Concomitant aortic root replacement during frozen elephant trunk implantation does not increase perioperative risk

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Glossary of Abbreviations

FET Frozen elephant trunk

Visual abstract

Key question. Is concomitant aortic root replacement during frozen elephant trunk total arch replacement safe? (96/120 characters)

Key findings. Concomitant root replacement prolongs operative times, but does not influence postoperative outcomes or operative risk. (119/120 characters)

Take-home message. The FET procedure should not be a contraindication for concomitant root replacement, particularity in patients with borderline indications. (140/140 characters)

Abstract

Word count: 218/250 words

Objectives. Our aim was to evaluate the risk of concomitant aortic root replacement during frozen elephant trunk (FET) total arch replacement.

Methods. Between 03/2013 and 02/2021, 303 patients underwent aortic arch replacement using the FET technique. Patient characteristics, intra- and postoperative data were compared between patients with (n=50) and without (n=253) concomitant aortic root replacement (implantation of a valved conduit or using the reimplantation valve sparing technique) after propensity score matching.

Results. After propensity score matching there were no statistically significant differences in preoperative characteristics including the underlying pathology. There was no statistically significant difference regarding arterial inflow-cannulation or concomitant cardiac procedures, while cardiopulmonary bypass ($p<0.001$) and aortic cross-clamp ($p<0.001$) times were significantly longer in the root replacement group. Postoperative outcome was similar between the groups and there were no proximal reoperations in the root replacement group during follow-up. Root replacement was not predictive for mortality ($p=0.133$, odds ratio: 0.291) in our Cox regression model. There was no statistically significant difference in overall survival (log rank: $p=0.062$).

Conclusions. Concomitant FET implantation and aortic root replacement prolongs operative times, but does not influence postoperative outcomes or increase operative risk in an experienced high-volume centre. The FET procedure did not appear to be a contraindication for concomitant aortic root replacement even in patients with borderline indications for aortic root replacement.

57 **Keywords**: frozen elephant trunk (FET); aortic root replacement; aortic root; aortic arch;

Introduction

The frozen elephant trunk (FET) procedure has evolved as an effective and common treatment in patients with thoracic aortic pathologies involving the aortic arch with good postoperative outcome but a high incidence of planned and unplanned distal aortic reinterventions **[1-7]**. However, the procedure remains complex and still carries a high risk for adverse events **[4, 7, 8]**. While FET implantation in our high-volume centre is already performed as a training procedure and therefore concomitant root replacement could be carried out more liberally, the addition of cardiac and aortic root procedures still increases the complexity of the procedure further **[9]**. Hence, surgeons may be hesitant to perform concomitant cardiac and/or aortic root procedures during FET total arch replacement particularly in patients with borderline indications. Therefore, our aim was to evaluate the risk of concomitant aortic root replacement during FET total arch replacement, i.e. the risk of a complete proximal thoracic aortic fix rom the root beyond the aortic arch.

Patients and Methods

Ethical statement. Our institutional review committee approved this retrospective study, and the need for informed consent was waived (number: 20-1302; approval date: February 4, 2021).

Patients and follow-up protocol. Between 03/2013 and 02/2021, 303 patients underwent FET total arch replacement in one aortic centre currently performing over 60 total aortic arch procedures per annum (as of 2021). Patients were followed-up for a total of 421 patient-years, with a median follow-up of 8 [first quartile: 1; third quartile 29] months. All patients were routinely followed-up after six months, twelve months and yearly thereafter in our dedicated aortic clinic. Computed tomography angiography (CTA) scans were done preoperatively, before discharge, during every follow-up visit, and when clinically warranted.

Surgical approach and technique. Our standardised, integrated surgical management of the FET technique has been reported **[10-12]**. In short, we carry out a full sternotomy and generally cannulate the right axillary artery for arterial inflow for cardiopulmonary bypass. Any concomitant procedures (valve, aortic root, coronary artery) take place while the patients are cooled down to a target core body temperature of 25°C. We routinely apply cold-blood cardioplegia or the beating-heart technique (using 300 mL of normothermic myocardial perfusion) **[12]**. Bilateral cerebral perfusion is normally used and we liberally perform trilateral antegrade cerebral perfusion (additional cannulation of the left subclavian artery) when needed. For this reason, today, our preoperative work-up includes a CTA of the supra-aortic vessels including the Circle of Willis.

