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Flow capacity of skeletonized versus pedicled internal thoracic artery in coronary artery bypass graft surgery: systematic review, meta-analysis and meta-regression

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Summary

Many surgeons are concerned about the flow capacity of a skeletonized internal thoracic artery (ITA) in comparison with a pedicled ITA used during coronary artery bypass graft (CABG). This work aims to summarize the evidence comparing the flow capacity of a skeletonized versus pedicled ITA during CABG. We performed systematic review and meta-analysis according to the PRISMA statement based on a search in MEDLINE, EMBASE, CENTRAL/CCTR, ClinicalTrials.gov, SciELO, LILACS, Google Scholar and reference lists of relevant articles. Studies included were original studies whose populations comprised patients undergoing CABG; compared outcomes between skeletonized versus pedicled ITA; the outcomes included data regarding intraoperative flow capacity of the grafts; the studies were prospective or retrospective or non-randomized or randomized controlled trials. In total, eight studies were identified and reviewed for eligibility and data were extracted. Forest plots and the summarized difference in means including 95% confidence intervals (CIs) were estimated and meta-regressions were performed. There was a statistically significant difference in favour of the skeletonized ITA compared with the pedicled ITA in terms of flow capacity (random-effect model: additional 20.8 ml/min, 95% CI 6.6–35.0, $P = 0.004$), being the summary measures under the influence of heterogeneity of the effects, but free from publication bias. We observed a difference with regard to the type of study, since non-randomized studies together demonstrated the superiority of a skeletonized ITA (random-effect model: additional 32.3 ml/min, 95% CI 21.0–43.6, $P < 0.001$), but the randomized studies together did not show it (random-effect model: additional 13.2 ml/min, 95% CI –1.1 to 27.6, $P = 0.071$). Meta-regression demonstrated some modulation influence by female gender, age and diabetes on the flow capacity of grafts. In summary, in terms of flow capacity, a skeletonized ITA appears to be superior in comparison with a pedicled ITA during CABG.

Keywords: Meta-analysis • Coronary artery bypass • Mammary arteries • Blood flow velocity

INTRODUCTION

Rationale

Sternal wound infection (SWI) is a recognized and important complication of coronary artery bypass graft (CABG) surgery [1]. The most serious manifestation of an SWI is mediastinitis, which extends the previous anatomical classification to the risk of sepsis. It is well known that an infection of the mediastinum can be severe and potentially lethal [2].

It is suggested that the method of internal thoracic artery (ITA) harvesting influences the incidence of postoperative SWI [3–5]. There are two established harvesting techniques: pedicled and skeletonized ITAs. Whereas the pedicled technique dissects the artery away from the sternum with its accompanying veins, fascia,

adipose tissue and lymphatics generating a pedicled graft, skeletonization requires the ITA to be dissected free of all surrounding tissue, solely yielding the artery [3].

A meta-analysis with 4817 patients from 22 studies observed that the skeletonized ITA appears to reduce the incidence of postoperative SWI in comparison with a pedicled ITA after CABG [6].

Despite these studies, many surgeons are concerned about the flow capacity of skeletonized ITA in comparison with a pedicled ITA, taking into consideration that the skeletonization technique may induce damage to the vessel wall, endothelial dysfunction, and loss of the vasa vasorum (which might lead to ischaemia in the media layer), leading to detrimental effects on the integrity of the ITA.

Our meta-analysis attempts to determine if there is any difference between skeletonized and pedicled ITA in terms of flow capacity of conduits.

Objectives

We performed a meta-analysis and meta-regression of studies to compare the flow capacity of the skeletonized versus pedicled ITA during CABG, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [7].

METHODS

Eligibility criteria

Using the PICOS (Population, Intervention, Comparison, Outcome, Study design) strategy, studies were considered if: (i) the population comprised patients undergoing CABG; (ii) they compared outcomes between skeletonized versus pedicled ITA; (iii) outcomes studied included those that reported data regarding the intraoperative flow capacity of the grafts; (iv) they were prospective or retrospective or non-randomized studies or randomized controlled trials.

