Featured Article

Warming up the frozen elephant trunk for aortic arch pathology

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Background: The frozen elephant trunk (FET) technique is a well-established procedure for chronic and acute aortic arch (AA) pathologies. Over time, practice has shifted from deep to moderate hypothermic circulatory arrest (HCA), especially for elective cases. This strategy might, however, impact neurological and renal outcomes. The aim of this single-center study is to assess the safety of very mild HCA (MiHCA) in patients who underwent FET with a core temperature ≥30 ℃.

Methods: Data on all consecutive patients who electively or urgently underwent FET requiring HCA at Cardiac Surgery Unit of the University of Pisa were collected. In all cases, antegrade selective cerebral perfusion was performed, and hypothermia was maintained only during circulatory arrest (CA). We assessed postoperative acute kidney injury (AKI), neurological events, and bleeding as primary endpoints. Multivariable analysis was performed to evaluate the predictors of the three outcomes.

Results: We included 92 patients, 86% of which presented with an acute aortic syndrome. Of this cohort, 17% had neurological deficits at baseline and 9% were intubated at arrival; the German Registry of Acute Aortic Dissection Type A (GERAADA) score was 24%±14%. The mean bladder temperature was 30±1.6 ℃, and the mean cardiopulmonary bypass (CPB) and CA times were 219±78 and 15 (I–III quartile, 13–19) min, respectively. Median cerebral perfusion time was 59 (I–III quartile, 31–113) min, bilateral antegrade cerebral perfusion (ACP) was performed in 96% of cases, and unilateral in 4%. Packing for bleeding was necessary in 4% of cases, and 21% of patients required surgical revision for bleeding within the first 24 hours from surgery. We had one (1%) fatal, eight (9%) disabling, and five (5%) non-disabling strokes, while 6% of patients developed renal impairment requiring temporary venovenous hemofiltration. Thirty-day mortality was 14%. Bladder temperature was not associated with outcomes, while retrograde perfusion and GERAADA score were predictors of neurological events. GERAADA score also tended to predict postoperative bleeding, while the involvement of the descending aorta tended to predict renal impairment.

Conclusions: CA with core temperatures above 30 ℃, paired with selective bilateral cerebral perfusion, resulted in the best outcomes in patients undergoing FET in case of acute aortic syndromes.

Keywords: Frozen elephant trunk (FET); mild hypothermic circulatory arrest (MiHCA); acute aortic syndrome; antegrade cerebral perfusion (ACP)

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Introduction

The frozen elephant trunk (FET) procedure is a complex technique used to treat both chronic and acute aortic arch (AA) disease. However, it necessitates hypothermic circulatory arrest (HCA) to operate in a bloodless environment and ensuring organ protection through metabolic suppression (1-3). While its introduction has reduced circulatory arrest (CA) times compared to the conventional elephant trunk procedure (2), it is still associated with neurological complications and perioperative mortality (4). The advent of antegrade cerebral perfusion (ACP) has led to a gradual increase in CA temperature, shifting from moderate HCA (MoHCA; temperature ≥22–27 ℃) to mild HCA (MiHCA; temperature ≥28–30 ℃), thereby reducing surgical times and the risk of bleeding (5-8). Recent studies support this trend, suggesting that higher temperatures can provide adequate neuroprotection and reduce systemic complications associated with deep hypothermia (9-11). Nevertheless, the debate over the optimal temperature strategy continues; some authors advocate for MiHCA combined with bilateral ACP, while others argue that deep hypothermia remains necessary in certain patients to prevent neurological events, visceral ischemia, and renal injury, especially when ACP is not feasible or when prolonged lower body ischemia is present (12). This study aims to assess the incidence of postoperative neurological events, bleeding, and kidney injury in patients who underwent FET with ACP at a core temperature >30 ℃.

