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Spinal cord injury during selective cerebral perfusion and segmental artery occlusion: an experimental study

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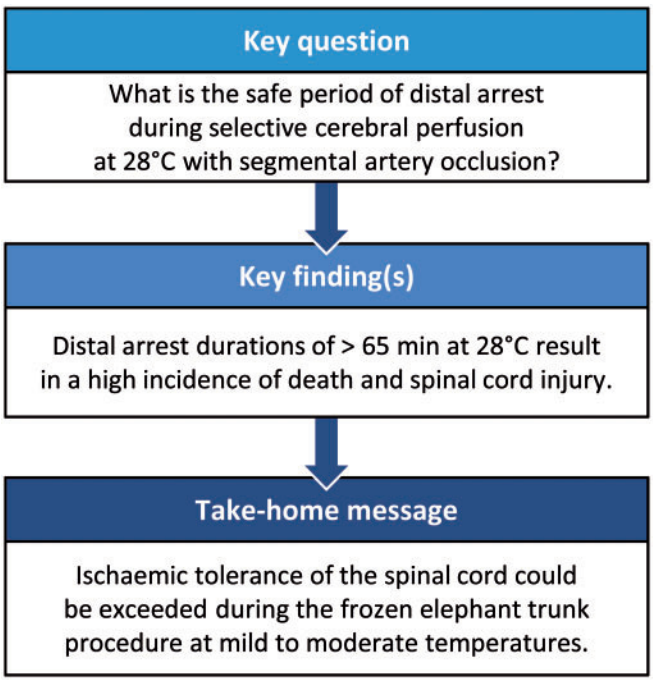

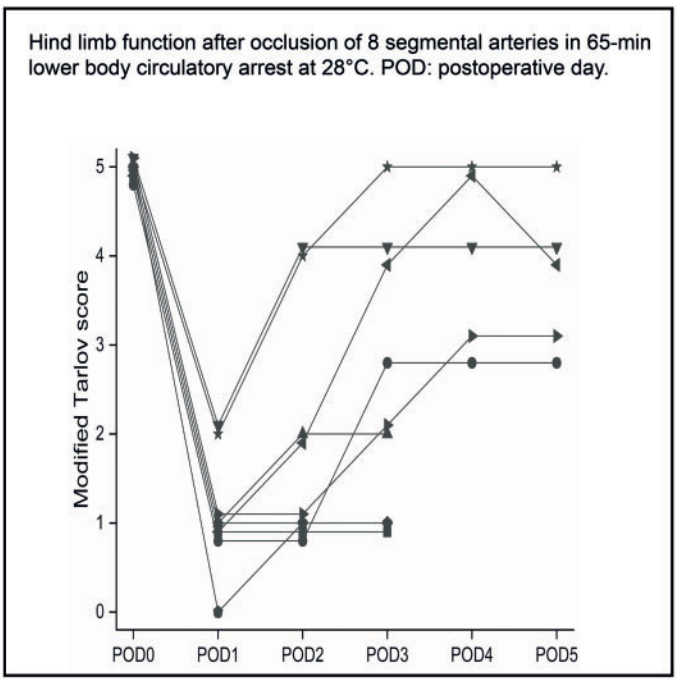

Abstract

OBJECTIVES: Since selective cerebral perfusion (SCP) has been used in aortic arch surgical procedures, the core temperature during lower body circulatory arrest (LBCA) has been steadily rising. Simultaneously, the use of a frozen elephant trunk (FET) graft has been increasing. The safe period of LBCA in relation to spinal cord ischaemic tolerance in combination with segmental artery occlusion by the FET procedure has not been defined.

[†] The first two authors contributed equally to this work.

METHODS: Sixteen pigs were assigned to undergo 65 ($n = 10$) or 90 min ($n = 6$) of SCP at 28°C with LBCA in combination with occlusion of the 8 uppermost segmental arteries in the thoracic (Th) aorta (15–20 cm FET, Th8-level). The follow-up period consisted of a 6-h intensive period and a 5-day observation period. Near-infrared spectroscopy of the collateral network was used to determine spinal cord oxygenation. The neurological status of the patients was evaluated daily, and the brain and the spinal cord were harvested for a histopathological analysis.

