


ORIGINAL ARTICLE

Outcomes of different aortic arch replacement techniques

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Abstract

Background: Consensus on the best treatment for aortic arch pathology is unresolved due to an emerging variety of procedures. We aimed to compare the outcomes of two major techniques for open aortic arch replacement involving the supra-aortic branches and to identify the risk factors for specific adverse events.

Methods: Between 1974 and 2017, 172 patients were treated with either the en bloc (island, $n = 59$; 34.3%) or branched graft technique ($n = 113$, 65.7%). Most of the patients were treated in an emergent/urgent setting (52.4%).

Results: Patients who underwent the en bloc procedure had significantly shorter cardiopulmonary bypass (median: 241 vs 271 minutes, $P = .041$) and aortic cross clamp times (median: 124 vs 168 minutes, $P = .005$) than patients who underwent the separate graft technique. Overall, the hospital mortality was lower in the en bloc group, 8.5% vs 19.5%, although the difference was not significant ($P = .077$). No difference was found in the survival between the separate graft and en bloc groups at 1 (77.0 vs 86.3%), 5 (67.7 vs 66.3%) and 10 years (42.4 vs 51.3%), ($P = .63$). The postoperative stroke rate was comparable between the en bloc and separate graft cohorts (14.3 vs 19.6%, $P = .52$). Diabetics and those who underwent an elephant trunk procedure were at a higher risk for reintervention.

Conclusions: The separate graft technique, which is more common today, showed no difference from the en bloc technique with regard to hospital mortality and morbidity. Furthermore, the late survival and reintervention rates were similar after both procedures.

KEYWORDS

aortic arch, aortic surgery, arch repair, arch replacement

1 | INTRODUCTION

Total aortic arch replacement is considered one of the most challenging procedures in adult cardiac surgery, although, in recent years, outcomes have substantially improved.¹⁻³ Changes in operative techniques, as well as in overall spectra of patient care, including

anesthesia, perfusion, and intensive care, have led to marked improvements in outcomes. However, most of the published literature on aortic arch surgery frequently includes a hemiarch replacement, which is technically less demanding and time-consuming operation. The outcomes of these heterogeneous cohorts are difficult to interpret, leading recently to more collaborative

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efforts to formulate and provide more uniform guidance for reporting the clinical results of aortic arch surgery.⁴

The current study is aimed to clarify the contemporary outcomes of open surgical aortic arch replacement involving the supra-aortic branches and to evaluate the predictive risk factors of adverse events of different reimplantation techniques.

2 | METHODS

2.1 | Patient population

Between November 1974 and February 2017, 172 consecutive patients underwent total or subtotal aortic arch replacement with either en bloc replacement of supra-aortic vessels as an island patch or separate reimplantation of these vessels at Erasmus Medical Center in Rotterdam, the Netherlands. The analysis included elective, urgent, and emergent cases performed due to any pathology with reimplantation of at least one aortic arch branch, regardless of the proximal or distal extent of the thoracic aorta repair. Patients that underwent open arch anastomosis (hemiarch) without arch artery involvement were excluded from the study.

2.2 | Operative technique

Over the last two decades, the surgical technique for an aortic arch replacement has been standardized at our institution.⁵

To approach the aortic arch, a median sternotomy was used in 156 (90.7%) patients, a posterolateral thoracotomy in 14 (8.1%) patients and a thoracotomy in 2 (1.2%) patients.

In most of the patients, cardiopulmonary bypass (CPB) was initiated with arterial cannulation of the ascending aorta (48.8%) or femoral artery (41.3%), whereas CPB initiation through the axillary artery or other sites was used in only 5.8% or 4.3%, respectively. The aortic arch replacement was performed under deep hypothermic circulatory arrest (DHCA) with a nasopharyngeal temperature of 18°C (bladder temperature of 20°C). Selective bilateral antegrade cerebral perfusion (ACP) was used in 77.1% of patients, selective retrograde cerebral perfusion (RCP) in 1.2%, and solely DHCA was used in 21.5% of patients.

