Association between cardiopulmonary bypass time and 90-day post-operative mortality in patients undergoing arch replacement with the frozen elephant trunk: a retrospective cohort study

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Abstract

Background: The aortic arch replacement and cardiopulmonary bypass (CPB) are both associated with the early mortality after cardiothoracic surgery. This study aimed to investigate the relationship between CPB time and 90-day post-operative mortality in patients undergoing aortic arch surgery using the frozen elephant trunk (FET) technique with selective ante-grade cerebral perfusion (SACP).

Methods: We retrospectively reviewed data of 377 adult patients undergoing aortic arch surgery via FET with SACP from July 1, 2017 to December 31, 2018 at Beijing Anzhen Hospital. The baseline characteristics, intra-operative data, and post-operative data were collected. Univariate and multivariate Cox regression analyses were used to determine independent predictors of 90-day post-operative mortality.

Results: The 90-day post-operative mortality was 13.53%. The 78.51% of patients were men. There were 318 (84.35%) type A aortic dissections and 28 (7.43%) aortic aneurysms. Among those, 264 (70.03%) were emergency operations. Median CPB time was 202.0 (176.0, 227.0) min. Multivariate Cox regression analysis revealed that CPB time was independently associated with 90-day post-operative mortality after adjusting confounding factors (hazard ratio: 1.21/10 min increase in CPB time, 95% confidence interval: 1.15–1.27, $P < 0.001$). Kaplan-Meier analysis based on CPB time tertiles revealed that the top tertile (median 236.0 min) was associated with reduced survival rate compared with middle and bottom tertiles ($P < 0.001$). Each sub-group analysis based on the complexity of the underlying disease process showed similar associations between CPB time and 90-day post-operative mortality.

Conclusions: CPB time remains a significant factor in determining 90-day post-operative mortality in patients undergoing aortic arch surgery using FET with SACP. Surgeons should be aware of the relationship between CPB time and 90-day post-operative mortality during operative procedures and avoid extended CPB time as far as possible.

Keywords: Aortic arch replacement; Moderate hypothermia circulatory arrest; Selective ante-grade cerebral perfusion; Frozen elephant trunk; Cardiopulmonary bypass time; Mortality

Introduction

Even though aortic arch replacement has become more common with the increase of atherosclerosis and hypertension, it is still a complicated surgery. There has been a comprehensive evolution since its first description in 1956,[1] such as the use of moderate hypothermic circulatory arrest (MHCA) and selective ante-grade cerebral perfusion (SACP) for cerebral protection,[2,3] and frozen elephant trunk (FET) deployment at the descending aorta for hemostasis of distal aortic anastomosis.[4-6] However, early post-operative mortality after aortic arch replacement remains high.[7-9]

Cardiopulmonary bypass (CPB) remains unavoidable for the vast majority of patients undergoing cardiac surgery. Prolonged CPB has been hypothesized to increase the risk of acute renal failure and cerebral injury after cardiothoracic surgery,[10,11] and suggestive evidence supports an association between CPB time and early mortality after cardiothoracic surgery.[12-16] In 2008, Salis *et al*[12] examined the association between CPB time and

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post-operative mortality, and reported that the risk of post-operative mortality increased by 57% for every 30 min of CPB prolongation after multivariate adjustment in patients undergoing cardiac surgery. However, the study population only included patients undergoing cardiac surgery such as coronary artery bypass grafting (CABG) and valve replacement. Khaladj *et al*[13] confirmed this relationship in a larger group of patients undergoing arch replacement during a 7-year period. A recent study found that CPB time was not an independent risk factor of post-operative mortality in 199 patients undergoing aortic arch surgery.[15]

Considering the obvious contradiction of previous studies and the significant heterogeneity of the research population, we conducted a retrospective cohort study to re-assess the association of CPB time with 90-day post-operative mortality in patients undergoing arch replacement using a multivariate-adjusted regression model containing all known associated major peri-operative variables. At the same time, interaction and stratified analysis were investigated based on the complexity of the underlying disease process. Our hypothesis was that the risk of 90-day post-operative mortality would increase as CPB time increased.

Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Human Subjects Review Committee of Beijing Anzhen Hospital (Approval No. 2017058X). Individual informed written consent was waived owing to the retrospective study.