RESULTS: Five out of 6 pigs after 90 min and 1 out of 10 pigs after 65 min of LBCA died within 48 h of multiorgan failure. Of the survivors in the 65-min group, 6 out of 9 had paraparesis/paraplegia; the remaining 3 reached normal function. The lone survivor after 90 min of LBCA was paraplegic. Nadir near-infrared spectroscopy of the collateral network values at Th8 and Th10 were 34 (±5) and 39 (±4), and they were reached within 35 min of SCP in both groups.

CONCLUSIONS: An extended FET graft with LBCA and SCP durations >65 min at 28°C results in a poor outcome.

Keywords: Aortic dissection • Spinal cord injury • Frozen elephant trunk • Selective cerebral perfusion

ABBREVIATIONS

ATAAD	Acute type A aortic dissection
CnNIRS	Near-infrared spectroscopy of the collateral network
CPB	Cardiopulmonary bypass
ET	Entry tear
FET	Frozen elephant trunk
LBCA	Lower body circulatory arrest
MAP	Mean arterial pressure
POD	Postoperative day
SA	Segmental artery
SCP	Selective cerebral perfusion
Th	Thoracic

INTRODUCTION

Since the widespread use of selective cerebral perfusion (SCP) in aortic arch surgery, acceptable perfusion temperatures have risen steadily. In clinical settings, the average temperature during lower body circulatory arrest (LBCA) currently ranges from 28°C to 30°C; even the use of normothermic temperatures has been reported [1–3]. The rationale for the tepid temperature is shorter cardiopulmonary bypass (CPB) time and therefore possibly a lower risk for coagulation disorders and a reduction in inflammatory response [4, 5]. However, this method may jeopardize the integrity of the viscera and the spinal cord during LBCA and result in excess morbidity and mortality [2, 6].

Ischaemic tolerance of the spinal cord during LBCA and SCP has been studied in an animal model [6]. The safe limits of LBCA were found to be surprisingly short; 50 min at 32°C and 75 min at 28°C, indicating that the safe margin of ischaemia was less than anticipated [7]. This finding was also reported in a clinical report with a paraplegia rate as high as 18% at 24–28°C with SCP and LBCA durations of over 60 min [2]. During SCP, the spinal cord blood flow was nearly absent below the thoracic (Th) 4–13 region, and it returned to baseline values in a delayed fashion after SCP if there were no alterations to the collateral network vasculature [6].

The frozen elephant trunk (FET) technique was designed on the basis of the elephant trunk procedure to enhance false lumen thrombosis and to aid future distal operations after acute type A aortic dissection (ATAAD) [8]. However, the extended closure of thoracic segmental arteries (SAs) by the FET technique has resulted in an increased incidence of spinal cord injuries. The incidence of spinal cord injury has ranged from 9% to 24%, depending on the length of the distal landing zone and the duration of LBCA [9–11]. The ischaemic tolerance of the spinal cord during SCP with LBCA and FET remains unclear [8].

To investigate this gap in evidence, the goal of the present study was to define the safe period of LBCA during SCP at 28°C with a simulated FET procedure by closing proximal thoracic SAs. The primary endpoints were neurological recovery, histopathological analysis and death.

MATERIALS AND METHODS

Preoperative management

All animals received humane care in accordance with the European Union directive on the protection of animals used for scientific purposes (2010/63/EU) and the Finnish act on the protection of animals used for scientific purposes (FINLEX 497/2013). The study protocol was approved by the Finnish National Animal Experiment Board [12].

Animal preparation

Sixteen female pigs (21–31 kg) were used for this study. Anaesthesia and monitoring protocols are described in detail in our previous study; therefore the method section is partly recycled from that study [12]. Forelimb blood pressure monitoring, collateral network near-infrared spectroscopy (cnNIRS) placement and SA harvesting were done in accordance with our previous study [13]. More detailed descriptions of materials and methods are presented as Supplementary Material.

Study protocol

Just after we made the baseline measurements, the pigs were allocated to undergo either 65 ($n = 10$) or 90 ($n = 6$) min of SCP at 28°C.