Following institutional policy, cold crystalloid cardioplegia was used for myocardial protection in all cases. Cerebral perfusion with cold blood (18°C) was initiated at a flow of 10 mL/kg/min. For partial arch repair, only one cannula was used, and ACP was delivered at a flow of 7 mL/kg/min. The right radial arterial pressure was maintained between 40 and 70 mmHg. Cerebral monitoring was secured with a right radial arterial pressure line and cerebral oxygen saturation by using near-infrared spectroscopy. Control of pH balance was carried out by integrating the pH-stat method during moderate to deep hypothermia and α -stat method for temperatures higher than 28°C. The left side of the heart was vented through the right superior pulmonary vein. Over the study period, two different techniques were used to replace the

aortic arch: brachiocephalic vessel implantation using an island technique or a branched prosthesis (Plexus 4; Vaskutek Ltd, Renfrewshire, Scotland, UK) with separate revascularization of arch vessels. Over time, the choice of a certain surgical technique depended on the patient's characteristics, for example, the presence of connective tissue disorder or extensive atherosclerotic disease and the surgeon's preference. According to the surgical plan, over the last 2 decades, either an "elephant trunk" (ET) or a "frozen elephant trunk" (FET) was placed through the opened aortic arch in the descending aorta in patients with extensive pathology of the thoracic aorta.

2.3 | Data collection and clinical endpoints

The Medical Ethics Committee of Erasmus Medical Center in Rotterdam granted approval for this study (MEC 2011-064). The data were extracted from our institutional Aortic Surgery Database, a prospectively maintained clinical registry of all patients undergoing thoracic aortic surgery at our institution and double-checked for accuracy (D.A. and J.B.).

All operative survivors were followed up regularly and recommended to undergo computed tomography (CT) at the time of discharge, after 6 months and annually thereafter. Follow up was complete in 100% of patients.

All clinically gathered data, including the occurrence of events during follow-up and cause of death, were registered and reported according to the expert consensus recommendation for reporting treatment results in the thoracic aorta.⁶ Any surgical or percutaneous interventional catheter procedure that repaired or otherwise adjusted any part of the aorta was defined as an aortic reintervention.

2.4 | Statistical analysis

Continuous data were presented as the means \pm standard deviation or medians with interquartile range (IQR) depending on the data distribution. Categorical variables were presented as frequencies and percentages. The patients were divided into 2 categories according to whether they were treated with an en bloc or a separate graft technique. The short- and long-term outcomes of the two patient groups were then compared. Continuous variables were examined using the two-sample *t* test or the Mann-Whitney U test, where appropriate. Categorical variables were compared using the χ^2 test or Fisher's exact test, when applicable.

The preoperative and intraoperative variables were first analyzed using univariate logistic regression, and then a ridge-penalized logistic regression model was used to assess independent predictors of hospital mortality and neurologic outcome.⁷

Univariate and multivariate Cox proportional hazard regression analyses were used to identify predictors for the predefined adverse events: all-cause mortality and aortic reintervention. Due to the low frequencies of the aforementioned events, a penalized likelihood approach was used in the multivariate Cox model.⁸ Patient survival was estimated using the Kaplan-Meier method and log-rank test. The

cumulative incidence of aortic reintervention in both groups was calculated by accounting for death as a competing risk.^{9,10} All statistical tests were two-sided with an α level set at 0.05 for statistical significance. Statistical analyses were performed with IBM SPSS Statistics for Mac, version 25.0 (IBM Corp, Armonk, NY) and R software, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Study population

Fifty-nine (34.3%) patients underwent surgery of the aortic arch utilizing the en bloc technique and 113 (65.7%) patients using the separate graft technique. The median age at operation of the entire cohort was 64 (IQR: 52-70) years, 92 patients (53.5%) were male, and 82 patients (47.7%) had their surgery in an elective setting (Table 1). The only significant difference in the preoperative characteristics between the two study groups was a higher baseline serum creatinine level in the separate graft group. However, no difference was noted in the number of patients affected by chronic kidney disease.