Information sources

The following databases were used (until December 2013): MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL/CCTR), ClinicalTrials.gov, SciELO (Scientific Electronic Library Online), LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde—The Latin American and Caribbean Health Sciences), Google Scholar and reference lists of relevant articles.

Search

We conducted the search using Medical Subject Heading (MeSH) terms ('skeletonized' OR 'skeletonization') AND ('pedicled' OR 'pedunculated' OR '*in situ*') AND ('arteries, mammary' OR 'artery, mammary' OR 'mammary artery' OR 'internal mammary artery' OR 'arteries, internal mammary' OR 'artery, internal mammary' OR 'internal mammary arteries' OR 'mammary arteries' OR 'mammary arteries, internal' OR 'mammary artery, internal' OR 'internal thoracic artery' OR 'arteries, internal thoracic' OR 'artery, internal thoracic' OR 'internal thoracic arteries' OR 'thoracic arteries, internal' OR 'thoracic artery, internal') AND ('coronary artery bypass graft' OR 'coronary artery bypass grafting' OR 'coronary artery bypass surgery' OR 'coronary bypass surgery' OR 'coronary artery bypass graft surgery' OR 'coronary artery bypass' OR 'coronary bypass').

Study selection

The following steps were followed: (1) identification of titles of records through searching of databases; (2) removal of duplicates; (3) screening and selection of abstracts; (4) assessment for eligibility through full-text articles; (5) final inclusion in study.

One reviewer followed Steps 1–3. Two independent reviewers followed Step 4 and selected studies. Inclusion or exclusion of studies was decided unanimously. When there was disagreement, a third reviewer took the final decision.

Data items

The end-points were means of free flow capacity (ml/min) of grafts performed during CABG using a skeletonized versus pedicled ITA.

Data collection process

Two independent reviewers extracted the data. When there was disagreement about the data, a third reviewer (the first author) checked the data and took the final decision about it. From each study, we extracted patient characteristics, study design and outcomes.

Risk of bias in individual studies

Included studies were assessed for the following characteristics: (i) sequence generation; (ii) allocation concealment; (iii) blinding; (iv) incomplete outcome data; (v) selective outcome reporting and (vi) other sources of bias. Taking these characteristics into account, the papers were classified into A (low risk of bias), B (moderate risk of bias) or C (high risk of bias).

Two independent reviewers assessed the risk of bias. Agreement between the two reviewers was assessed using κ statistics for full text screening, and rating of relevance and risk of bias. When there was disagreement about the risk of bias, a third reviewer (the first author) checked the data and took the final decision about it.

Summary measures

The principal summary measures were difference in means with 95% confidence interval (CI) and *P*-values (considered statistically significant when <0.05). The meta-analysis was completed using the software Comprehensive Meta-Analysis version 2 (Biostat, Inc., Englewood, NJ, USA).

Synthesis of results

Forest plots were generated for graphical presentations of clinical outcomes, and we performed the I^2 test and χ^2 test for the assessment of heterogeneity across the studies [8]. Inter-study heterogeneity was explored using the χ^2 statistic, but the I^2 -value was calculated to quantify the degree of heterogeneity across the studies that could not be attributable to chance alone. When I^2 was more than 50%, significant statistical heterogeneity was considered to be present. Each study was summarized by the difference in means of flow capacity for a skeletonized ITA compared with a pedicled ITA. The differences in means were combined across studies using a weighted DerSimonian-Laird random-effects model [9].

Risk of bias across studies

To assess the publication bias, a funnel plot was generated, being statistically assessed by Begg and Mazumdar's test [10] and Egger's test [11].

Sensitivity analysis

We performed a subgroup analysis in regards to the presence or absence of randomization to verify whether there was any difference regarding the type of study.

Meta-regression analysis

Meta-regression analyses were performed to determine whether the effects of a skeletonized ITA were modulated by prespecified factors. Meta-regression graphs describe the effect of a skeletonized ITA on the outcome (on the y-axis) as a function of a given factor (on the x-axis). The predetermined modulating factors to be examined were: sex, age, diabetes. Sex was represented as the proportion of females in the study. Age was represented as the mean age of the patients participating in the study. Diabetes was represented as the proportion of diabetics (insulin-dependent or noninsulin-dependent) in the study.