Methods

This retrospective observational study includes all consecutive patients who underwent the FET procedure at the Cardiac Surgery Unit of the University of Pisa from January 2019 to March 2025. The cohort comprises both elective and urgent patients who underwent surgery for acute aortic syndromes or chronic aneurysmal disease. CA and ACP were performed in all the included patients. All procedures were conducted in MiHCA with a core temperature of approximately 30 ℃. Core temperature was continually monitored via a dedicated Foley bladder catheter with a temperature probe. Throughout the procedure, continuous bilateral monitoring of cerebral oxygen saturation was achieved using Near Infrared Spectroscopy (NIRS-Medtronic INVOS).

ACP was either performed through direct cannulation of the supra-aortic vessels, according to the Kazui technique and using a dedicated cannula (TrueFlow RDB), right axillary artery cannulation, left axillary artery, or a combination of axillary artery/arteries and supra-aortic vessels cannulation. Cerebral perfusion flow was maintained between 8 and 10 mL/kg/min until physiological antegrade perfusion was restored. Anesthesia management during CA was standardized with head ice packing and administration of high-dose corticosteroids and phenobarbital to suppress cerebral activity a few minutes before the arrest. Bilateral radial or brachial invasive artery pressure monitoring was always present. At the Cardiac Surgery Unit of the University of Pisa, when necessary, root surgery is typically performed first. After completing the distal arch anastomosis and restoring systemic flow, the arch prosthesis is connected to the aortic root, enabling heart perfusion. Supra-aortic vessel reconstruction is then performed as the final step, with a left subclavian artery extra-anatomic bypass in cases of complex intrathoracic management. All procedures were performed by staff surgeons, with the choice of arterial and venous cannulation, cardioplegia delivery, and ACP configuration made at the surgeon's discretion. Preoperative, intraoperative, and postoperative data were collected retrospectively through the review of electronic medical records.

The following outcomes were evaluated: (I) 30-day mortality; (II) occurrence of any postoperative neurological events (including transient ischemic attacks and disabling or not-disabling strokes); (III) postoperative major bleeding events, defined as either need for mediastinal packing for hemostatic control at the end of index surgery and/or re-sternotomy for bleeding in the first 72 hours after index surgery; and (IV) acute kidney injury (AKI), defined as a ≥150% increase in baseline creatinine within 72 hours and/or need for continuous venovenous hemofiltration (CVVH). Postoperative neurological events were assessed either with neurological examination by local expert neurologist and/or with computed tomography (CT) scan (at assessment and after 48 and 72 hours). Continuous variables were presented as mean ± standard deviation (SD) or as median with I–III quartile, according to data distribution, and were compared using Student's *t*-test or the Mann-Whitney *U* test, as appropriate. Categorical variables were expressed as absolute numbers and percentages and were compared using the chi-square test or Fisher's exact test, as applicable. To identify variables independently associated with neurological events, bleeding events, and renal events, multivariable regression models were employed. For each of these outcomes, one model was developed based on baseline characteristics and another based on intraprocedural variables, allowing for the separate evaluation of pre-procedural and procedural risk factors. The variables used to develop the model were chosen according to clinical experience and published literature and included, for baseline, age, sex, German Registry of Acute Aortic Dissection Type A (GERAADA) score, history of chronic kidney disease, previous cardiac surgery, acute aortic syndrome as presentation, involvement of the descending aorta and shock status upon arrival, while for intraprocedural,

Table 1 Baseline characteristics

Variables	Data (n=92)
Male	68 [74]
Marfan's syndrome	2 [2]
Chronic kidney disease	6 [7]
Dialysis	2 [2]
Redo-cardiac surgery	9 [10]
Diabetes	6 [7]
COPD	5 [5]
GERAADA score (%)	24±14
Neurological events	16 [17]
Hemiparesis or hemiplegia	12 [13]
Coma	4 [4]
Aortic disease	
Acute aortic syndrome	79 [86]
Chronic aneurysm	13 [14]
Aortic insufficiency	34 [37]
Pericardial effusion	26 [28]
Tamponade	8 [9]
Intubation at referral	8 [9]
Preoperative shock status	15 [16]
Preoperative catecholamine support	5 [5]
Resuscitation before surgery	2 [2]
Descending aorta involvement	62 [67]
Preoperative malperfusion coronary	16 [17]
Preoperative malperfusion visceral	15 [16]
Preoperative malperfusion peripheral	18 [20]

