in patients where only one ITA was used, 37 in patients with bilateral ITA utilization, and 167 in patients with no ITA grafting, respectively.

3.1. Survival analysis

Unadjusted cardiac-specific survival rates (Fig. 1) at 5, 7, and 10 years were 98.4%, 97.8%, and 96.5% for patients with

Table 1
Perioperative data in patients with one, two, and no internal thoracic artery grafting

	No ITA, n = 1277	1 ITA, n = 9566	2 ITA, n = 1388	p value
Female gender (%)	41.3	23.4	10.7	<0.0001
Age (mean ± SD)	70.5 ± 8.9	63.7 ± 9.6	55.0 ± 8.7	0.0002
BMI (mean ± SD)	27.3 ± 5.1	27.7 ± 4.5	27.3 ± 3.7	<0.0001
Previous MI (%)	60.9	53.7	52.1	<0.0001
Cerebro-vascular accident (%)	11.5	6.5	3.5	<0.0001
Chronic pulmonary disease (%)	23.1	15.8	8.4	<0.0001
Chronic renal failure (%)	15.9	8.7	3.7	<0.0001
Hypertension (%)	65.7	59.9	45.0	<0.0001
Diabetes (%)	31.9	31.0	10.9	<0.0001
Insulin-dependent (%)	10.1	9.6	2.5	<0.0001
Dyslipidemia (%)	64.6	69.6	67.1	0.0006
Urgent/emergent operation (%)	21.5	20.5	19.7	0.002
Peripheral vascular disease (%)	23.1	14.8	8.4	<0.0001
Low ejection fraction (<35%)	9.3	5.0	2.2	<0.0001
Three-vessel disease (%)	62.1	59.4	64.2	0.001
Vessels bypassed (mean ± SD)	3.1 ± 1.0	3.3 ± 1.0	3.5 ± 0.9	<0.0001
Mean follow-up (mean ± SD)	5.9 ± 3.0	5.5 ± 3.7	6.6 ± 4.0	<0.0001

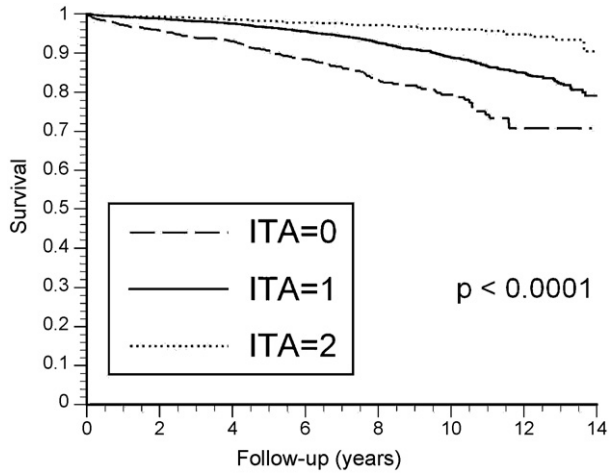

Fig. 1. Unadjusted cardiac-specific survival analysis in patients with one, two, and no internal thoracic artery grafting.

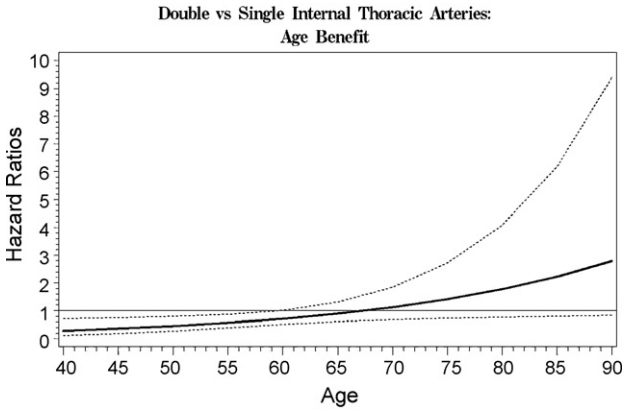

Fig. 2. Hazard ratios and 95% confidence intervals for bilateral vs single ITA grafting according to age of patients at the time of surgery.

bilateral ITA use, which were significantly higher ($p < 0.0001$) compared to the patients where one (96.6%, 94.3%, and 88.9%, respectively) or no ITA were used (90.7%, 86.4%, and 79.4%, respectively), over the same follow-up period. Unadjusted cardiac-specific survival rates for patients with single ITA use were significantly higher ($p < 0.0001$) compared to the patients without ITA use.