RESULTS

Study selection

A total of 542 citations were identified, of which 82 studies were potentially relevant and retrieved as full text. Eight [12–19] publications fulfilled our eligibility criteria. Interobserver reliability of study relevance was excellent ($\kappa = 0.86$). Agreement for decisions related to study validity was very good ($\kappa = 0.82$). The search strategy can be seen in Fig. 1.

Study characteristics

Characteristics of each study are given in Table 1. A total of 907 conduits were studied, 360 being skeletonized ITA and 547 pedicled ITA, including the years 1996–2011, being 6 prospective (75.0%), 5 randomized (62.5%), all single-centre. All studies used a multivariable adjustment for possible confounders. The information not given in Table 1, but noteworthy, is that all studies consisted of patients in about the sixth decade of their life and mostly male. The overall internal validity was considered a moderate risk of bias. The preoperative characteristics of patients are described in Table 2.

Synthesis of results

The differences in means of flow capacity in the skeletonized ITA group compared with the pedicled ITA group in each study are reported in Fig. 2. There was evidence of important heterogeneity of treatment effect among the studies for the difference in means of flow capacity. The overall difference in means showed statistically significant difference between groups in favour of a skeletonized ITA (random-effect model: additional 20.8 ml/min, 95% CI 6.6–35.0, $P = 0.004$).