The majority of patients suffered from degenerative aneurysms ($n = 84$, 48.8%), and medial degeneration was the main etiology for the aortic dilatation ($n = 82$, 47.7%) (Table S1).

Of the 172 patients, 39 (22.7%) had undergone prior aortic surgery, the most common being the open repair of the abdominal aortic aneurysm (18.3%) (Table S2).

3.2 | Intraoperative data

The extent of surgery depended on the extent of aortic arch disease and coexistence of other cardiac pathologies (Table 1, Complete results are presented in Table S3). Arch repair involving all 3 arch arteries (total aortic arch), 2 arch arteries or 1 arch artery was performed in 91 (52.9%), 46 (26.7%) and 35 (20.3%) patients, respectively. The extent of aortic pathology required additional replacement of the ascending aorta in 112 (65.1%) patients. In 24 (14.0%) patients with subsequent disease of their descending aorta, conventional ET was deployed. A FET procedure was performed in 6 (3.5%) patients (Table S3).

Compared with the en bloc procedure, the patients who underwent separate graft reimplantation of their brachiocephalic vessels showed significantly longer CPB and aortic cross-clamp times (241 vs 271 minutes, $P = .041$) and (124 vs 168 minutes, $P = .005$), respectively (Table 1).

3.3 | Hospital mortality and morbidity

Overall hospital mortality was 15.7% ($n = 27$), with rates of 7.3% (6/82 patients) after elective surgery and 23.3% (21/90 patients) after urgent/emergent surgery ($P = .006$). Nine patients (5.2%) died in the operating theater during the urgent surgical procedure due to acute aortic

dissection. The hospital mortality tended to be higher for the separate graft cohort than for the en bloc reimplantation cohort, though no statistically significant difference was found (19.5 vs 8.5%, $P = .077$).

No significant differences were found in other clinical outcomes between the en bloc and separate graft cohorts, with comparable rates of cerebrovascular accidents (CVAs; 14.3 vs 19.6%, $P = .52$), paraplegia (1.79 vs 1.87%, $P > .99$) and reoperations for bleeding (23.2 vs 34.6%, $P = .16$) (Table 2).

Several variables were identified as risk factors by means of univariate analysis for in-hospital mortality and the occurrence of postoperative stroke (Table S4). None of these predictors maintained their significance in the multivariate penalized regression model (Table S5).

The two reimplantation techniques of the supra-aortic vessels were not associated with an increased risk of the postoperative development of stroke or hospital mortality.

3.4 | Late survival

The median follow-up duration was 4.5 years (IQR: 1.8-8.5 years). During the follow-up, 58 more deaths occurred, thus resulting in a total of 85 (49.4%) deaths. The longest survival was 26 years in a patient who underwent total aortic arch replacement with reimplantation of all three supra-aortic vessels with the en bloc technique.

The overall survival rates at 1, 5, and 10 years were 80.2%, 67.3%, and 45.1%, respectively. No significant difference was found in survival between en bloc and separate graft surgical replacement of supra-aortic vessels (log-rank, $P = .63$) (Figure 1).

The multivariable penalized model revealed that increased age (HR, 1.05, 95% CI, 1.02-1.08) and increased preoperative creatinine (HR, 1.42, 95% CI, 1.05-1.92) were predictive factors for long-term mortality (Table S7). Furthermore, being asymptomatic at admission for surgery (HR, 0.43, 95% CI, 0.21-0.88) and having an idiopathic or other etiologies of the aortic disease showed protective effects on the long-term mortality (HR, 0.39, 95% CI, 0.16-0.93) and (HR, 0.17, 95% CI, 0.04-0.74), respectively.

3.5 | Reinterventions

Two patients required aortic reintervention due to acute dissection during the in-hospital stay after initial separate reimplantation of the supra-aortic branches.