Study design and study population

From July 1, 2017 to December 31, 2018, consecutive patients undergoing aortic arch surgery with the FET technique were retrospectively identified at the Aortic Center in Beijing Anzhen Hospital. Patients who underwent total arch replacement using the FET technique with MHCA and SACP were collected in this observational cohort study. Patients who (1) underwent hemi-arch replacement ($n = 31$) or (2) with bilateral ante-grade cerebral perfusion ($n = 43$) or (3) with redo-sternotomy ($n = 19$) or (4) without the FET technique ($n = 40$) were excluded [Figure 1].

Study endpoint

The endpoint of this observational study was defined as early mortality during the hospital stay or within 90 days after surgery. The causes of death, including multiple organ failure, permanent neurologic dysfunction (stroke/coma), circulatory failure, and infectious toxic shock, were based on the corresponding documentation of the clinical condition in medical records.

Definition and procedure

The pathological type of aortic diseases included aortic dissection and aortic aneurysm, intra-mural hematoma and atherosclerotic ulcer. The type of dissection was defined according to the Stanford classification.[17] An emergent operation was defined as surgery performed within 24 h after admission. Acute dissection was traditionally diagnosed when the clinical symptoms had lasted 14 days or less.[18] Hypertension was defined as taking anti-hypertension drugs, or having a systolic or diastolic blood pressure >140 or 90 mmHg, respectively, at the time of admission. Diabetes mellitus was defined as treatment with oral hypoglycemic drugs or insulin, or having a fasting blood glucose level ≥7.0 mmol/L (1260 mg/L). Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[19] Renal insufficiency was defined as eGFR <60 $mL{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$. A history of cardiac artery diseases was considered if patients had a clinical history of myocardial infarction or underwent percutaneous coronary intervention or CABG before the current hospitalization. Cerebrovascular disease was defined as having relevant neurologic dysfunction before surgery or a previous stroke. Pericardial tamponade was diagnosed using echocardiography.

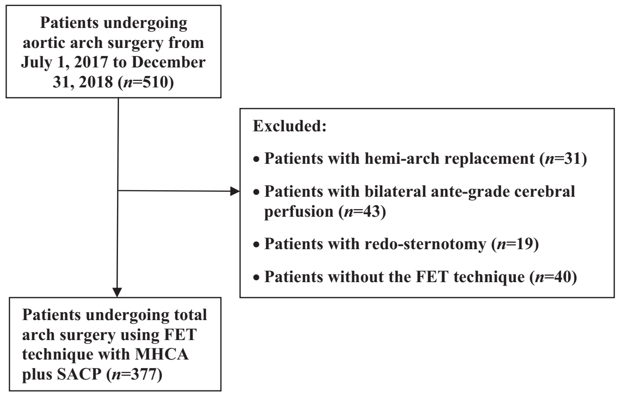

Figure 1: Flow chart of this study. FET: Frozen elephant trunk; MHCA: Moderate hypothermic circulatory arrest; SACP: Selective ante-grade cerebral perfusion.

Details of total arch replacement and FET implantation have been described elsewhere by our team.[20,21] Briefly, right axillary artery is the most commonly used artery in arterial cannulation. After the ascending aorta is cross-clamped, the heart is perfused with the cardioplegia solution. Any root procedure including root repair, Bentall procedure or others is done during cooling. Under MHCA (around 25°C) and SACP through the right axillary artery, the arch is opened. The FET (Cronus Microport, Shanghai, China) is deployed into the descending aorta. Its proximal end is connected with a four-branched vascular graft. Distal perfusion is resumed. Left common carotid artery, left sub-clavian artery, and innominate artery are reconstructed with branches of the four-branched graft one by one.

Data collected for the analysis

Clinical, operative, perfusion, and post-operative data were retrospectively collected from the department database, while further data were extracted from operation reports, perfusion reports, intra-operative computerized records, and medical record reviews. The database was filtered to identify all patients undergoing aortic arch surgery with the FET technique in July 2017. Data were compiled using the Empower Dataweb Data Collection Management System (X&Y Solutions, Inc., Boston, MA, USA). Follow-up data were obtained from medical records and telephone calls.