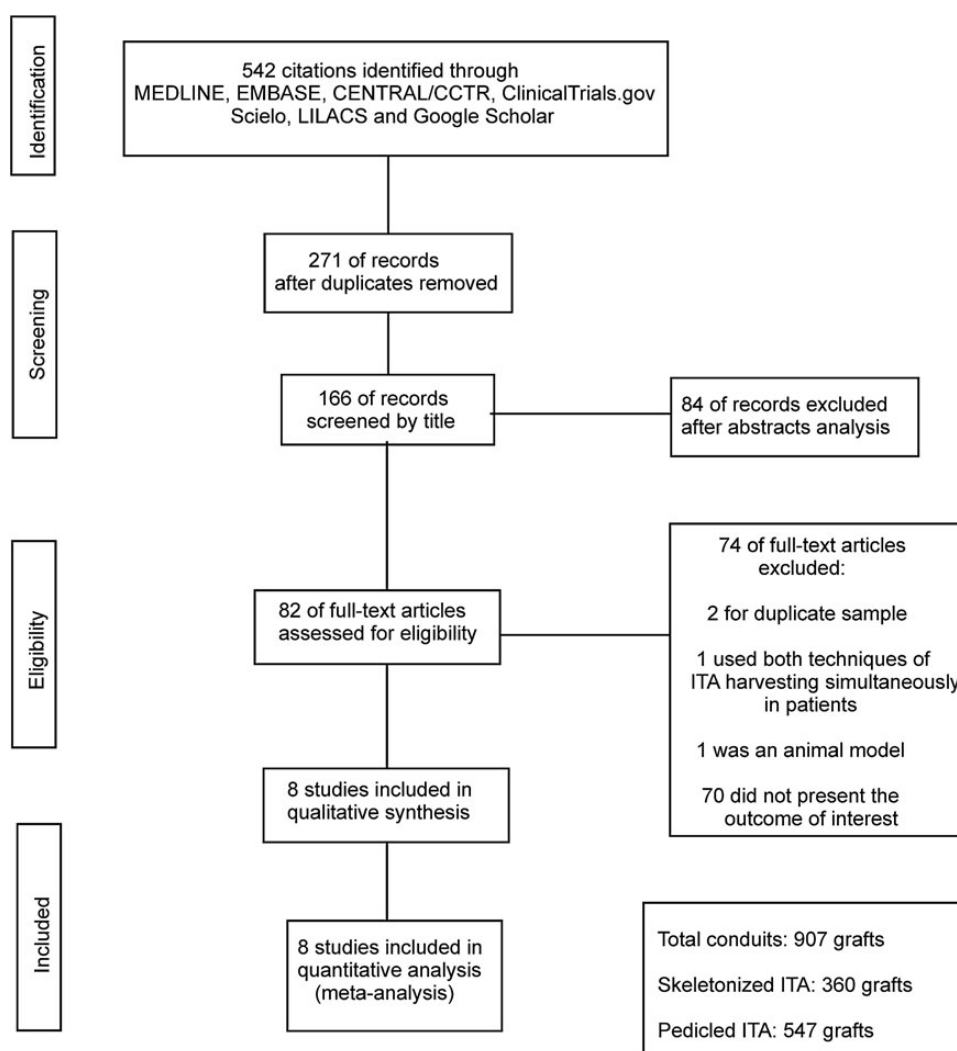


Figure 1: Flow diagram of studies included in the data search. ITA: internal thoracic artery.

Table 1: Study characteristics and risk of bias (internal validity)

Study	Study design	Selection bias	Performance bias	Attrition bias	Detection bias	Multivariable adjustment for possible confounders
Mannacio et al. [12]	P, R, NM	A	B	A	B	Probably adequate
Kandemir et al. [13]	P, R, NM	B	B	A	B	Probably adequate
Boodhwani et al. [14]	P, R, NM	B	B	A	B	Probably adequate
Castro et al. [15]	P, R, NM	B	B	A	B	Probable adequate
Takami and Ina [16]	P, R, NM	B	B	A	B	Probably adequate
Huang et al. [17]	NP, NR, NM	B	B	A	B	Probably adequate
Deja et al. [18]	P, NR, NM	B	B	A	B	Probably adequate
Choi and Lee [19]	NP, NR, NM	B	B	A	B	Probably adequate

A: risk of bias is low; B: risk of bias is moderate; C: risk of bias is high; D: incomplete reporting; P: prospective; NP: non-prospective; R: randomized; NR: non-randomized; M: multicentre; NM: non-multicentre.

Table 2: Preoperative characteristics of patients

Study	SKT/PED female (%)	SKT/PED hypertension (%)	SKT/PED diabetes (%)	SKT/PED smoking (%)	SKT/PED dyslipidaemia (%)	SKT/PED age (mean ± SD)
Mannacio et al. [12]	29.0/32.0	39.0/34.0	24.0/21.0	NA	44.0/41.0	67.0 ± 15/65.0 ± 12
Kandemir et al. [13]	15.0/18.2	NA	35.0/36.4	NA	NA	65.3 ± 6.5/63.1 ± 5.5
Boodhwani et al. [14]	10.0 ^a	67.0 ^a	17.0 ^a	NA	81.0 ^a	57.9 ± 1.3/57.9 ± 1.3
Castro et al. [15]	24.0/36.0	84.0/88.0	60.0/40.0	60.0/44.0	44.0/48.0	60.0 ± 11.5/63.0 ± 10.2
Takami and Ina [16]	24.4/16.7	NA	42.0/45.0	NA	NA	57.2 ± 8.8/66.2 ± 7.2
Huang et al. [17]	24.0/30.0	NA	30.0/30.0	NA	NA	62.1 ± 9.6/64.3 ± 9.0
Deja et al. [18]	12.8/17.1	NA	21.4/16.7	NA	NA	56.4 ± 7.9/54.2 ± 9.2
Choi and Lee [19]	30.4/14.3	NA	34.7/25.0	NA	NA	61.9 ± 8.3/54.6 ± 7.5

ITA: internal thoracic artery; SKT: skeletonized ITA; PED: pedicled ITA; SD: standard deviation; NA: nonavailable. ^aBoodhwani et al. reported the overall data, and not separately (SKT/PED).