During the follow-up, a total of 36 (22.1%) patients required aortic reintervention. Ten (6.1%) patients underwent a subsequent thoracic endovascular repair (TEVAR), and 4 (2.5%) underwent an endovascular aneurysm repair (EVAR) for their distal aortic pathology.

In competing risks analysis, no difference was found in the cumulative probability of aortic reintervention, accounting for death as a competing risk, between the en bloc and separate graft operative groups at 5 (23.1 vs 18.6%), 10 (34.3 vs 23.0%) and 15 years (34.3 vs 31.3%) ($P = .56$) (Figure 2).

TABLE 1 Baseline and intraoperative characteristics of the patients

Baseline characteristics				
	Entire cohort n = 172	En bloc n = 59	Separate grafts n = 113	P value
Age, y	64 (52-70)	65 (54-70)	63 (52-71)	.96
Male	92 (53.5)	30 (50.8)	62 (54.9)	.63
Diagnosis				
<i>Degenerative aneurysm</i>	84 (48.8)	33 (55.9)	51 (45.1)	.13
<i>Acute dissection</i>	58 (33.7)	20 (33.9)	38 (33.6)	
<i>Chronic dissection</i>	19 (11.0)	2 (3.4)	17 (15.0)	
<i>Other</i>	11 (6.40)	4 (6.8)	7 (6.2)	
Asymptomatic	57 (33.1)	20 (33.9)	37 (32.7)	>.99
Hypertension	99 (57.6)	33 (55.9)	66 (58.4)	.87
Diabetes	11 (6.4)	6 (10.2)	5 (4.4)	.19
COPD	21 (12.2)	7 (11.9)	14 (12.4)	>.99
Prior MI	7 (4.1)	2 (3.4)	5 (4.4)	>.99
History of CVA	16 (9.3)	2 (3.4)	14 (12.4)	.058
Serum creatinine, mg/dL	1.00 (0.84-1.19)	0.89 (0.79-1.12)	1.02 (0.88-1.24)	.026
GFR <60 mL/min/1.73 m ³	49 (28.5)	13 (22.0)	36 (32.4)	.21
Hemodialysis	1 (0.6)	1 (1.7)	0 (0)	.34
Prior aortic surgery	39 (22.7)	12 (20.3)	27 (23.9)	.70
Urgency of the procedure				
<i>Elective (>24 h)</i>	82 (47.7)	22 (37.3)	45 (39.8)	.82
<i>Urgent (<24 h)</i>	23 (13.4)	7 (11.9)	16 (14.2)	
<i>Emergent (<1 h)</i>	67 (39.0)	30 (50.8)	52 (46.0)	
Extent of aortic disease				
<i>Ascending aorta</i>	140 (81.4)	52 (88.1)	88 (77.9)	.15
<i>Aortic arch</i>	166 (96.5)	59 (100.0)	107 (94.7)	.095
<i>Descending aorta</i>	99 (57.6)	26 (44.1)	73 (64.6)	.014
Intraoperative characteristics				
CPB time, min	259 (212-321)	241 (208-294)	271 (222-324)	.041
ACC time, min	147 (96-190)	124 (83-164)	168 (99-225)	.005
Circulatory arrest time, min	71 (47-99)	69 (48-99)	73 (46-99)	.71
Cerebral perfusion time, min	68 (29-118)	43 (22-71)	81 (30-130)	<.001
Selective cerebral perfusion				
<i>None</i>	37 (21.5)	13 (22.0)	24 (21.2)	.89
<i>Antegrade</i>	133 (77.3)	45 (76.3)	88 (77.9)	
<i>Retrograde</i>	2 (1.2)	1 (0.9)	1 (0.9)	
Extension of arch replacement				
<i>1 arch vessel</i>	35 (20.3)	0 (0)	35 (31.0)	<.001
<i>2 arch vessels</i>	46 (26.7)	24 (40.7)	22 (19.5)	
<i>3 arch vessels</i>	91 (52.9)	35 (59.3)	56 (49.6)	

Note: The values are presented as median and IQR or n/N (%).