Statistical analysis

Categorical variables were presented as frequencies and percentages, whereas continuous variables were expressed as mean ± standard deviation for normal distribution data or median (Q1, Q3) for abnormal distribution data. Between-group differences in baseline characteristics, operative, perfusion, and post-operative data were analyzed using the Student's *t* test or Mann-Whitney *U* test for continuous variables and Chi-square test for categorical variables. Cox regression analyses were applied to identify the predictors of 90-day post-operative mortality. Multivariate Cox regression models were used to examine whether CPB had an independent effect on 90-day post-operative mortality. We also adjusted variables in the multivariate Cox regression models that, when added to this model, changed the matched hazard ratio (HR) by at least 10%, with the inclusion of additional covariates of known clinical importance. And CPB time was scaled by a factor of 5, 10, 15, and 20 to increase, respectively. A factor of ten to increase was chosen for better clinical interpretation [Supplementary Table 1, http://links.lww.com/CM9/A93]. Trend tests were computed by modeling the CPB time tertiles as continuous variables. Subsequently, survival estimates and cumulative event rates were compared using the Kaplan-Meier methods using the time-to-first event for each endpoint among the CPB time tertiles. The log-rank test was used to compare the Kaplan-Meier HRs for early post-operative mortality, and their corresponding 95% confidence intervals (CIs). Finally, interaction and stratified analysis based on the complexity of the underlying disease process was performed by Cox model. All analyses were performed using Empower (R) (http://www.empowerstats.com; X&Y solutions, Inc) and R (http://www.R-project.org).

Results

Demographic characteristics

The final analysis included 377 patients undergoing total arch replacement using the FET technique with MHCA plus SACP [Figure 1]. Among these 377 patients, mean age was 47.9 ± 10.7 years at admission, 296 (78.51%) were men, 187 (49.60%) had smoking history; on echocardiography, the mean left-ventricular ejection fraction (LVEF) was 62.58 ± 5.50%, and 55 patients (14.59%) presented severe aortic regurgitation; moreover, 300 patients (79.58%) had previous hypertension, 17 (4.51%) were previously diagnosed with diabetes mellitus, 56 (14.85%) had chronic kidney diseases, 26 (6.90%) had coronary artery disease, and 19 (5.04%) had cerebrovascular disease. At admission, lower-extremity ischemia was observed in 23 (6.10%) of all patients, 12 (3.18%) patients presented acute cardiac tamponade, 6 (1.59%) patients had acute visceral ischemia, and 1 (0.27%) patient presented spinal cord injury. The aortic diseases affecting the patients were: Stanford type A aortic dissection (84.35%), type B aortic dissection (5.84%), aortic aneurysm (7.43%), and others (2.39%). Of these, 264 (70.03%) were emergency operations [Table 1].

According to CPB time, patients were divided into three tertile groups: bottom tertile (111.0–181.9 min), middle tertile (182.0–214.9 min), and top tertile groups (215.0–547.0 min). No significant difference was found in patients' age, sex, smoking history, comorbidities, LVEF, left ventricular ejection fraction, left ventricular ejection fraction, severe aortic regurgitation or severe aortic stenosis between CPB time top tertile and bottom tertile. In addition, patients in top tertile had a higher body mass index (BMI) than those in bottom CPB tertile ($P < 0.001$). In top tertile group, Stanford type A aortic dissection accounted for a higher proportion (92.59%); at the same time, 80.00% of these patients underwent emergency surgery, and Bentall's operation was conducted in 52.59% of these patients, more frequently than the other two groups ($F = 23.497$, $P < 0.001$). In top tertile group, 14.07% of the patients underwent CABG and valve surgery simultaneously. Cross-clamp time ($F = 18.428$, $P < 0.001$) and SACP time ($F = 150.933$, $P < 0.001$) in top tertile group were longer than those in bottom tertile group.

CPB time and 90-day post-operative mortality

During the hospital stay or within 90 days after surgery, 51 (13.53%) patients developed early mortality events: 30 (7.96%) patients died of multiple organ failure, 15 (3.98%) patients died of permanent neurologic dysfunction, 2 (0.53%) patients died of circulatory failure, three patients (0.80%) died of infectious toxic shock, and one (0.27%) patient died of aortic rupture [Table 2].