Data are presented as n [%] or mean ± SD. COPD, chronic obstructive pulmonary disease; GERAADA, German Registry of Acute Aortic Dissection Type A; SD, standard deviation.

bladder temperature, arterial cannulation strategy (antegrade or retrograde), cardiopulmonary bypass (CPB), cross-clamp, ACP and CA times, cerebral perfusion strategy (unilateral or bilateral), INVOS value and re-sternotomy for bleeding. All statistical tests were two-sided, and P values <0.05 were considered statistically significant. Analysis was performed using SPSS Statistics 28 (IBM; SPSS Inc. Chicago, IL, USA) and MedCalc (MedCalc Soft Ltd., Ostend, Belgium).

Results

Ninety-two patients were included, of whom 74% were male with a mean age of 64±13 years. In 86% of cases, patients presented with acute aortic syndromes, while 14% had chronic thoracic aortic aneurysms. The descending aorta was involved in 68% of cases, and 37% of patients had hemodynamically relevant aortic valve regurgitation. Overall, patients did not present many comorbidities; however, their general condition at presentation was compromised, with a mean GERAADA score of 24%±14%. At arrival, 13% presented hemiparesis or hemiplegia, while 4% had coma, and 9% were intubated. Pericardial effusion was present in 28% of patients; of those, 9% presented with tamponade, and 16% were shocked. Peripheral, visceral, and coronary malperfusion wer observed in 20%, 16%, and 17% of cases, respectively. Complete baseline characteristics are reported in *Table 1*.

All patients underwent aortic ascending replacement and arch replacement with the FET technique. Root surgery was performed in 26 patients (28%), and aortic valve replacement was done in 19 patients (20%). Canulation with retrograde perfusion was performed in the majority of cases (57%), anterograde perfusion in 29% of cases, and 14% of patients underwent a combination of the two strategies. Total CPB and cross-clamp times were 219±78 and 123±55 min, respectively, while median CA time was 15 (I–III quartile, 13–19) min. Mean bladder temperature was 30±1.6 ℃. Almost all patients (96%) received bilateral ACP, while 4% received unilateral ACP with a median perfusion time of 59 (I–III quartile, 31–113) min. Five patients (5%) experienced intraoperative death due to descending thoracic aorta rupture and massive bleeding. Four patients (4.3%) needed packing at exit from the operating room to control diffuse oozing. Intraoperative data are reported in *Table 2*. Thirty-day mortality was 14%, and eight patients (9%) died for cardiovascular causes, while five (5%) died for sepsis or respiratory causes. Neurological events were observed in 16% of patients (fifteen patients), of those 9% (eight patients) were disabling and 1% (one patient) led to death. Renal or visceral complications occurred in nine patients (10%), one patient (1%) developed bowel ischemia, and eight patients (9%) required CVVH (2% resulting in chronic dialysis). Re-sternotomy for bleeding was necessary in nineteen patients (21%), and six patients (7%) developed tamponade within the hospital admission. Postoperative events are reported in *Table 3*.

At multivariable analysis, 30-day mortality was associated

Table 2 Intraoperative data

Variables	Data (n=92)
Cross-clamp time (min)	123±55
CPB time (min)	219±78
Cerebral perfusion time (min)	59 [31–113]
CA time (min)	15 [13–19]
Skin-to-skin time (min)	415±132
INVOS	
Basal	
Left	62±10
Right	62±9
Lowest	
Left	54±9
Right	55±9.3
Bladder temperature (℃)	30±1.6
Arterial cannulation	
Antegrade	27 [29]
Retrograde	52 [57]
Both	13 [14]
Cerebral perfusion technique	
Antegrade unilateral Kazui	4 [4]
Antegrade bilateral Kazui	88 [96]
Aortic valve surgery	19 [20]
Root surgery	26 [28]

Data are presented as mean ± SD, median [I–III quartile], or n [%]. CA, circulatory arrest; CPB, cardiopulmonary bypass; SD, standard deviation.