3.2. Cox multivariate analysis

Cox multivariate proportional hazards analysis was performed to control for confounding variables. Independent predictors of late cardiac-related deaths based on this analysis are indicated in Table 2. The Cox regression model building demonstrated that among the selected variables there was an interaction between age and bilateral vs single ITA use. After adjustments for different selected variables, the cardiac-related survival benefit in patients undergoing CABG with two ITAs was significantly superior to that of single ITA grafting up to the seventh decade of life, displaying a constant decrease over time (Fig. 2). This superiority is lost after 60 years. Hazard ratio of the different selected categories of age in patients with bilateral ITA grafting compared to the patients with single ITA grafting is depicted in Table 3. The use of a single ITA was beneficial on cardiac-related survival in all age groups, including octogenarians, compared to patients receiving only vein grafts. Hazard ratio of the different selected age categories of age in patients with single ITA grafting compared to the patients with no ITA grafting are depicted in Table 4.

Table 2
Predictors of long-term cardiac death expressed by hazard ratio: multivariate Cox regression analysis

Variable	Hazard ratio (95% CI)	*p* value
Age	1.04 (1.02–1.06)	<0.0001
Non-insulin dependent diabetes	1.10 (0.92–1.32)	0.3
Insulin dependent diabetes	1.85 (1.48–2.31)	<0.0001
Hypertension	1.20 (1.03–1.40)	0.01
Cerebro-vascular accident	2.24 (1.62–3.09)	<0.0001
Previous myocardial infarction	1.61 (1.32–1.94)	<0.0001
Low ejection fraction (<35%)	2.33 (1.14–3.17)	<0.0001
Peripheral vascular disease	1.59 (1.41–2.01)	<0.0001
Chronic renal failure	2.25 (1.84–2.72)	<0.0001
SITA vs NITA use	0.54 (0.11–2.69)	0.5
BITA vs SITA use[a]	0.02 (0.002–0.40)	0.009
Age–single ITA interaction	1.00 (0.98–1.02)	0.8
Age–bilateral ITA interaction	1.04 (1.01–1.09)	0.03

SITA: single internal thoracic artery; NITA: no internal thoracic artery; BITA: bilateral internal thoracic artery.
[a] Hazard ratio is influenced by age.

Table 3
Hazard ratio of cardiac-related survival benefit in patients with bilateral internal thoracic artery vs single internal thoracic grafting in different age groups

Age (years)	Hazard ratio (95% CI)	*p* value
50	0.45 (0.25–0.78)	0.005
51	0.47 (0.28–0.79)	0.005
52	0.49 (0.30–0.81)	0.005
53	0.51 (0.32–0.82)	0.005
54	0.54 (0.34–0.84)	0.006
55	0.56 (0.37–0.86)	0.007
56	0.59 (0.40–0.88)	0.009
57	0.62 (0.42–0.90)	0.013
58	0.65 (0.45–0.93)	0.019
59	0.68 (0.48–0.96)	0.03
60	0.71 (0.50–1.00)	0.05
61	0.74 (0.53–1.04)	0.09
62	0.78 (0.55–1.10)	0.15
63	0.81 (0.57–1.16)	0.25
64	0.85 (0.59–1.22)	0.39
65	0.89 (0.61–1.30)	0.56
66	0.93 (0.62–1.39)	0.74
67	0.98 (0.64–1.48)	0.92
68	1.02 (0.65–1.59)	0.91
69	1.07 (0.67–1.71)	0.76
70	1.12 (0.68–1.84)	0.64
71	1.17 (0.69–1.99)	0.54
72	1.23 (0.70–2.15)	0.46
73	1.28 (0.71–2.32)	0.40
74	1.34 (0.72–2.51)	0.35
75	1.40 (0.72–2.72)	0.30
76	1.47 (0.73–2.95)	0.27
77	1.54 (0.74–3.20)	0.24
78	1.61 (0.75–3.47)	0.21
79	1.69 (0.75–3.76)	0.19
80	1.76 (0.76–4.08)	0.18

Table 4
Hazard ratio of cardiac-related survival benefit in patients with single internal thoracic artery vs no internal thoracic grafting (use of veins only) in different age groups