A membrane oxygenator (Inspire 6, LivaNova, Mirandola, Italy) was primed with 15 000 IU of heparin, 1000 ml of Ringer acetate and 1000 ml of blood from a donor pig. A left-sided thoracotomy

to the third intercostal space was made to expose the heart and the aortic arch. Prior to cannulation, 500 IU/kg of heparin was administered for anticoagulation. The ascending aorta was cannulated with a 16-Fr aortic cannula and the right atrial appendage with a 24-Fr atrial cannula through purse-string sutures. The left ventricle was decompressed with a 12-Fr vent cannula through the left atrial appendage. CPB was adjusted to achieve a mean arterial pressure (MAP) of 70 mmHg. The perfusion was carried out with an alpha-stat strategy [12].

The pigs were cooled to a rectal and blood temperature of 28°C in 30 min. The aorta was then clamped distally to the cannula, and diastolic cardiac arrest was achieved by an injection of potassium chloride (40 mmol) into the aortic cannula. Ice slush at 4°C was then applied to the pericardium. The clamp was opened and placed just distally to the left subclavian artery so that antegrade perfusion of all supra-aortic vessels could be performed. The SCP and LBCA were then initiated. The heart was perfused during the whole SCP. To simulate the FET procedure, the SAs to the level of Th8/Th9 (7–8 arteries) were ligated with metal clips during the first 5 min of SCP. MAP of the foreleg was kept at 50 mmHg during the SCP period. After the SCP, the aortic clamp was opened, and the systemic circulation was continued. During the warming perfusion, MAP was kept at 70–80 mmHg and the heart was defibrillated at 32°C, if necessary. After the warming perfusion, the heart was decannulated at a blood temperature of 36°C.

After the monitoring period of 6 h, the pigs were extubated and followed in the laboratory until the next morning, after which they were transferred back to their stalls. The pigs were followed up for 5 days with adequate pain relief; the neurological evaluation was done every day at noon. After 5 days, the pigs were euthanized with sodium pentobarbital (90 mg/kg). Whole blood harvested from the donor pigs (35–45 kg) was used to prevent haemodilution during CPB. The donor pigs were euthanized with sodium pentobarbital (90 mg/kg) after the blood was harvested [12].

Sample collection

The same basic sample collection protocol was used as in our previous study [12]. Haemodynamic measurements were recorded, and arterial and venous blood samples were collected at 6 time points: at baseline, at the end of the cooling period, during 45 min of SCP and at 30 min, 2 h, 4 h, and 6 h after the start of rewarming. Haemodynamic and metabolic measurements included proximal and distal arterial blood pressure, pulmonary artery pressure, central venous pressure, cardiac output, pulmonary capillary wedge pressure, urine output, fluid input, inotropes, blood temperature and rectal temperature. Blood gas analysis, pH, electrolytes, plasma lactate, venous glucose, haematocrit and haemoglobin levels were measured from the blood samples. A blood gas analyser (iSTAT analyzer, iSTAT corporation East Windsor, NJ, USA) was used [12].

Neurobehavioural assessment

Neurological recovery was evaluated daily by an experienced animal housekeeper blinded to the operative protocol. The evaluation of hind limb motor function was assessed with a modified Tarlov score (0–5 points, 0–1 meaning paraplegia) as in our previous study [13]. Additionally, a more thorough neurobehavioural assessment regarding appetite and mental status combined with hind limb motor function was done as described in our previous study [12].

Histopathological analysis

After the 5-day evaluation period, the pigs were euthanized with sodium pentobarbital (90 mg/kg). The brain and the spinal cord were harvested and treated with principles described in our previous studies [12, 13]. The spinal cord was analysed with a Kleinman score (0–8 points) [14]. The brain was evaluated with our previously described scoring system [12]. Both scorings were done by an experienced neuropathologist blinded to the operative protocol.

Statistical analyses

Statistical analyses were performed using SPSS (IBM Corp., Released 2019, IBM SPSS Statistics for Windows, Version 26.0. IBM Corp, Armonk, NY, USA.) and SAS (Version 9.4; SAS Institute, Cary, NC, USA) statistical software. The analysis was done according to principles described in our previous studies [12]. The normality of continuous data was assessed with the Shapiro–Wilk test. Continuous and ordinal variables are presented as medians and 25th and 75th percentiles or as means with 95% confidence intervals. The Mann–Whitney *U*-test or the 'Student's *t*-test' was used to determine the *P*-values between the groups for continuous variables, depending on the normality of the data. Fisher's exact test was used to determine the *P*-values between the groups for categorical variables. A linear mixed model analysis was performed to analyse repeatedly measured data, if applicable. Experimental and metabolic data were not analysed with repeated measure protocols because they were actively balanced by infusions, inotropes and ventilator settings. The pigs were fitted at random, and the best covariance pattern was chosen using Akaike's information criterion. Reported *P*-values were exact two-tailed. Analyses were exploratory in nature. A *P*-value of <0.05 was considered significant. *P* between groups was marked with P_g, and *P* between groups and time was marked as $P_{g \times t}$.