Table 3 Postoperative data

Variables	Data (n=92)
Neurological events	15 [16]
Fatal	1 [1]
Disabling stroke	8 [9]
Non disabling stroke	5 [5]
TIA	1 [1]
Bleeding	24 [27]
Re-sternotomy for bleeding	19 [21]
Packing exit OR	5 [5]
Renal impairment	8 [9]
AKI	0 [0]
Temporary dialysis	6 [7]
Permanent dialysis	2 [2]
Orotracheal intubation (hours)	24 [19–88]
ICU stay (days)	5 [3–12]
Tracheostomy	5 [5]
Early aortic root related events	1 [2]
Vascular major events	1 [2]
Post operatory pericardial effusion	10 [11]
Abdominal complication requiring surgery	1 [2]
Atrial fibrillation	45 [49]
Mortality	
Intraoperative	4 [4]
30-day	13 [14]
Cause of death	
Cardiovascular	8 [9]
Non-cardiovascular	5 [5]

Data are presented as n [%] or median [I–III quartile]. AKI, acute kidney injury; ICU, intensive care unit; OR, operating room; TIA, transient ischemic attack.

with presence of shock at arrival in the OR [odds ratio (OR) =1.336; 95% confidence interval (CI): 0.063–1.485; P=0.012], necessity of resuscitation before surgery (OR =0.321; 95% CI: −1.408 to 0.421; P=0.02), and with GERAADA score (OR =1.557; 95% CI: 0.004–2.018; P=0.002). The GERAADA score (OR =1.038; 95% CI: 1.009–1.068; P=0.009), retrograde perfusion (OR =0.395; 95% CI: 0.145–1.080; P=0.070), and lower right INVOS value (OR =0.934; 95% CI: 0.869–1.005; P=0.066) tended to be associated with the onset of postoperative neurological events (*Table 4*). Bleeding was associated with the GERAADA score (OR =1.028; 95% CI: 1.000–1.057; P=0.049) and with the cannulation strategy (retrograde OR =2.807; 95% CI: 1.11–7; P=0.028; antegrade OR =0.365; 95% CI: 0.129–1.031; P=0.057) (*Table 5*). Renal events tended to be associated with preoperative involvement of the descending aorta (OR =7.175; 95% CI: 0.839–61.367;

Table 4 Multivariable regression for neurological events

Variables	β	95% CI	P value
Preoperative			
GERAADA score	1.038	1.009–1.068	0.009
Intraoperative			
Cannulation strategy	0.395	0.145–1.080	0.070
Bladder temperature	1.223	0.894–1.672	0.207
Lowest INVOS right	0.934	0.869–1.005	0.066
Basal INVOS left	1.043	0.969–1.125	0.260
CPB time	1.011	0.999–1.024	0.083
CA time	0.962	0.861–1.076	0.500
ACP time	0.991	0.976–1.006	0.248
ACP techniques	0.292	0.032–2.680	0.277

ACP, antegrade cerebral perfusion; CA, circulatory arrest; CI, confidence interval; CPB, cardiopulmonary bypass; GERAADA, German Registry of Acute Aortic Dissection Type A.

P=0.072), while there was no association with intraoperative variables. For all outcomes, bladder temperature presented no influence (*Table 6*).