Age (years)	Hazard ratio (95% CI)	*p* value
50	0.60 (0.36–0.99)	0.048
51	0.61 (0.37–0.98)	0.044
52	0.61 (0.38–0.96)	0.036
53	0.61 (0.39–0.95)	0.029
54	0.61 (0.40–0.93)	0.021
55	0.61 (0.41–0.91)	0.017
56	0.61 (0.42–0.90)	0.012
57	0.61 (0.43–0.88)	0.009
58	0.61 (0.44–0.87)	0.006
59	0.62 (0.44–0.85)	0.003
60	0.62 (0.45–0.84)	0.002
61	0.62 (0.46–0.83)	0.001
62	0.62 (0.47–0.81)	<0.0001
63	0.62 (0.48–0.80)	<0.0001
64	0.62 (0.49–0.79)	<0.0001
65	0.62 (0.50–0.78)	<0.0001
66	0.63 (0.50–0.78)	<0.0001
67	0.63 (0.51–0.77)	<0.0001
68	0.63 (0.52–0.76)	<0.0001
69	0.63 (0.52–0.76)	<0.0001
70	0.63 (0.52–0.76)	<0.0001
71	0.63 (0.53–0.76)	<0.0001
72	0.63 (0.53–0.76)	<0.0001
73	0.64 (0.53–0.77)	<0.0001
74	0.64 (0.52–0.77)	<0.0001
75	0.64 (0.52–0.78)	<0.0001
76	0.64 (0.51–0.79)	<0.0001
77	0.64 (0.51–0.81)	<0.0001
78	0.64 (0.50–0.82)	0.0004
79	0.64 (0.50–0.83)	0.0009
80	0.64 (0.49–0.85)	0.001

4. Discussion

The long-term results of CABG surgery are influenced by several factors, including the type of conduit used for bypasses. The use of ITA has been associated with improved long-term outcome after CABG [7]. Given the clinical evidence of long-term superiority of ITAs over venous grafts after CABG surgery, bilateral ITA grafting can be expected to provide an additional beneficial impact on patients' survival. Accordingly, previous authors [8] documented a significant increase in survival after bilateral ITA use in a non-randomized study.

In the current era, the use of at least one ITA is the gold standard procedure for CABG surgery, and particular settings where no ITA is used are extremely limited. In the present study the use of a single ITA was independently associated with better cardiac-specific survival compared to patients for whom no ITA was used as a graft. This benefit was present in all age groups of patients during follow-up. Octogenarians, despite a lower life expectancy, have also experienced a better cardiac-related survival with the use of an ITA.

Bilateral ITA grafting is better in terms of long-term cardiac-specific survival than single ITA grafting, however we found that the benefit was not present in all age ranges of patients. The significant cardiac-specific survival benefit of bilateral ITA use is lost after the age of 60 when compared to patients with single ITA use. Between 60 and 65 years of age the benefit gradually becomes not only statistically but also clinically non-significant. As bilateral ITA grafting has traditionally been preferentially performed in low surgical risk patients with long life expectancy, outcome analysis could be biased by preoperative patient selection. The Cox regression model has been used to adjust the final results by neutralizing the selected risk factors. The negative impact of these variables in the long-term outcomes of patients undergoing isolated CABG surgery has been extensively studied [9,10].

Although some earlier studies demonstrated no survival benefit for bilateral ITA grafting [11–13], recent studies are consistent with our data with respect to improved long-term survival associated with this approach [2,5,14]. However, none of these studies showed the age cut-off for the loss of benefit with this technique. Sergeant et al. [15] in a study with a large number of patients also showed the loss of survival benefit in the patients entering the seventh decade of life. Although the choice of surgical technique should be individualized for each patient, our study shows that the use of bilateral ITA is not associated with a better cardiac-related survival after 60 years of age compared to single ITA grafting, even in low-risk patients. In a multivariate analysis, age was an independent predictor for the loss of survival benefit associated with bilateral ITA grafting. Because this approach is associated with more significant sternal devascularization and higher risks of infectious complications [16,17] at least in some subgroups of patients, such as those suffering from diabetes, obesity, or chronic pulmonary artery disease, care should be taken to balance the risk–benefit ratio and consider age in the equation. Interestingly and maybe in part due to these factors, only 10% of patients receiving two ITAs were female, although female patients represented 23.5% of the cohort studied. Although chronic pulmonary obstructive disease was not more prevalent in women than in men (14.4% vs 15.7%, respectively, p = NS), there was a higher proportion of female patients presenting with diabetes mellitus (36.2% vs 26.6%, $p < 0.0001$) and with a body mass index over 30 kg/m^2 (29.2% vs 25.0%, $p < 0.0001$). Moreover, female patients were generally older at the time of surgery (mean age 67.4 years vs 62.5 years for men, $p < 0.0001$), another factor in favor of using only one ITA.

Our findings do obviously not support the stopping of performing bilateral ITA grafting as soon as patients reach 60 years of age, but the rapid fall in statistical and clinical benefit associated with the technique after that age emphasizes the importance of revascularization strategy selection for patients between 60 and 65 years of age, where the benefit in terms of long-term survival appears to be lost.