RESULTS

There were no differences between the groups regarding weights [24.3 kg (23.6–26.0) vs 24.3 kg (21.9–30.2); *P* = 1.00] or the amount of administered donor blood [41.2 ml/kg (38.5–42.4) vs 41.2 ml/kg (33.1–45.8); *P* = 1.00]. However, the number of ligated SAs was higher in the 65-min group than in the 90-min group [8.0 (8.0–8.0) vs 7.0 (6.8–8.0); *P* = 0.01]. There were minor statistically significant differences in baseline measures regarding pulse, MAP, pH, arterial carbon dioxide tension and haemoglobin (Tables 1 and 2). However, these differences were not clinically significant. Blood temperature was higher in the 65-min group 1 than in the 90-min group at the beginning of SCP. This difference resulted

Table 1: Experimental data

Variable	Baseline	30 min of cooling	45 min of SCP	30 min of warming	2 h after SCP	4 h after SCP	6 h after SCP
Heart rate (bpm)							
Group 65	96 (80–99)[a]	81 (65–93)	111 (21–133)	118 (93–127)	105 (97–117)	115 (102–118)	118 (109–125)
Group 90	108 (97–115)[a]	84 (65–92)	61 (0–127)	92 (79–139)	116 (100–126)	118 (112–131)	132 (113–141)
MAP (front limb) (mmHg)							
Group 65	113 (107–121)[a]	79 (74–83)	51 (50–52)	93 (85–95)[a]	83 (79–96)	77 (70–85)	77 (69–92)
Group 90	104 (97–111)[a]	76 (69–84)	51 (50–51)	75 (69–90)[a]	79 (66–84)	69 (61–74)	73 (69–80)
MAP (hind limb) (mmHg)							
Group 65	115 (109–121)[a]	77 (74–80)	8 (6–9)[a]	93 (84–94)[a]	83 (80–97)	79 (74–85)[a]	76 (70–84)
Group 90	106 (99–112)[a]	80 (68–82)	10 (8–21)[a]	73 (71–89)[a]	78 (73–86)	67 (65–76)[a]	76 (70–90)
CVP (mmHg)							
Group 65	4 (4–5)	7 (4–7)	2 (0–3)	5 (4–7)	6 (5–6)	6 (5–7)	7 (6–8)
Group 90	5 (1–5)	7 (4–7)	1 (0–4)	6 (5–8)	6 (4–6)	6 (5–6)	8 (7–9)
Cardiac index ($ml \cdot m^{-2} \cdot min^{-1}$)							
Group 65	3.31 (2.88–3.51)	3.52 (2.95–3.77)	0.36 (0.34–0.40)	2.76 (2.33–2.95)	1.55 (1.39–1.72)	2.03 (1.80–2.33)	2.10 (2.03–2.47)
Group 90	3.42 (3.25–3.61)	3.54 (3.31–3.63)	0.42 (0.38–0.62)	2.78 (2.40–3.13)	2.02 (1.51–2.45)	2.01 (1.81–2.43)	2.35 (2.06–3.02)
Blood temperature (°C)							
Group 65	37.6 (37.3–38.4)	29.5 (29.1–29.6)[a]	28.7 (28.3–29.0)	37.7 (37.5–38.0)	36.5 (36.1–36.9)[a]	37.9 (37.0–38.2)	38.2 (38.0–38.5)
Group 90	37.5 (36.5–38.3)	28.5 (28.3–28.6)[a]	28.3 (28.0–28.4)	37.5 (37.4–37.6)	35.7 (35.5–36.1)[a]	37.2 (36.3–37.7)	37.5 (37.2–37.9)
Rectal temperature (°C)							
Group 65	36.2 (36.0–37.0)	28.4 (28.3–28.6)	28.7 (28.2–29.0)	33.5 (31.9–34.9)	34.3 (34.0–34.6)	35.6 (35.1–35.8)[a]	35.9 (35.7–36.6)
Group 90	36.8 (36.3–38.3)	28.6 (28.3–28.6)	28.8 (28.2–29.6)	35.3 (33.5–36.0)	35.2 (33.7–36.0)	36.3 (35.6–37.1)[a]	37.1 (36.1–37.7)

Group 65 = 90 min SCP, $n = 6$; Group 90 = 65 min SCP, $n = 10$. Values are shown as medians with interquartile range (25th and 75th percentiles).