Abbreviations: ACC, aortic cross-clamp; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; CVA, cerebrovascular accident; GFR, glomerular filtration rate; MI, myocardial infarction.

The multivariable penalized model revealed that being diabetic (HR, 5.45, 95% CI, 1.05-28.13, $P = .043$) and receiving the ET procedure (HR, 4.42, 95% CI, 1.30-15.02, $P = .017$) were associated with a higher risk of repeat surgery or aortic reintervention (Table S7). Contrarily, male sex (HR, 0.35, 95% CI, 0.14-0.89, $P = .030$) and a history of cardiac surgery (HR, 0.12, 95% CI, 0.02-0.66, $P = .015$) were protective factors, and these patients were less likely to undergo aortic reintervention.

4 | DISCUSSION

This study contributes to the current literature with a unique homogeneous cohort of patients who underwent open aortic arch replacement utilizing contemporary neuroprotective and surgical techniques with either the en bloc or a separate graft technique. The most important findings from the present study were as follows: (a) Operative mortality was markedly higher in urgent/emergent cases; (b) The

TABLE 2 In-hospital mortality and morbidity

	Entire cohort n = 172	En bloc n = 59	Separate grafts n = 113	P value
Hospital mortality	27 (15.7)	5 (8.5)	22 (19.5)	.077
Intraoperative mortality	9 (5.2)	3 (5.1)	6 (5.3)	>.99
^a Operative survivals	N = 163	N = 56	N = 107	
Reoperation for bleeding	50 (30.7)	13 (23.2)	37 (34.6)	.16
Length of ICU stay, d	2.0 (1.0-9.0)	2.0 (1.0-6.0)	3.0 (1.0-9.0)	.47
Length of hospital stay	13.0 (8.0-25.0)	11.5 (6.8-23.3)	15.0 (8.0-26.8)	.15
Ventilation support, d	1.0 (1.0-5.0)	1.0 (1.0-4.0)	1.0 (1.0-6.0)	.63
Tracheostoma	15 (9.2)	4 (7.1)	11 (10.3)	.58
Myocardial infarction	3 (1.8)	1 (1.8)	2 (1.9)	>.99
Atrial fibrillation	58 (35.6)	15 (26.8)	43 (40.2)	.12
CVA	29 (17.8)	8 (14.3)	21 (19.6)	.52
TIA	7 (4.3)	1 (1.79)	6 (5.61)	.42
Paraplegia	3 (1.8)	1 (1.79)	2 (1.87)	>.99
Nervus recurrens deficit	25 (15.3)	9 (16.1)	16 (15.0)	.82
Delirium	40 (24.5)	14 (25.0)	26 (24.3)	>.99
Sepsis	21 (12.9)	5 (8.9)	16 (15.0)	.33
Mediastinitis	3 (1.8)	0(0)	3 (2.8)	.55
Renal failure	54 (33.1)	17 (30.4)	37(34.6)	.61
Renal failure requiring dialysis	19 (11.7)	6 (10.7)	13 (12.1)	>.99
Renal failure requiring permanent dialysis	6 (3.7)	2 (3.6)	4 (3.7)	>.99
Postoperative highest creatinine	1.39 (1.07-2.14)	1.30 (0.97-2.05)	1.46 (1.10-2.19)	.069
Aortic reintervention	36 (22.1)	15 (26.8)	21 (19.6)	.32

Abbreviations: CVA, cerebrovascular accident; ICU, intensive care unit; TIA, transient ischemic attack.

The values are presented as median and IQR or n/N (%).

^aOperative survivors (n = 163).

hospital mortality using the reimplantation of supra-aortic vessels with a separate graft technique was more than twice higher than when the en bloc technique was utilized. However, we emphasize that patients in the separate graft group had a greater extent of aortic disease; (c) Increased age, being symptomatic at presentation and baseline creatinine were the strongest independent predictive factors for the long-term mortality utilizing a modern approach of penalized regression; (d) The penalized regression model revealed that the ET technique and diabetes at baseline were important predictors for aortic reintervention.