Discussion

The use of MiHCA for acute aortic syndromes has gained traction in recent years, as it appears to provide outcomes comparable or superior to those of MoHCA and deep HCA, particularly in terms of neurological events and renal injury (13-16). The results of our study corroborate this evidence. In our study population, the mean bladder temperature was 30±1.6 ℃, with 115 patients (67%) being treated at a core temperature above 29 ℃. Notably, unlike other studies that analyzed homogeneous groups of elective chronic AA aneurysms (17-19), our experience predominantly involved emergent surgeries for acute aortic dissections. These cases are typically managed with deeper HCA to mitigate the damage associated with the common preoperative hypoperfusion status. Despite the high-risk profile presented by our population, we did not observe an association between postoperative outcomes and core temperature, suggesting that even in the subset of acute pathologies, MiHCA can be safely carried out. Along with MiHCA, selective bilateral cerebral perfusion

Table 5 Multivariable regression for bleeding

Variables	OR	95% CI	P value
Preoperative			
Age	0.979	0.953–1.006	0.124
Gender (female)	0.763	0.348–1.674	0.500
CKD	1.194	0.309–4.612	0.796
Redo cardiac surgery	0.891	0.215–3.698	0.874
Acute aortic syndrome	0.734	0.200–2.699	0.642
GERAADA score	1.028	1.000–1.057	0.049
Intraoperative			
CPB time	1.000	0.994–1.005	0.970
Bladder temperature	1.015	0.811–1.271	0.895
CA time	1.023	0.966–1.085	0.432
Retrograde cannulation	2.807	1.11–7	0.028
Antegrade cannulation	0.365	0.129–1.031	0.057

CA, circulatory arrest; CI, confidence interval; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; GERAADA, German Registry of Acute Aortic Dissection Type A; OR, odds ratio.

Table 6 Multivariable regression for renal dysfunction

Variables	OR	95% CI	P value
Preoperative			
Age	0.976	0.930–1.024	0.316
Sex	0.386	0.093–1.604	0.190
CKD	2.888	0.284–29	0.370
Preoperative shock	1.421	0.163–12.361	0.750
Descending aorta involvement	7.175	0.839–61.367	0.072
Intraoperative			
Bladder temp	0.818	0.546–1.226	0.332
Cannulation strategy	1.309	0.446–3.845	0.624
CPB time	1.000	0.99–1.010	0.966
CA time	0.992	0.918–1.072	0.841
Resternotomy for bleeding	1.711	0.391–7.483	0.476

CA, circulatory arrest; CI, confidence interval; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; OR, odds ratio.

was performed in more than 90% of patients to guarantee optimal cerebral protection. This strategy resulted in 12% postoperative permanent neurological events, which is comparable to or inferior to other reports (5). Regarding the findings of Zhu *et al.* (14), who reported a 16% incidence of neurological events, our rate was lower, potentially due to the systematic use of bilateral ACP combined with standard pharmacological protocols, which provided comprehensive brain protection. Other groups did not find a significant difference between unilateral and bilateral ACP in large cohorts in terms of permanent neurological events (20). In contrast, other single-center studies and large meta-analyses did not find a significant benefit of bilateral over unilateral ACP (21,22). Bilateral ACP was associated with lower events in case of longer CA and ACP times (21). Given that our strategy involves reconstructing the supra-aortic vessels as the final step, leading to extended ACP time, we prefer bilateral ACP whenever feasible. In multivariable analysis, core temperature did not influence the occurrence of ischemic stroke. However, ischemic stroke was associated with the preoperative GERAADA score (23) and tended to be affected by the use of retrograde cannulation and lower right INVOS values during surgery. The association with retrograde perfusion aligns with previous literature (24), as retrograde flow may dislodge atherosclerotic or calcific plaques along the descending aorta, resulting in embolic stroke. Additionally, when retrograde systemic perfusion was employed, axillary artery cannulation, later used for ACP, was often not performed. This led to direct cannulation of both the innominate and left common carotid arteries, which in some cases, correlated with higher stroke rates due to the mobilization of intimal plaques during cannula insertion (21). On the other hand, events were strongly associated with the GERAADA score, highlighting the significant impact preoperative critical status has on outcomes.