[a]$P < 0.05$ at single time point.

CVP: central venous pressure; MAP: mean arterial pressure; SCP: selective antegrade cerebral perfusion.

Table 2: Metabolic data

Variable	Baseline	30 min of cooling	45 min of SCP	30 min of warming	2 h after SCP	4 h after SCP	6 h after SCP
pH							
Group 65	7.54 (7.51–7.55)[a]	7.61 (7.57–7.63)[a]	7.71 (7.68–7.73)[a]	7.43 (7.42–7.49)[a]	7.37 (7.33–7.39)[a]	7.44 (7.40–7.46)[a]	7.49 (7.40–7.46)
Group 90	7.48 (7.44–7.49)[a]	7.53 (7.50–7.58)[a]	7.58 (7.53–7.65)[a]	7.37 (7.30–7.39)[a]	7.28 (7.27–7.32)[a]	7.39 (7.31–7.42)[a]	7.43 (7.41–7.46)
pCO_2 (kPa)							
Group 65	5.2 (5.0–5.3)[a]	4.0 (3.7–4.1)	2.3 (2.2–2.5)[a]	3.2 (2.9–3.3)	5.6 (5.3–5.8)	5.8 (5.4–6.0)	5.6 (5.5–6.4)
Group 90	5.7 (5.6–6.0)[a]	4.1 (3.5–4.6)	2.9 (2.5–3.5)[a]	3.0 (2.6–3.4)	5.9 (5.3–6.2)	5.6 (5.1–5.8)	5.6 (5.1–5.8)
pO_2 (kPa)							
Group 65	28 (27–30)	50 (48–52)	24 (23–24)[a]	34 (31–37)	35 (21–51)	28 (24–32)	26 (25–28)
Group 90	30 (27–30)	49 (44–50)	22 (21–23)[a]	32 (26–36)	28 (24–59)	26 (25–26)	26 (25–31)
Haemoglobin (g/l)							
Group 65	94 (88–103)[a]	80 (74–86)	71 (71–78)[a]	96 (90–106)	107 (101–114)[a]	89 (81–96)	73 (67–81)
Group 90	87 (83–93)[a]	73 (65–76)	63 (60–75)[a]	83 (58–96)	87 (78–96)[a]	75 (64–87)	62 (51–76)
Haematocrit (%)							
Group 65	27 (25–29)	24 (22–25)[a]	21 (21–23)	28 (27–32)	32 (30–34)[a]	26 (24–29)[a]	22 (20–24)[a]
Group 90	26 (25–27)	22 (19–22)[a]	19 (18–22)	25 (17–28)	26 (23–28)[a]	22 (19–25)[a]	18 (15–21)[a]
Glucose (mmol/l)							
Group 65	4.1 (3.6–6.6)	4.5 (3.4–5.5)	5.2 (3.8–7.4)	5.5 (4.1–9.4)	5.3 (3.6–6.2)	6.9 (5.9–8.2)	6.8 (6.4–8.2)
Group 90	6.1 (5.6–7.0)	4.6 (3.5–5.1)	4.7 (4.1–9.2)	5.2 (3.5–11.4)	7.2 (4.6–8.5)	5.7 (5.4–7.0)	7.2 (6.5–8.1)

90 min SCP, $n = 6$; 65 min SCP, $n = 10$. Values are shown as medians with interquartile range (25th and 75th percentiles).

[a]$P < 0.05$ at single time point.

SCP: selective cerebral perfusion.