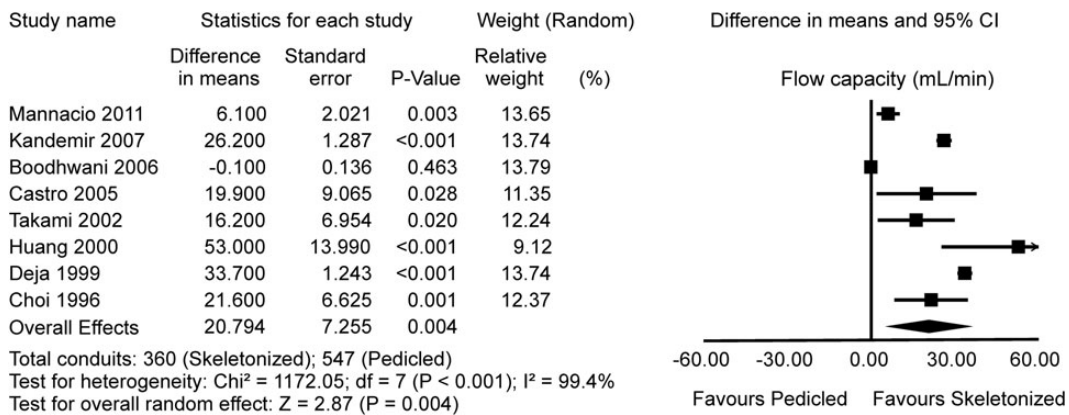


Figure 2: Difference in the means and conclusions plot of flow capacity of a skeletonized versus pedicled internal thoracic artery. CI: confidence interval; df: degrees of freedom.

Risk of bias across studies

Funnel plot analysis (Fig. 3) disclosed statistical symmetry around the axis for the treatment effect, which means that we probably do not have a publication bias related to the end-point.

Sensitivity analysis

The differences in means of flow capacity in the skeletonized ITA group compared with the pedicled ITA group in non-randomized studies are reported in Fig. 4A. There was evidence for important heterogeneity of treatment effect among the studies for the

difference in means of flow capacity. The overall difference in means showed a statistically significant difference between groups in favour of a skeletonized ITA (random-effect model: additional 32.3 ml/min, 95% CI 21.0–43.6, $P < 0.001$).

The differences in means of flow capacity in the skeletonized ITA group compared with the pedicled ITA group in randomized studies are reported in Fig. 4B. There was evidence for important heterogeneity of treatment effect among the studies for the difference in means of flow capacity. The overall difference in means showed no statistically significant difference between groups (random-effect model: additional 13.2 ml/min, 95% CI -1.1 to 27.6, $P = 0.071$).

Meta-regression analysis

Concerning the gender, we observed a statistically significant coefficient for the proportion of female patients and the difference in means of flow capacity in skeletonized ITA (Fig. 5A). We can

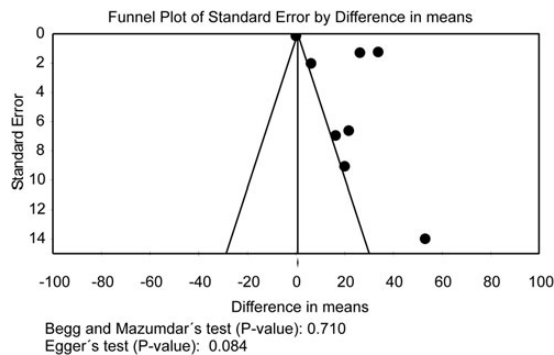


Figure 3: Publication bias analysis by funnel plot graphic.

observe that the greater the proportion of female patients, the greater is the difference in means of flow capacity in a skeletonized ITA in comparison with a pedicled ITA.

With regard to age, we observed a statistically significant coefficient for means of age and the difference in means of flow capacity in a skeletonized ITA (Fig. 5B). We can observe that the greater the mean of age, the greater is the difference in means of flow capacity in a skeletonized ITA in comparison with a pedicled ITA.

With respect to diabetes, we observed a statistically significant coefficient for the proportion of diabetic patients and the difference in means of flow capacity in a skeletonized ITA (Fig. 5C). We can observe that the greater the proportion of diabetic patients, the greater is the difference in means of flow capacity in a skeletonized ITA in comparison with a pedicled ITA.

DISCUSSION

Summary of evidence

The results of this meta-analysis demonstrate that there is a statistically significant difference in favour of a skeletonized ITA compared with a pedicled ITA in terms of flow capacity, being the summary measures under the influence of heterogeneity of the effects, but free from a publication bias. In the sensitivity analysis, we observed that there was a difference with regard to the type of study, since non-randomized studies together demonstrated the benefit of a skeletonized ITA in comparison with a pedicled ITA, but the randomized studies together did not show this difference (although not so far from statistical significance). Meta-regression demonstrated some modulation influence by female gender, age and diabetes.