The results of the univariate analyses of 90-day post-operative mortality are summarized in Table 3. Univariate analyses showed that the history of coronary artery disease and cerebrovascular disease, smoking history, emergency surgery, CPB time, cross-clamp time, and concomitant procedures (CABG and valve surgery) were associated with significant increases in the 90-day post-operative mortality. In the multivariable analysis, CPB time was the independent risk factor for 90-day post-operative mortality in Model I ($HR_{adjust\ I}$: 1.16/10 min increase, 95% CI: 1.12–1.20, $P < 0.001$) after adjustment for patients' age, sex, and BMI, and in Model II ($HR_{adjust\ II}$: 1.21/10 min increase, 95% CI: 1.15–1.27, $P < 0.001$) after adjustment for patients' age, sex, BMI, smoking history, coronary artery disease and cerebrovascular disease, aortic dissection A, emergency setting, concomitant procedures, clinical status, aortic root procedure, and the lowest bladder temperature [Table 4]. Kaplan-Meier survival analysis showed a significant difference among patients stratified by CPB tertile [Figure 2]. CPB time in the top tertile (median 236.0 min) was associated with the reduced survival rate compared with the middle and bottom tertiles (Log-rank, $P < 0.001$).

Table 1: Baseline characteristics of all patients according to CPB time tertiles.

Characteristics	Total (111.0–547.0 min) (*n* = 377)	Bottom tertile group (111.0–181.9 min) (*n* = 112)	Middle tertile group (182.0–214.9 min) (*n* = 130)	Top tertile group (215.0–547.0 min) (*n* = 135)	Statistical values	*P*
CPB time (min)	202.0 (176.0, 227.0)	160.5 (151.0, 172.3)	199.0 (190.0, 205.8)	236.0 (226.0, 263.0)	271.295*	<0.001
Age (years)	47.90 ± 10.73	47.35 ± 11.38	48.51 ± 10.75	47.76 ± 10.20	0.366*	0.694
Male	296 (78.51)	85 (75.89)	104 (80.00)	107 (79.26)	0.671	0.715
BMI (kg/m^2)	26.72 ± 4.36	25.41 ± 4.55	26.83 ± 4.21	27.68 ± 4.09	8.652*	<0.001
Smoking history	187 (49.60)	49 (43.75)	66 (50.77)	72 (53.33)	2.517	0.284
Comorbidities						
Diabetes mellitus	17 (4.51)	5 (4.46)	6 (4.62)	6 (4.44)	0.005	0.997
Hypertension	300 (79.58)	91 (81.25)	102 (78.46)	107 (79.26)	0.301	0.860
Coronary artery disease	26 (6.90)	6 (5.36)	9 (6.92)	11 (8.15)	0.743	0.690
Acute cardiac tamponade	12 (3.18)	2 (1.79)	6 (4.62)	4 (2.96)	1.596	0.450
Cerebrovascular disease	19 (5.04)	4 (3.57)	9 (6.92)	6 (4.44)	1.568	0.457
Acute visceral ischemia	6 (1.59)	0	3 (2.31)	3 (2.22)	2.580	0.275
Lower extremity ischemia	23 (6.10)	2 (1.79)	9 (6.92)	12 (8.89)	5.626	0.060
Spinal cord injury	1 (0.27)	0	0	1 (0.82)	1.817	0.403
Marfan syndrome	7 (1.86)	4 (3.57)	2 (1.54)	1 (0.74)	2.802	0.246
Chronic kidney disease	56 (14.85)	15 (13.39)	18 (13.85)	23 (17.04)	0.802	0.670
LVEF (%)	62.58 ± 5.50	63.15 ± 6.07	62.63 ± 5.27	62.07 ± 5.22	1.134*	0.323
LVEDD (mm)	50.87 ± 7.28	51.25 ± 7.36	50.56 ± 6.88	50.86 ± 7.62	0.263*	0.769
LVESD (mm)	33.59 ± 6.22	33.65 ± 6.49	33.30 ± 5.73	33.82 ± 6.47	0.216*	0.806
Severe aortic regurgitation	55 (14.59)	16 (15.53)	20 (15.87)	19 (14.39)	4.712	0.581
Severe aortic stenosis	1 (0.28)	1 (0.98)	0	0	3.478	0.481
Pathological type						
Acute	306 (81.17)	74 (66.07)	113 (86.92)	119 (88.15)	23.818	<0.001
Chronic	71 (18.83)	38 (33.93)	17 (13.08)	16 (11.85)	23.818	<0.001
Aortic dissection Stanford						
Aortic dissection A	318 (84.35)	79 (70.54)	114 (87.69)	125 (92.59)	24.239	<0.001
Aortic dissection B	22 (5.84)	18 (16.07)	2 (1.54)	2 (1.48)	30.381	<0.001
Aortic aneurysm	28 (7.43)	12 (10.71)	9 (6.92)	7 (5.19)	3.4659	0.177
Other	9 (2.39)	2 (1.79)	4 (3.08)	3 (2.22)	0.6487	0.723
Emergency surgery	264 (70.03)	57 (50.89)	99 (76.15)	108 (80.00)	28.258	<0.001
Aortic root procedure					23.497	<0.001
Ascending aortic replacement	212 (56.38)	77 (68.75)	76 (58.91)	59 (43.70)		
Bentall's procedure	151 (40.16)	33 (29.46)	47 (36.43)	71 (52.59)		
Aortic root repair	8 (2.13)	2 (1.79)	5 (3.88)	1 (0.74)		
Other	5 (1.33)	0 (0.00)	1 (0.78)	4 (2.96)		
Concomitant procedures (CABG and valve surgery)	33 (8.75)	10 (8.93)	4 (3.08)	19 (14.07)	10.034	0.007
Lowest nasopharyngeal temperature (°C)	23.99 ± 1.28	24.21 ± 1.13	23.93 ± 1.57	23.85 ± 1.04	2.612*	0.075
Lowest bladder temperature (°C)	25.41 ± 1.52	25.79 ± 1.37	25.41 ± 1.73	25.10 ± 1.34	6.474*	0.002
Times						
SACP (min)	37.06 ± 9.21	33.69 ± 7.75	36.47 ± 7.74	40.44 ± 10.44	150.933*	<0.001
Cross-clamp time (min)	114.55 ± 29.54	88.25 ± 16.18	113.75 ± 16.99	137.15 ± 29.32	18.428*	<0.001
MHCA (min)	27.70 ± 9.81	28.05 ± 7.78	26.82 ± 10.04	28.25 ± 11.03	0.805*	0.448
Flow for SACP (mL·kg^{-1}·min^{-1})	6.07 ± 2.07	5.97 ± 1.85	6.14 ± 2.56	6.09 ± 1.68	0.216*	0.806