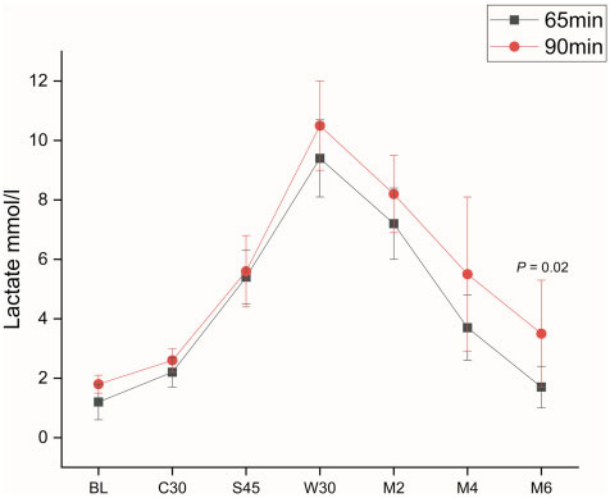

Figure 1: Central venous lactate levels in both groups. Values are presented as means and with 95% confidence intervals. BL: baseline; C: cooling; M: monitoring period; S: selective cerebral perfusion; W: warming. P_g= 0.06, $P_{g\,x\,t}$ = 0.45.

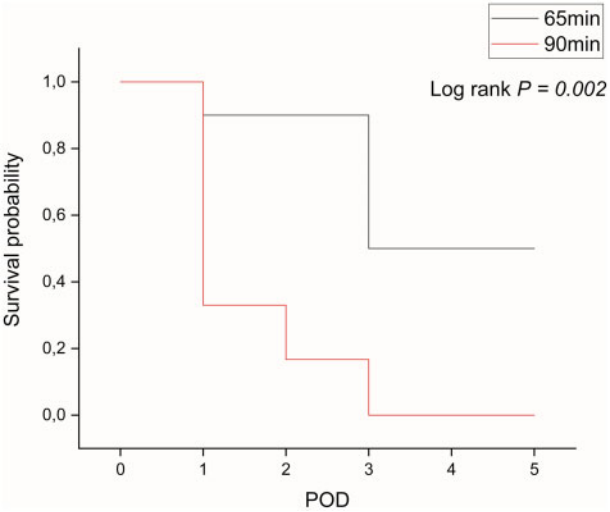

Figure 2: Kaplan–Meier plot for overall survival. 65-min group: $n = 10$; 90-min group: $n = 6$. POD: postoperative day.

from balancing the rectal temperatures before SCP. Central venous lactate levels rose during the SCP period and peaked at 30 min of the reperfusion period. The 90-min group had slightly higher lactate discharge (Fig. 1).

Mortality

All pigs could be weaned from the respirator. However, 4 pigs in the 90-min group and 1 in the 65-min group died of multiorgan injury during the first postoperative day (POD). One pig in the 90-min group died of multiorgan failure on the second POD. Four pigs in the 65-min group and 1 pig in the 90-min group had to be euthanized on the third POD due to animal welfare regulations because they were paraplegic and could not move on their own to get food and water. Five pigs in the 65-min group reached the fifth POD but

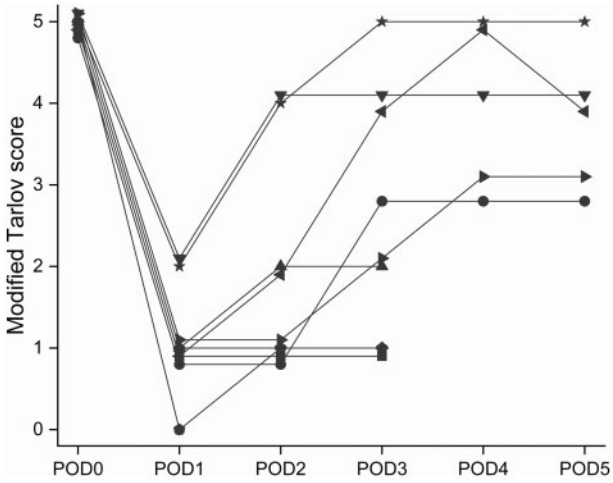

Figure 3: Modified Tarlov scores in the 65-min group. POD: postoperative day.