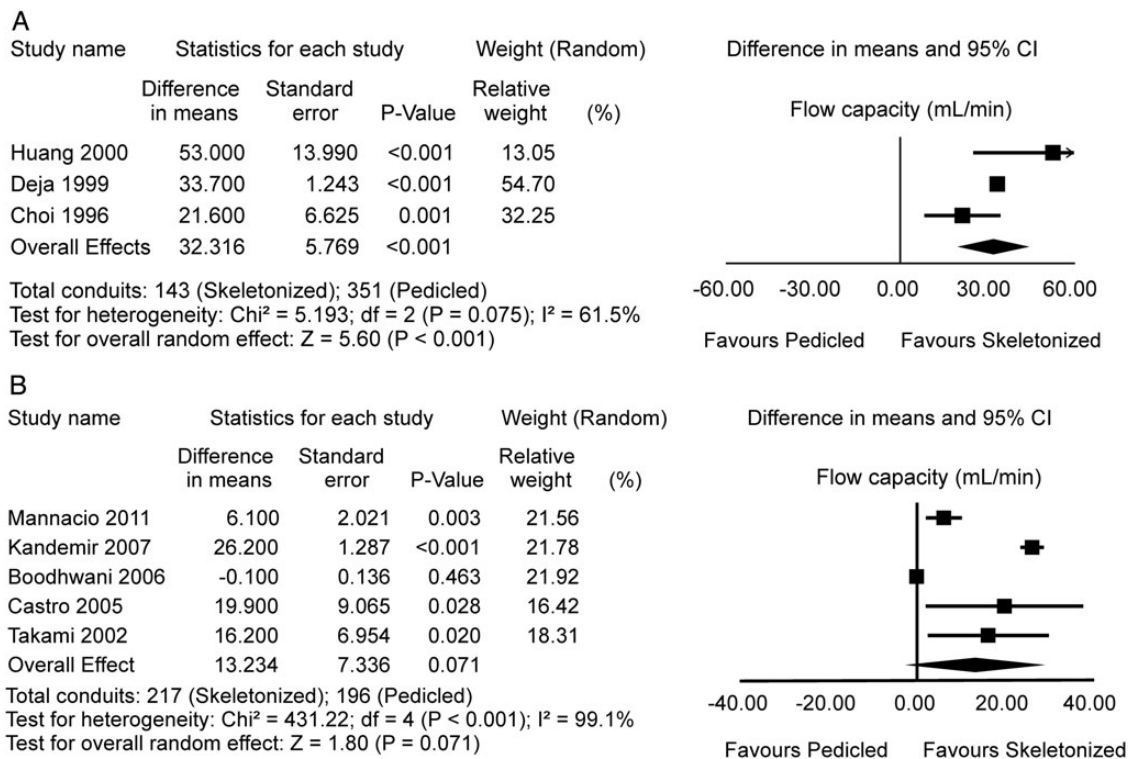


Figure 4: Sensitivity analysis. (A) Non-randomized studies; (B) Randomized studies. CI: confidence interval; df: degrees of freedom.