The data are shown as mean ± standard deviation, median (Q1, Q3), or *n* (%). * *F* values, otherwise χ^2 values. CPB: Cardiopulmonary bypass; BMI: Body mass index; LVEF: Left ventricular ejection fraction; LVEDD: Left ventricular ejection fraction; LVESD: Left ventricular ejection fraction; CABG: Coronary artery bypass graft; SACP: Selective ante-grade cerebral perfusion; MHCA: Moderate hypothermia circulatory arrest time.

Sub-group analysis between CPB time and the 90-day post-operative mortality

Interaction and a sub-analysis were conducted stratifying patients by age tertiles, sex, BMI tertiles, smoking history, and the complexity of the underlying disease process [Table 5]. Interestingly, all sub-groups demonstrated a similar overall relationship between CPB time and 90-day post-operative mortality in patients undergoing total arch replacement using the FET technique with MHCA and SACP.

Table 2: Adverse outcome in all patients undergoing arch replacement using FET with MHCA and SACP.

Characteristics	Total (111.0–547.0 min) ($n=377$)	Bottom tertile group (111.0–181.9 min) ($n=112$)	Middle tertile group (182.0–214.9 min) ($n=130$)	Top tertile group (215.0–547.0 min) ($n=135$)	χ^2	*P*
90-day mortality	51 (13.53)	4 (3.57)	15 (11.54)	32 (23.70)	21.881	<0.001
Causes of death					26.074	0.004
Multiple organ failure	30 (7.96)	3 (2.68)	8 (6.15)	19 (14.07)		
Permanent neurologic dysfunction	15 (3.98)	1 (0.89)	5 (3.85)	9 (6.67)		
Circulatory failure	2 (0.53)	0	0	2 (1.48)		
Infectious toxic shock	3 (0.80)	0	1 (0.77)	2 (1.48)		
Aortic rupture	1 (0.27)	0	1 (0.77)	0 (0.00)		

The data are shown as *n* (%). FET: Frozen elephant trunk; MHCA: Moderate hypothermic circulatory arrest; SACP: Selective ante-grade cerebral perfusion; CPB: cardiopulmonary bypass.