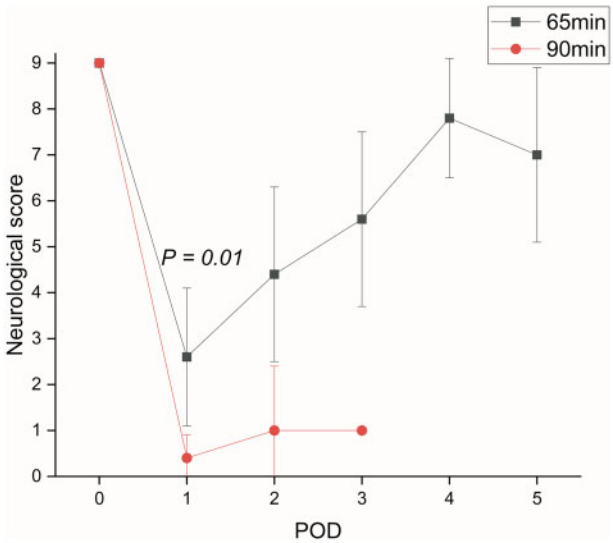

Figure 4: Postoperative neurobehavioural evaluation. $P < 0.05$: statistical difference at a single time point. POD: postoperative day.

none in the 90-min group ($P = 0.04$). A Kaplan–Meier plot for overall survival is presented in Fig. 2.

Neurobehavioural assessment

Due to poor survival after 90 min of LBCA, modified Tarlov scores could not be compared between groups. The only pig in the 90-min group that survived to the third POD had a Tarlov score of 1. None of the other pigs in that group received any points. Figure 3 represents graphically modified Tarlov scores for each individual pig in the 65-min group. Neurobehavioural scoring is represented graphically in Fig. 4.

Histopathological analysis

The brain and the spinal cord could be obtained from 5 pigs in the 90-min group and 9 pigs in the 65-min group. There were

no differences in the Kleinman scores between the groups. The findings were modest, partly due to the early deaths. The most vulnerable part of the spinal cord was the Th4-Th6 section, with a Kleinman score of 1.0 (0.0–6.5); other sections only had scores of 0–2.

Histopathological analysis of the brain did not reveal haemorrhage, neuronal degeneration or cerebral infarction. Only oedema was present. The brains of the animals in the 65-min group were significantly less oedematous compared to those of the animals in the 90-min group [4.0 (2.0–5.0) vs 6.0 (8.0–9.0); $P = 0.03$]. The difference was present in the cortex [1.0 (0.5–1.0) vs 2.0 (1.5–2.0); $P = 0.004$], cerebellum [1.0 (1.0–1.0) vs 2.0 (1.0–2.0); $P = 0.008$] and pons [0.0 (0.0–1.0) vs 1.0 (1.0–2.0); $P = 0.02$].

Collateral network near-infrared spectroscopy

CnNIRS curves from Th8 and Th10 sections are presented in Fig. 5A and B. CnNIRS values decreased rapidly in both groups and in both spinal cord sections at the beginning of the SCP period. Nadir values were reached in the Th8 section within 35 min but in the 90-min group, the cnNIRS values kept decreasing in the Th10 section even at the end of the SCP period. The 65-min group had better cnNIRS values in both sections than the 90-min group at 45 min of warming perfusion [47 (44–49) vs 38 (35–42); $P = 0.004$] in the Th8 section; [52 (48–55) vs 46 (41–48); $P = 0.01$ in the Th10 section].

DISCUSSION

The main finding of this study was that SCP at 28°C with the simulated FET procedure closing SAs to the level of Th8-Th9 exceeds the ischaemic tolerance of the spinal cord and the viscera when LBCA duration is greater than 65 min. However, the brain remained practically unharmed, suffering only from mild to moderate oedema depending on the length of the SCP. This finding supports the hypothesis that the safety of SCP in regard to cerebral protection even at mild to moderate temperatures for long perfusion periods could create a false sense of security regarding the protection of distal organs [7].

This study also confirms the finding that SCP does not provide blood flow to distal thoracic and lumbar spinal cord areas [6, 14]. This finding was noted prior to ligation of SAs from a sharp reduction in cnNIRS values since the initiation of SCP and LBCA. The difference between groups in cnNIRS after 45 min of rewarming may be because of the greater ischaemia–reperfusion damage and the interruption in the autoregulation of the spinal cord vasculature in the 90-min group. There was no difference between the groups for the given time period in variables such as MAP, central venous pressure or temperatures that could have an effect on cnNIRS and thus explain the difference between the groups. In contrast to previous studies, spinal cord blood flow was assessed with cnNIRS instead of microspheres. CnNIRS was previously validated as a real-time spinal cord tissue oxygenation monitor by von Aspern *et al.* [15], because paraspinous vasculature is directly linked to the spinal cord microcirculation. Our previous studies with thoracic aortic SA ligation have shown that cnNIRS values remain significantly lower compared to baseline at least 5 h after the operation [13, 16]. Therefore, the spinal cord suffers from acute ischaemia during LBCA, but it is thought to continue even after the systemic circulation is continued because the vasculature of the spinal cord was altered. The triad of spinal cord injury is finally completed by the systemic inflammation reaction and vasodilation resulting from lactatemia, CPB and visceral ischaemia.