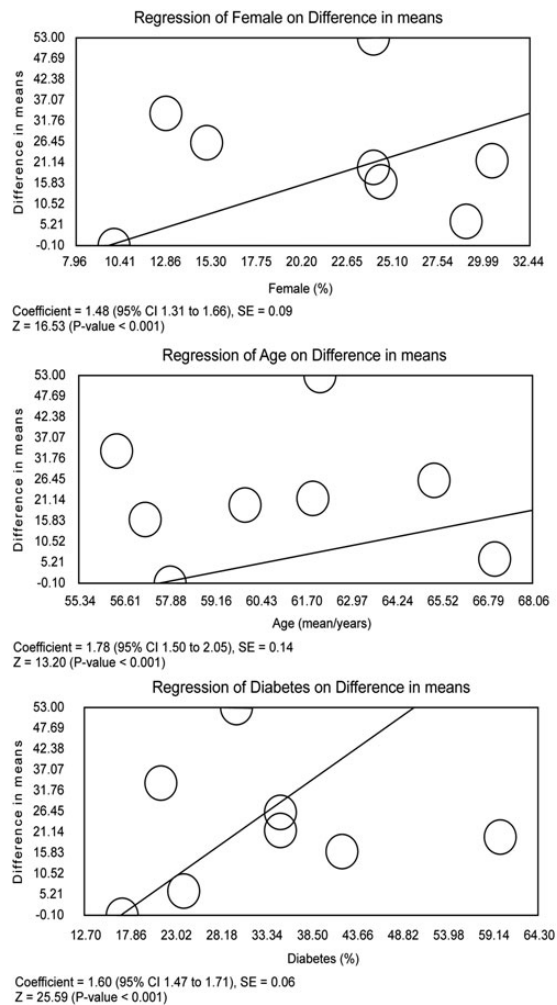


Figure 5: Meta-regression analysis by representative plots. SE: standard error.

Considerations about this meta-analysis

To our knowledge, this is the first meta-analysis of studies performed to date regarding the flow capacity of a skeletonized ITA versus a pedicled ITA, and it demonstrates that a skeletonized ITA seems to be superior to a pedicled ITA on this aspect, a finding of interest for the daily surgical practice.

Skeletonization is certainly more traumatic for the arterial wall than pedicled preparation, and the possibility that mechanical peeling of the adventitia combined with the repeated stretching may affect ITA integrity has never been clearly denied. In our meta-analysis, we showed that the difference of flow capacity between the two harvesting techniques shows some advantage in favour of the skeletonized ITA; further, the concern of some surgeons, based on the rationale of the possibility of endothelial dysfunction, ischaemia of the media layer and damage to adventitia, appears unnecessary; these findings are based on the laboratorial research of other authors.

Gaudino *et al.* [20] showed preservation of the endothelium in the skeletonized ITA by an immunohistochemical technique. Deja *et al.* [18] demonstrated that skeletonization did not damage endothelial function in acetylcholine-induced arterial relaxation, and a skeletonized ITA presented a higher blood flow in comparison with a pedicled ITA. Noera *et al.* [21] showed that blood

effusion in adventitia of a skeletonized ITA was maintained after harvesting and it did not exhibit impaired morphology, histology and tissue viability. Sá *et al.* [22] recently performed a meta-analysis and observed that, in terms of patency, the skeletonized ITA appears to be noninferior in comparison with a pedicled ITA after CABG.

Curiously, we have observed through the meta-regression that the greater the proportion of females and diabetics and mean age of patients in the populations in the studies, the greater were the respective differences in means of flow capacity of a skeletonized ITA compared with a pedicled ITA. This finding shows that these groups of patients, although regarded as patients under higher risk, benefit more from the adoption of ITA skeletonization during CABG in terms of blood flow in the grafts, since they have been demonstrating a greater flow capacity with the skeletonized ITA than the pedicled ITA.

Risk of bias and limitations

This meta-analysis included data from non-randomized and/or observational studies, which reflects the 'real world', but they are limited by treatment bias, confounders and a tendency to overestimate treatment effects. Patient selection alters outcome and thus makes non-randomized studies obviously less robust. Additionally, important statistical heterogeneity among studies was observed.

There are inherent limitations with meta-analyses, including the use of cumulative data from summary estimates. Patient data were gathered from published data, not from individual patient follow-up. Access to individual patient data would have enabled us to conduct further subgroup analysis and propensity analysis to account for differences between the treatment groups.

Future perspectives

Because the findings support a potential benefit from a specific harvesting method and as part of the regular curriculum in cardiovascular surgery, we recommend that the skeletonization technique should become a mandatory part of the training of cardiovascular surgery residents. The results of this study suggest the need for large-scale (with a calculated probabilistic sample size), multicentre, prospective, randomized trials of skeletonized versus pedicled ITA grafts to verify that there is indeed a difference regarding the flow capacity.

CONCLUSION

In terms of flow capacity, a skeletonized ITA appears to be superior in comparison with a pedicled ITA during CABG.

Conflict of interest: none declared.

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