Table 3: Univariate Cox regression analysis of 90-day post-operative mortality in all patients undergoing arch replacement using FET with MHCA plus SACP.

Items	HR (95% CI)	*P*
Age	1.02 (0.99–1.04)	0.253
Female	1.40 (0.76–2.59)	0.283
BMI	1.01 (0.95–1.08)	0.664
Smoking history	1.79 (1.01–3.16)	0.044
Diabetes mellitus	0.81 (0.20–3.33)	0.770
Hypertension	1.05 (0.53–2.09)	0.891
Coronary artery disease	3.36 (1.64–6.91)	0.001
Acute cardiac tamponade	1.31 (0.32–5.38)	0.709
Cerebrovascular disease	2.81 (1.20–6.58)	0.018
Acute visceral ischemia	1.33 (0.18–9.62)	0.778
Lower extremity ischemia	2.15 (0.92–5.05)	0.077
Spinal cord injury	0.00 (0.00–Inf)	0.996
Marfan syndrome	0.00 (0.00–Inf)	0.996
Clinical status		
Chronic	Reference	
Acute	1.52 (0.68–3.37)	0.304
Emergency surgery		
No	Reference	
Yes	2.13 (1.03–4.37)	0.040
Pathological type		
No- Aortic dissection A	Reference	
Aortic dissection A	3.14 (0.98–10.10)	0.054
Aortic root procedure		
Ascending aorta replacement	Reference	
Bentall's procedure	1.21 (0.69–2.11)	0.506
Aortic root repair	0.00 (0.00–Inf)	0.995
Other	1.57 (0.21–11.54)	0.659
Concomitant procedures (CABG and valve surgery)	2.63 (1.28–5.41)	0.008
Lowest nasopharyngeal temperature	0.98 (0.79–1.23)	0.889
Lowest bladder temperature	0.97 (0.80–1.16)	0.724
SACP	1.02 (0.99–1.05)	0.186
Cross-clamp time	1.01 (1.00–1.02)	<0.001
MHCA	1.00 (0.97–1.03)	0.975
Flow	1.05 (0.94–1.16)	0.411
CPB per 10 min	1.16 (1.12–1.20)	<0.001
CPB time tertiles		
Bottom tertile	Reference	
Middle tertile	3.36 (1.12–10.13)	0.031
Top tertile	7.35 (2.60–20.79)	<0.001
P for trend		<0.001

FET: Frozen elephant trunk; MHCA: Moderate hypothermic circulatory arrest; SACP: Selective ante-grade cerebral perfusion; HR: Hazard ratio; CI: Confidence interval; BMI: body mass index; CABG: Coronary artery bypass grafting; CPB: Cardiopulmonary bypass; Inf: Infinity (the model failed because of the small sample size).

Table 4: Multivariable Cox regression analyses of 90-day post-operative mortality in all patients undergoing arch replacement using FET with MHCA plus SACP.

	Non-adjusted		Adjust I		Adjust II	
Items	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
CPB time (per 10 min)	1.16 (1.12–1.20)	<0.001	1.16 (1.12–1.20)	<0.001	1.21 (1.15–1.27)	<0.001
CPB time tertile						
Bottom tertile	Reference		Reference		Reference	
Middle tertile	3.36 (1.12–10.13)	0.031	3.40 (1.12–10.30)	0.030	3.06 (0.98–9.56)	0.054
Top tertile	7.35 (2.60–20.79)	<0.001	7.54 (2.63–21.63)	<0.001	6.67 (2.22–20.09)	0.001
P for trend	<0.001	<0.001	<0.001			

Non-adjusted model adjust for: none. Adjust I model adjust for: age, sex, and body mass index. Adjust II model adjust for: age, sex, and body mass index; history of coronary artery disease, cerebrovascular disease and smoking, aortic dissection A, emergency surgery, concomitant procedures (coronary artery bypass grafting and valve surgery), clinical status (acute and chronic), aortic root procedure, lowest bladder temperature. FET: Frozen elephant trunk; MHCA: Moderate hypothermic circulatory arrest; SACP: Selective ante-grade cerebral perfusion; HR: Hazard ratio; CI: Confidence interval; CPB: Cardiopulmonary bypass.