This study was performed in a non-randomized manner and in a single tertiary center. The development of risk factors and/or comorbidities, which had been used in our primary adjustment risk factor analysis, was not identified during follow-up. The prevention of graft disease has evolved with the introduction of new drugs during follow-up, but we expect these new treatments to have been equally distributed among the groups we studied. Although long-term survival benefits are lost between 60 and 65 years of age for patients undergoing bilateral ITA grafting, these patients may experience sustained improvements in anginal status and quality of life owing to better long-term patency of ITAs

compared to venous grafts, but these outcomes were not addressed in this study.

In conclusion, the use of at least one ITA is associated with increased long-term cardiac-specific survival in all age groups of patients compared to venous-only CABG, even in octogenarians. The additional cardiac-related survival benefit of using a second ITA decreases gradually with age, and although a benefit extending into older age cannot be formally excluded, it appears to be significantly lost after 60 years of age at least in our large cohort of patients.

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Appendix A. Conference discussion

Dr P. Sergeant (*Leuven, Belgium*): The authors have created an interesting manuscript using a large data set. They have identified an age-related effect with loss of benefit of more extensive arterial grafting. This effect has been identified before. I therefore agree with the inferences made. We have identified earlier an effect that is not just uni-axial(age) but multi-axial, involving also pulmonary function, ventricular function, renal function, extensive vascular disease. In addition, this same effect is also valid for zero vs single arterial grafting. Why have the authors failed to identify this multi-axial effect?

The authors used nominal variables for the other co-morbidities, so yes/no variables vs continuous variables.

A critical review is part of appreciation. I therefore have two questions:

My first question is why have they used cardiac mortality? It is well known that cardiac mortality is a biased event and, for example, that death is always perceived by the family to be sudden even though it is sometimes preceded by extensive hospitalizations for a failing heart.

My second question is, why have they not used a rich collection of variables that would allow them extensive saturated propensity scoring to correct for the variabilities between data sets and why have they only used a logistic regression?

Dr Mohammadi: Regarding your first question, I agree that cardiac death can be biased and overestimated compared to all-cause death or overall mortality, but we chose cardiac-related death because this is specifically what is meant to be prevented by CABG surgery. Moreover, if there is any overestimation, it should be equally distributed in all three groups. However yours is a very good point, but I think that with the large number of patients we have, it should not introduce a lot of bias in this study.

Regarding your second question, it would have been an optimal situation to have continuous variables in our study. It is a good message to send for everybody, to have a database with continuous variables for future studies, but sometimes to have a continuous variable is very difficult in some patients. For example, in a patient who comes for a straightforward CABG surgery, it is not always justified to perform pulmonary function tests. Once again, having continuous variables would represent an optimal situation, but our database is, unfortunately, based on nominal variables only, and we accept that could probably have introduced some bias in the statistical analysis.

Dr Y. Balbaa (*Cairo, Egypt*): My question to you was I was surprised that the mean follow-up of the patients was 5.7 years, and I am surprised that you even found any statistical benefit of the bilateral mammary, even in young patients below 65, because in the literature at 5.7 years I think surgery with even old veins will have the same survival.

Dr Mohammadi: I didn't understand very well your question.

Dr Balbaa: I mean at 5.7 years it is very difficult to prove any benefit even with bilateral mammary in a young patient.

Dr Mohammadi: The study has been performed over a large period of time, spanning up to 13 years, and 5.7 years was the mean follow-up. We agree that we would have more information with a longer follow up, but even with what we have some conclusions can be drawn, specifically on cardiac-related death.

Dr B. Buxton (*Richmond, Australia*): Although this paper is well done, I agree with the criticism of Dr Sergeant, that it may create the wrong impression, that is, over the age of 60 we should not do bilateral internal thoracic artery grafting. In fact, if it can be done with the same morbidity and

mortality rate, what is the objection to doing it? Because it is hard to predict at the age of 60 whether a patient will live for a short or long time, I would not like to let the conclusion from this observational study go without query.

Secondly, perhaps we should wait for the results of the ARTS Randomized Controlled study from Oxford designed to answer this question rather than using a database analysis, which can be biased.

Dr Mohammadi: What I can say about your comment is that there is no benefit after 60 years of age only regarding cardiac-survival death. That is the major finding in our study. For sure, every patient has individual characteristics and we have to tailor our strategy for each patient, and bilateral ITA use is not associated with the same mortality and morbidity in all patients. I cannot say that only age can play an important role in postoperative mortality, but I can tell you that after age 60 we don't have any benefit in cardiac-related survival.