With the advent of endovascular stent-grafting of the thoracic aorta, alternative methods to manage disorders involving the aortic arch have been explored. To date, the available information shows a paucity in long-term follow-up, and open surgery remains the gold standard for extensive aortic arch pathology, even in high-risk patients.¹¹

Different institutions have published their experience and post-operative results on open surgical aortic arch replacement, although heterogeneity persists in procedural methods and complete long-term follow-up data are lacking.¹²

In our experience, hospital mortality and postoperative stroke occurred in 15.7% and 17.8% of all patients, respectively, and were acceptable, particularly considering that this study included an exceptionally high number of patients with acute aortic dissections who required an emergent/urgent operation (52.4%). Although it would

be important to determine the number of patients with connective tissue disorders and their specific outcomes, due to the retrospective nature of this study, this was impossible. Of note, according to only histopathological reports, in 47.7% of patients histopathologist indicated cystic medial degeneration, and in 7.6%, Marfan syndrome.

Given the complexity of the surgical procedures and high risk of the patients, including a high rate of patients with acute dissections, this study showed that the results of open aortic arch replacement are satisfactory in terms of both mortality and morbidity and in line with other reports.¹³⁻¹⁶

Different techniques have been described for total aortic arch replacement and have been modified over time.^{1,17} For the past two decades, the branched graft technique for supra-aortic vessel reimplantation has become the preferred surgical technique at our institution. This technique described by Kazui et al^{18,19} is believed to demonstrate several advantages. Replacing the proximal portion of the arch vessels where clots, atheroma, and calcifications are located can reduce the cerebral embolic risk. Furthermore, this technique should permit a shorter duration of CPB and DHCA and the use of bilateral ACP for cerebral protection.

Another older and common technique for aortic arch replacement is the island or en bloc technique. Since the island technique limits the number of anastomoses, it's believed that it decreases the overall circulatory arrest duration.