MiHCA has been shown to be protective against postoperative renal impairment according to previous publications (15,19). In our cohort, higher core temperatures did not appear to be associated with the development of renal impairment, which was observed in only a small proportion of patients. Specifically, no patients increased postoperative creatinine above 150% respect to baseline, and only 6% required temporary renal replacement therapy. This lower incidence of AKI might be explained by the short CA time observed in our patients. Previous studies have demonstrated that the onset of renal dysfunction is associated with preoperative patient conditions and prolonged CA times, typically exceeding 60 min (18). We achieved short CA times through a surgical strategy that involved performing the distal anastomosis first, followed by the restoration of antegrade systemic perfusion and proximal anastomosis with the interruption of cross-clamping. Present data also showed that the involvement of the descending aorta can affect the development of renal impairment. This finding is consistent with results published by Li *et al.*, who identified the involvement of the renal arteries as a factor leading to the necessity of CRRT in a machine-learning model (25).

The evaluation of intraoperative variables did not show correlation with the onset of renal dysfunction, confirming that our surgical protocol, paired with MiHCA, is effective in preventing visceral ischemia. In particular, the early restoration of antegrade perfusion through the side branch of the ascending aorta prosthesis and short CA time likely ensured optimal visceral protection. The rate of bleeding events that required surgical revision within the first 48 hours from surgery (11%) is consistent with previous analysis (5) and correlated with a higher GERAADA score at admission. This correlation can be attributed to the parameters collected at admission to calculate the score, which highlight worse preoperative conditions that can lead to postoperative complications. MiHCA also facilitated a reduction in CPB time and total surgical time. Compared to other studies, we observed slightly longer CPB times (14,15), which may be due to the high number of emergent acute aortic syndromes in our cohort, resulting in more complex and time-consuming repair procedures.

Thirty-day mortality was higher in our cohort compared to other reports (5,15,26). This could be attributed to the high incidence of acute aortic syndromes in our patient population, along with the high-risk profiles as indicated by the GERAADA score. Detter *et al.* (27) showed that early mortality after FET was mainly influenced by preoperative critical state, including signs of cerebral or systemic malperfusion, preoperative cardiogenic shock with resuscitation, and orotracheal intubation upon arrival in the operating room. Conversely, other studies assessing the impact of MiHCA in elective FET procedures for AA aneurysms reported lower mortality and postoperative complication rates, reinforcing the rationale for reducing the degree of hypothermia during CA (14). Our results are encouraging, supporting the use of MiHCA and paving the way for the adoption of even higher temperatures provided that bilateral ACP is maintained, and CA time is relatively short. *In-vivo* studies have demonstrated the safety of MiHCA within certain time limits, indicating that CA times exceeding 60 min at 32 °C may eventually lead to neurological and visceral injury (28). To address this issue, authors have proposed new strategies to maintain systemic flow throughout the surgery, such as inflating a Foley catheter in the descending aorta to deliver systemic flow to the lower body (24,29,30). Following the introduction of ACP, we transitioned from deep HCA to MoHCA. With the improvement of devices and the introduction of FET procedure, which reduced surgical time for distal anastomosis, we were further prompted to shift from MoHCA to MiHCA. Once we standardize methods to avoid interrupting lower body systemic flow, aided by advancements in FET devices, we anticipate being able to transition from MiHCA to normothermic CA.

The main limitation of this study is represented by its retrospective nature; nevertheless, our surgical perfusion and anesthesia strategies are well-standardized and homogeneous, limiting the selection bias. Another limitation is the lack of a control group represented by MoHCA and deep HCA. We decided not to include patients treated before 2020, when MoHCA was still used, because the operative management during that period was less standardized. This lack of standardization could have introduced additional variables that might have impacted the outcomes.

Conclusions

MiHCA is safe for patients requiring complex AA surgery and in those with acute aortic syndromes, with low rates of neurological events, renal dysfunction, and no increase in postoperative bleeding. However, it must be paired with bilateral ACP and a well-standardized technical strategy and anesthesia management. Outcomes are, however, impacted by patients' preoperative conditions. Further studies are necessary to support the introduction of normothermic CA.

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Footnote

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