Discussion

The present retrospective cohort study demonstrated the association of CPB time with 90-day post-operative mortality in a consecutive series of 377 patients who underwent aortic arch surgery using FET with MHCA plus SACP, the refined surgical techniques have become the routine application in our institution in less than 2 years. With every 10-min increase in CPB time, the risk of 90-day post-operative mortality increased by 16% (HR: 1.16, 95% CI: 1.12–1.20, $P < 0.001$). Moreover, the association between CPB time and 90-day post-operative mortality in patients undergoing the above-mentioned surgical approach remained the same after adjusting the confounding factors.

Our results were consistent with the study of Salis *et al*,[12] which found a 57% increased risk of post-operative mortality for 30-min increments of increased CPB time despite the heterogeneous populations who underwent different cardiac surgeries, such as CABG and vascular operation. Khaladj *et al*[13] also found that CPB duration was a risk factor for 30-day post-operative mortality in patients undergoing arch replacement. However, aortic aneurysms accounted for more than half of the study population (51.1%) in this previous study, while type A aortic dissection accounted for the vast majority in our current study (84.35%). A recent study did not find that CPB time was an independent risk factor for operative mortality in patients with total aortic arch repair.[15] Nevertheless, the sample size, in this recent study, of 199 patients was relatively small. Moreover, this recent study did not collect pre-operative status variables, such as comorbidities, that might affect the early post-operative mortality.[15] Our current study not only adjusted the pre-operative status in multiple regression models, but also performed interaction and stratified analysis based on associated major peri-operative predictors.

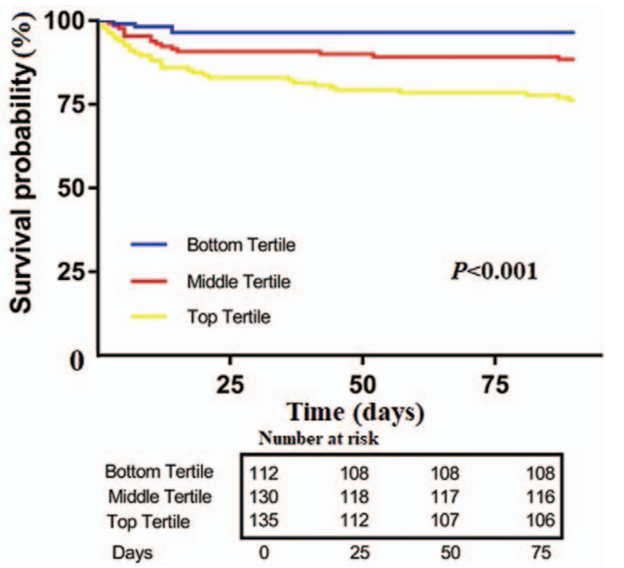

Figure 2: Kaplan-Meier analysis of freedom from 90-day post-operative mortality based on the CPB time tertiles (Log-rank, $P < 0.001$). CPB: Cardiopulmonary bypass time.

Our results indicated that CPB time in the top tertile of patients (median 236.0 min) who underwent arch replacement using FET with MHCA plus SACP was associated with poor outcomes. Side effects of CPB commonly have been attributed to the complex-associated inflammatory response. It activated the coagulation and fibrinolytic system,[22] the complement system,[23] and leukocytes as well as the release of cytotoxic enzymes and inflammatory mediators,[24] such as tumor necrosis factor-α, interleukin (IL)-1β, IL-6, and IL-8. The inflammatory mediators cause the activation of various inflammatory cascades that are thought to be responsible for parenchymal organ dysfunction, increasing the risk of post-operative multi-organ failure and infectious complications. A recent study found that prolonged CPB time could be a risk factor for infection after a cardiovascular operation.[25] In the present study, the 90-day post-operative mortality was 13.53%. However, of the 51 patients who died within 90 days after surgery, 30 died of multiple organ failure, accounting for 58.82% of all causes of death. The negative effect of CPB seemed to worsen with the increasing duration of CPB, accounting for the high rate of multiple organ failure (as high as 30%) in patients with the top CPB time tertiles.

Table 5: Effects of CPB time on 90-day post-operative mortality in each sub-group by Cox model.