Zone 2 is our standard anastomosis site for FET implantation, and today, we use the short version (100 mm) of the Thoraflex (Terumo Aortic, Inchinnan, UK) hybrid-graft exclusively. In case of classical aneurysm formation, we oversize the stent-graft component by 10% at the distal landing zone and in case of aortic dissections we avoid oversizing and choose the FET stent-graft size according to institutional standards. We do not routinely implant cerebrospinal fluid drainage before surgery.

Indication for aortic root replacement. In the vast majority of patients root replacement was carried out according to the 2014 ESC guidelines **[13]**. In selected cases of young patients or/and patients with connective tissue disease especially if the wall of the aortic root appeared considerably thin intraoperatively, root replacement was done in root diameters lower than the guideline´s threshold in an anticipative manner.

Data collection and definition of parameters. Data were collected retrospectively relying on our prospectively-maintained aortic database. Acute aortic dissection was defined as a symptom onset fewer than 14 days before hospital admission and was classified as chronic if symptoms had occurred >14 days beforehand. The TEM classification was used to categorise aortic dissections (Type A, Type B, Type non-A non-B) **[14]**. The modified Rankin Scale (mRS) was used to classify the postoperative-stroke severity. Consulting neurologists evaluated all the strokes. Postoperative strokes causing no clinical symptoms (mRS 0), no significant disability (mRS 1), or slight disability (mRS 2) were classified as non-disabling postoperative strokes.

Statistical Analysis. Since the data has been collected during an observational study, we applied propensity score matching. This mitigated the risk of confounding variables distorting the results. We achieved this by identifying pairs of observation that had the same propensity to experience the treatment, but which differ in their actual treatment. To estimate propensity scores, we used the following variables: aneurysm, penetrating aortic ulcer, male, age, diabetes, history of stroke, history of smoking, hyperlipidaemia, hypertension, history of renal failure, chronic obstructive pulmonary disease, coronary artery disease, bicuspid aortic valve, and connective tissue disease. We used a nearest neighbor method and a caliper of 10% of the standard deviation of the propensity score logit. This approach lead to a total sample of 96 observations, with 48 patients with and without concomitant aortic root replacement. To measure treatment effects, we employed standard statistical techniques at a 5% signifiance level. A Student t tests or Wilcoxon signed-rank tests was used to compare continuous variables as appropriate. McNemar tests was used for comparing frequencies. Data are presented as absolute and relative frequency or as median [first quartile, third quartile]. A Cox regression analyses was performed to investigate the influence of clinically selected variables on overall mortality (selected variables: sex, age, concomitant root replacement, redo case, acute pathology) and the Kaplan Meier method was used to analyse and compare overall survival. No primary analysis was defined, therefore p-values may not be interpreted as confirmatory but rather descriptive. The analysis was performed with the statistical software R (version 4.1.1) and the library "MatchIt" (version 4.3.4), running on MacOS x86_64-apple-darwin17.0.

Results

Patient characteristics. Concomitant aortic root replacement was performed in 50 (17%) patients using a valved conduit (n=27, 54%) or the valve-sparring reimplantation technique (n=23, 46%). These patients were significantly younger (p=0.002), predominantly male (p=0.051), commonly presented with a bicuspid aortic valve (p=0.016), underwent prior aortic valve replacement (p=0.024) and more commonly presented with a Type A aortic dissection (p=0.018). Patient characteristics are summarised in **Table 1**. There were no statistically significant differences between patients with and without concomitant aortic root replacement after propensity score matching (**Supplemental Table 1**).

Surgical details. As **Table 2** shows, the right axillary artery was the preferred arterial inflow site in most patients and there were no statistically significant differences regarding the cannulation site or the incidence of additional cardiac procedures between the two matched groups. However, cardiopulmonary bypass (p<0.001), aortic cross-clamp (p<0.001) times were significantly longer in the root replacement group significantly prolonging the duration of the surgery (p=0.001). Unmatched data is presented in **Supplemental Table 2**. Indications for root replacement are summarized in **Table 3**.

Outcome characteristics. Outcome characteristics are summarised in **Table 4** and **Supplemental Table 3**. There was no difference between the two groups regarding postoperative outcomes. In fact, in-hospital mortality tended to be lower in patients undergoing concomitant aortic root replacement, but the difference did not reach statistical significance (p=0.111). In addition, overall survival tended to be higher in these patients as well but the difference did also not reach statistical significance (log rank: p=0.062). No proximal reoperation was necessary in any patient in the root replacement group during follow-up.