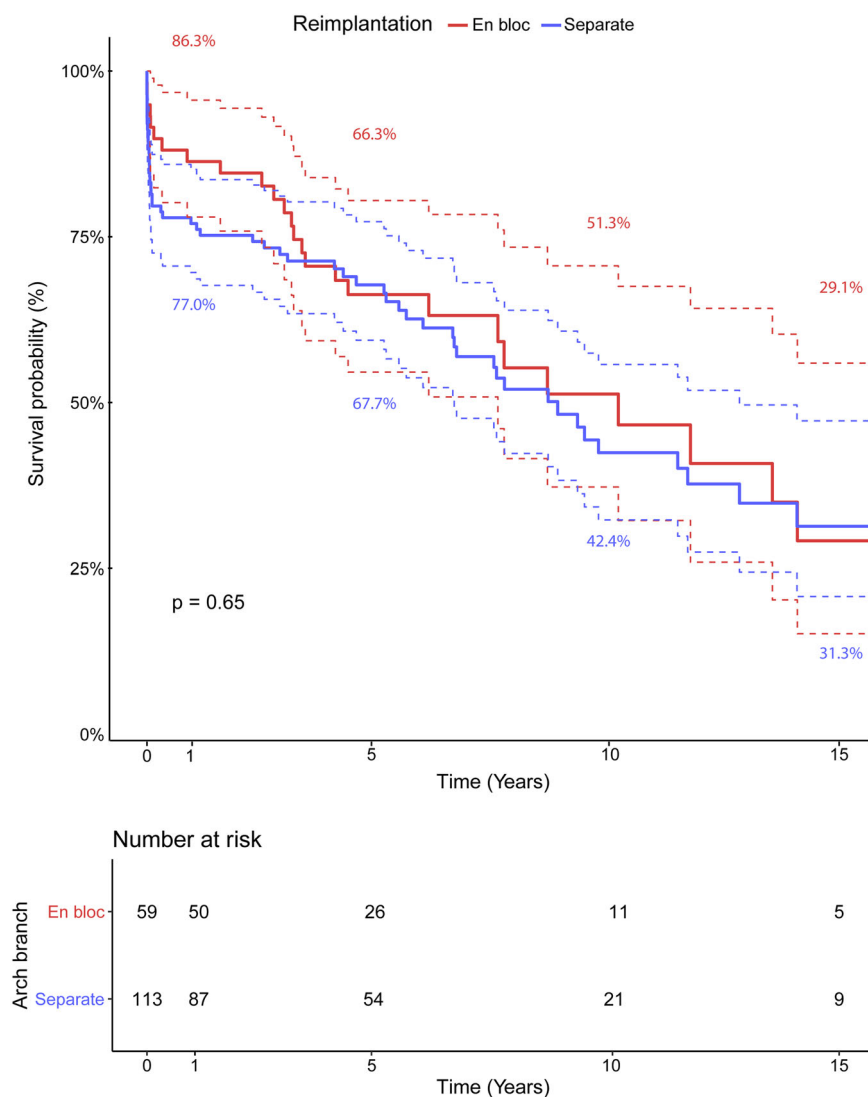


FIGURE 1 Late survival for patients who underwent aortic arch replacement, comparing the separate reimplantation (represented by the blue line) of supra-aortic vessels with the en bloc island patch (represented by the red line). The blue dashed lines represent 95% confidence intervals of the cumulative survival of the separate graft technique, and the red dashed lines represent the 95% confidence intervals of the cumulative survival of the en bloc technique

Comparing these two techniques, no difference was found in our study in terms of hospital mortality and the occurrence of postoperative stroke. However, the duration of CPB, ACC, and selective cerebral perfusion differed significantly between the two groups, with significantly longer times in the separate graft group. No cases of spinal cord and visceral injury were noted in this study, regardless of the period of lower body ischemia.

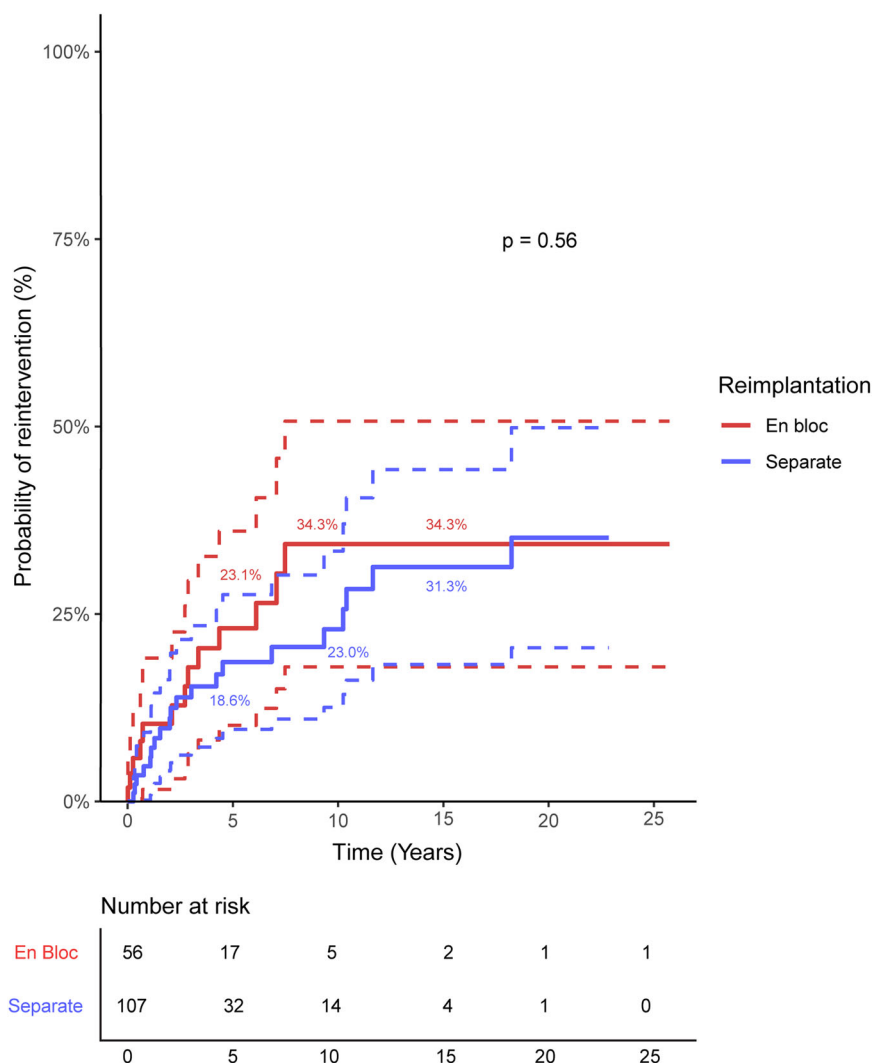
Di Eusano et al²⁰ found no difference in hospital mortality and morbidity between patients treated with the separate and en bloc techniques. However, their intraoperative results showed significantly higher duration times of CPB, DHCA, and ACP in patients treated with the en bloc technique. A recent report by Schoenhoff et al²¹ contradicted these findings by upholding significantly higher CPB, ACC and DHCA times in matched and unmatched cohort patients who underwent aortic arch replacement utilizing the separate graft technique. Furthermore, they confirmed our findings and found no difference in the stroke and mortality rates using the two techniques. Shrestha et al²² maintained that the branched graft technique is not inferior to the en bloc technique perioperatively or at the midterm follow-up of 103 patients who had undergone total aortic arch replacement.