CPB per 10 min	No. of participants	HR (95% CI)	*P*	*P* for interaction
Age				0.537
19.00–43.00 years	120	1.14 (1.01–1.28)	0.022	
44.00–52.00 years	136	1.22 (1.13–1.30)	<0.001	
53.00–75.00 years	121	1.14 (1.09–1.20)	<0.001	
Sex				0.317
Male	296	1.14 (1.10–1.19)	<0.001	
Female	81	1.20 (1.12–1.28)	<0.001	
BMI tertiles*				0.275
14.93–24.46 kg/m^2	116	1.13 (1.07–1.18)	<0.001	
24.47–27.75 kg/m^2	127	1.16 (1.07–1.26)	<0.001	
27.76–54.64 kg/m^2	132	1.21 (1.13–1.30)	<0.001	
Cerebrovascular disease				0.999
No	358	1.16 (1.12–1.20)	<0.001	
Yes	19	1.08 (0.88–1.33)	0.462	
Coronary artery disease				0.219
No	351	1.16 (1.12–1.20)	<0.001	
Yes	26	1.14 (1.03–1.25)	0.010	
Smoking history†				0.057
No	189	1.20 (1.15–1.26)	<0.001	
Yes	187	1.13 (1.06–1.19)	<0.001	
Aortic dissection A				0.859
No	59	1.15 (1.03–1.27)	0.009	
Yes	318	1.18 (1.13–1.23)	<0.001	
Emergency surgery				0.599
No	113	1.16 (1.08–1.24)	<0.001	
Yes	264	1.18 (1.12–1.23)	<0.001	
Clinical status				0.919
Acute	306	1.18 (1.13–1.24)	<0.001	
Chronic	71	1.16 (1.08–1.24)	<0.001	
Concomitant procedures (CABG and valve surgery)				0.576
No	344	1.15 (1.10–1.20)	<0.001	
Yes	33	1.12 (1.05–1.20)	0.001	
Aortic root procedure‡				0.886
Ascending aorta replacement	212	1.18 (1.12–1.24)	<0.001	
Bentall's procedure	151	1.16 (1.07–1.26)	<0.001	
Aortic root repair	8	0.90 (0.00–Inf)	1.000	
Other	5	2.74 (0.00–Inf)	0.997	

Adjusted for age, sex, BMI, the history of smoking, coronary artery disease and cerebrovascular disease, the type A of aortic dissection, emergency surgery, clinical status (acute and chronic), concomitant procedures (coronary artery bypass grafting and valve surgery), and aortic root procedure except the sub-group variable. *BMI tertiles: two missing values, †Smoking history: one missing values, ‡Aortic root procedure: one missing value. CPB: Cardiopulmonary bypass; HR: Hazard ratio; CI: Confidence interval; BMI: Body mass index.

In addition, a longer CPB time might reflect the complexity of the pre-operative patient condition and the heterogeneous pathological type of aortic disease. There were 306 patients (81.17%) with acute aortic disease and type A aortic dissection accounted for 84.35% in this cohort. Also, 264 (70.03%) cases were operated upon as an emergency. In clinic, the patients who require emergency surgery generally have a more acute symptom onset, are at high-risk of aortic rupture or have dissection-related complications. Previous studies have shown the association between emergency surgery and high mortality in aortic operations.[26] Therefore, we adjusted these potential confounding factors in multiple Cox regression models. At the same time, we performed sub-group analysis according to the pre-operative clinical status and intra-operative conditions. However, the relationship between CPB time and 90-day mortality remained unchanged.

There were several limitations to our study. First, this study was retrospective design from a single-center and lacked representativeness. Future clinical studies using multi-center data to validate or disagree with our findings are appropriate. Second, although type A aortic dissection accounted for the majority of the pathological type of aortic diseases in this study, the pathological type was also heterogeneous, and surgical treatment of aortic root was diverse. However, we performed sub-group analyses to explore the effects of each sub-group on 90-day post-operative mortality. Third, there was an inescapable possibility that longer CPB time was associated with the conduct of less experienced surgeons, which was difficult to quantify. However, this retrospective study was conducted in a single-center. Our center is the largest referral center for aortic disease in China, and all surgeons received standard training. Furthermore, the study represented real-world practice and provided the surgeons with guidance on real-time decision making in the operating room.

In conclusion, despite the improvements in organ protection in the past decades, such as MHCA and SACP for cerebral protection, CPB time remains a significant independent risk factor for 90-day post-operative mortality in our patient population. Surgeons should be aware of the relationship during operative procedures in patients with arch replacement and attempt to avoid longer CPB times as far as possible.

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Conflicts of interest

None.

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