Regression analysis. Concomitant root replacement was not identified as a significant variable in our Cox regression model. The full model is shown in **Table 5**.

Discussion

Our study's most important findings can be summarised as: (i) Concomitant FET implantation and aortic root replacement is common particularly in patients with Type A aortic dissection and in redo scenarios. (ii) Concomitant aortic root replacement prolongs operative times, but does not impact postoperative outcomes or increases operative risk. (iii) The FET procedure should not be a contraindication for concomitant aortic root replacement by itself, particularity in patients with borderline indications for aortic root replacement.

There were statistically significant differences regarding the baseline characteristics between the two unmatched groups, in particular, patients undergone concomitant aortic root replacement were significantly younger and more commonly men in our cohort. Both difference may be associated with the significantly higher incidence of patients with bicuspid aortic valves in this study. In fact, a bicuspid aortic valve is generally more common in male patients and patients with bicuspid aortic valve have a significantly higher risk for adverse aortic events at younger ages with lower cardiovascular risk factors present **[15, 16]**. This fact may also explain the significantly higher incidence of Type A aortic dissections (acute or residual after prior repair) in patients with concomitant aortic root replacement. According to previous reports of patients with acute Type A dissections, the need for concomitant root replacement has been reported to be higher in patients with a bicuspid compared to patients with a tricuspid aortic valve **[16, 17]**. In residual aortic dissection cases after previous repair for acute type A aortic dissection, it seems plausible that surgeons tend to aim for a complete aortic repair when performing the frozen elephant trunk technique as a redo case in order to prevent any third step intervention for any residual root pathology and because the frozen elephant trunk procedure has been shown to be safe in redo scenarios **[18, 19]**.

Intraoperative data reflect our standardized, integrated surgical approach to the FET procedure with the right axillary artery as our routine choice for arterial inflow. The carotid artery remains a back-up option for arterial inflow in stable patients with compromised supraaortic perfusion due to an acute dissection of the brachiocephalic trunk even though we usually also cannulate the right axillary artery, as we did not see a higher risk for cerebral malperfusion in these patients **[20, 21]**. In selected scenarios (hemodynamically unstable patients, severe risk for spinal cord ischemia, re-do cases with retrosternal adhesions), the femoral artery may also be used. We generally switch to central perfusion or establish concomitant axillary and femoral artery perfusion (e.g. in atherosclerotic scenarios with risk for spinal cord ischemia, when iliac artery perfusion is compromised preoperatively).

The beating heart technique is liberally performed in our centre and may simply be performed when an artificial graft is present in the ascending aorta **[12, 22]**. This may explain the numerically higher rate of beating heart procedures in patients with concomitant root replacement, since the procedure is usually carried out during cooling of the patient. Cardioplegia may then be stopped for the arch procedure and the FET can be implanted with a beating heart. The benefits of the beating heart technique during FET total arch repair have been shown by the Hannover group and by us previously **[12, 22, 23]**.

The addition of a concomitant root replacement obviously caused longer operative times but did not affect postoperative outcomes. In fact, while there were not statistically significant difference in postoperative outcome, there was a numerically better outcome in patients with concomitant root replacement. Similar results have previously been reported in isolated Type A aortic dissection populations **[23]**. Hence, in patients with borderline indications for root replacement, this data suggests that the procedure can be performed safely.

Limitations and strengths. Our study is limited by its small sample size and retrospective nature. Of note, concomitant root replacement revealed favourable results in our and other high-volume centres but these results may not be reproducible in less experienced centres. However, this investigation contributes valuable knowledge on outcomes after concomitant aortic root replacement during FET total arch replacement.

Conclusion

Concomitant FET implantation and aortic root replacement prolongs operative times, but does not influence postoperative outcomes or increase operative risk in an experienced high-volume centre. The FET procedure did not appear to be a contraindication for concomitant aortic root replacement even in patients with borderline indications for aortic root replacement. Further prospective multicentre studies or registry data are needed to confirm our results and their reproducibility.

Acknowledgments and Disclosures

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Data availability statement

The datasets presented in this article are not readily available because of the requirements of our institutional review board. Individual reasonable requests will be evaluated by the corresponding author.