Neither of the techniques increased the risk of a postoperative permanent neurological deficit. It appears reasonable to conclude that the suggestion that the additional manipulation of supra-aortic vessels during selective reimplantation is not associated with a higher stroke rate.

The overall survival rates at any point during the ten-year follow-up were in line with those of previous reports.^{11,21,23} Importantly, no significant difference was found in survival between the two cohorts. The penalized regression model revealed that older, symptomatic patients with preoperative renal dysfunction have a higher risk of dying in the long term.

The residual aortic tissue left during en bloc reimplantation of the supra-aortic branches can dilate over time and may result in the need for more reinterventions. Our findings showed no significant difference in aortic reinterventions, accounting for death as a competing risk, between the two surgical cohorts. The conventional ET technique was associated with a higher rate of aortic reinterventions. This finding is consistent with the ET procedure being usually utilized when subsequent surgical replacement of thoracic aorta is anticipated and can serve as an ideal landing zone for TEVAR.

FIGURE 2 Comparison of the cumulative incidence of aortic reinterventions between separate reimplantation (represented by a blue line) of supra-aortic vessels and the en bloc island patch (represented by a red line), accounting for death as a competing risk. The blue dashed lines represent 95% confidence intervals of the cumulative incidence of aortic reinterventions after the separate graft technique, and the red dashed lines represent 95% confidence intervals of the cumulative incidence of aortic reinterventions after the en bloc technique



4.1 | Study strengths and limitations

The current study was limited by several weaknesses. Although all-inclusive, it was a retrospective, single-center, and observational study. This study included only patients, whose replacement of aortic arch involved supra-aortic vessels, providing certain homogeneity. Nevertheless, the differences in presenting pathology and status may account for heterogeneity.

It's also important to emphasize the strength of the statistical approach. The penalized regression model used in this study is a more evolved method that is particularly suited when the number of covariates is large relative to the number of observations in the data set. Thus, the problem of overfitting was avoided.

5 | CONCLUSIONS

Although the current study was limited by the shortcomings of retrospective nature, it presents a detailed and complete follow-up of patients who underwent open replacement of the aortic arch, utilizing modern statistical methods. Our data suggest that open repair of the

aortic arch can be addressed with highly satisfactory early and late results. The current data show that the choice of the reimplantation technique does not affect hospital mortality, morbidity, or late survival.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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