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Tables

Table 1. Patient characteristics (unmatched data)

	No root replacement (n=253)	Root replacement (n=50)	p-value
Age (years)	67 [59, 75]	62 [56, 70]	0.022
Male	160 (63)	39 (78)	0.051
Diabetes mellitus type 2	0 (0)	8 (16)	0.361
Hyperlipidemia	85 (34)	15 (30)	0.627
Hypertension	216 (85)	40 (80)	0.280
Coronary artery disease	77 (30)	13 (26)	0.613
History of smoking	113 (45)	20 (40)	0.538
COPD	26 (10)	4 (8)	0.798
History of stroke	33 (13)	6 (12)	1.000
Renal impairment	34 (13)	7 (14)	1.000
Bicuspid aortic valve	8 (3)	6 (12)	0.016
Connective tissue disease	19 (8)	8 (16)	0.098
Redo case	79 (31)	19 (38)	0.229
CABG	7 (3)	1 (2)	1.000
AVR	32 (13)	1 (2)	0.024
MVR	2 (31)	0 (9)	1.000
Ascending	78 (31)	19 (38)	0.407
Hemi-arch	31 (12)	9 (18)	0.360
Other	55 (22)	12 (24)	0.852
Type A dissection *	90 (36)	27 (54)	0.018
Acute	38 (15)	9 (18)	0.669
Type B dissection	34 (13)	5 (10)	0.646
Acute	22 (9)	2 (4)	0.391
Type non-A-non-B dissection	34 (13)	3 (6)	0.163
Acute	22 (9)	1 (2)	0.143
Aneurysm	69 (27)	14 (28)	1.000
PAU	23 (9)	1 (2)	0.147
Other	3 (1)	2 (4)	0.192

Values are n (%) or median [fist quartile, third quartile].
COPD; chronic, obstructive pulmonary disease; CABG, coronary artery bypass graft; AVR, aortic valve replacement; MVR, mitral valve reconstruction; PAU, penetrating aortic ulcer
*including chronic residual dissections

Table 2. Surgical details (propensity score matched population)

	No root replacement (n=48)	Root replacement (n=48)	p-value
Cannulation			
Aorta	0 (0)	1 (3)	1.000
Femoral	3 (7)	0 (0)	0.242
Axillary	47 (98)	45 (94)	0.612
Carotid	1 (3)	4 (9)	0.362
Valved conduit	-	26 (55)	--
VSARR	-	22 (46)	--
AVR	8 (17)	-	--
CABG	6 (13)	8 (17)	0.772
Beating heart	6 (13)	13 (28)	0.124
CPB time (min)	208 [167, 253]	246 [218, 285]	<0.001
CX time (min)	106 [91, 156]	176 [124, 205]	<0.001
SACP time (min)	103 [81, 128]	113 [53, 169]	0.526
Duration of surgery (min)	372 [325, 415]	422 [371, 501]	0.001
Lowest body temperature (°C)	25 [24, 25]	25 [24, 25]	0.772

Values are n (%) or median [fist quartile, third quartile]. VSARR, valve sparring aortic root replacement; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; CX, aortic cross-clamp; SAP, selective antegrade cerebral perfusion

Table 3. Indications for root replacement	
Root aneurysm	33 (66)
Root dissection	15 (30)
Severe aortic regurgitation + Aneurysm	2 (4)

Values are n (%).

Table 4. Outcome characteristics (propensity score matched population)

	No root replacement (n=48)	Root replacement (n=48)	p-value
Dialysis	5 (11)	1 (3)	0.204
Tracheotomy	5 (11)	2 (5)	0.435
Paraplegia	0 (0)	0 (0)	--
Stroke	8 (17)	4 (9)	0.355
Non-disabling	3 (7)	1 (3)	0.617
In-hospital mortality	6 (13)	1 (3)	0.111
Proximal reoperation*	1 (3)	0 (0)	1.000

Values are n (%).
*during follow-up

Table 4. COX Regression: Overall mortality (propensity score matched population)			
Variable	p	OR	95% CI
Sex	0.975	1.026	0.206-5.116
Age	0.330	1.030	0.971-1.092
Root replacement	0.133	0.291	0.058-1.454
Redo case	0.422	1.703	0.464-6.248
Acute pathology	0.355	1.893	0.489-7.320

OR, odds ratio; CI, confidence interval

Figure Legend

Central Image.

Kaplan-Meier curve of overall survival of patients following frozen elephant trunk total arch replacement with (turquois) or without (red) concomitant aortic root replacement. Log rank: p=0.062). Time in years.

Central image