The purpose of this study was to define the permissible period of LBCA regarding spinal cord ischaemic tolerance during SCP at 28°C with an FET graft extending to the level of Th8-Th9. However, due to the unexpectedly high number of early deaths, this goal could not be achieved because mortality was a

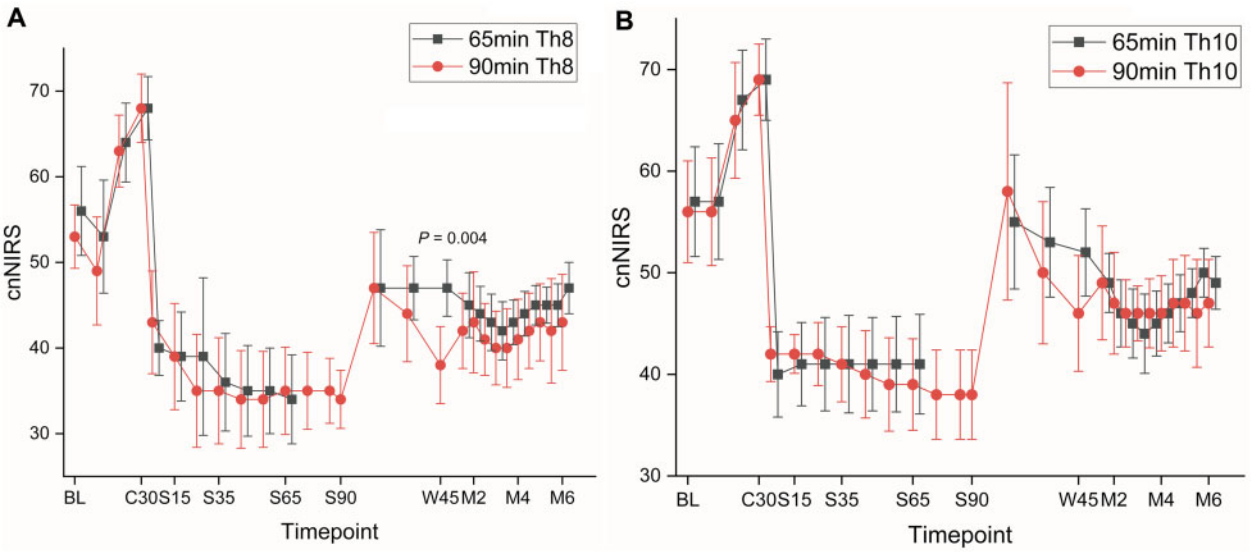

Figure 5 (**A** and **B**) Near-infrared spectroscopy of the collateral network (cnNIRS) during the operation and intensive monitoring period: 65-min group: $n = 10$; 90-min group: $n = 6$. BL: baseline; C: cooling; M: monitoring period; S: selective cerebral perfusion; Th: thoracic spinal cord; W: warming. Values are presented as means with 25th and 75th interquartile ranges. $P < 0.05$ = statistical difference at a single time point. (**A**) $P_g = 0.10$, $P_{g \times t} = 0.008$; (**B**) $P_g = 0.13$, $P_{g \times t} < 0.001$.

competing endpoint to paraplegia/paraparesis. Reflecting on the results by Etz *et al.* [6], 65 min of SCP at 28°C with SA occlusion to Th8-Th9 compared to 90 min of SCP at 28°C without SA occlusion results in approximately equal incidences of early mortality, paraplegia and paraparesis. The same comparison could be made between 90 min of SCP at 28°C with SA occlusion to Th8-Th9 compared to 120 min of SCP at 28°C without SA occlusion.

Our own recent study provided the valuable information that a 25-min aortic occlusion at 37°C accompanied by simultaneous SA closure to Th11 resulted in a 50% paraplegia rate in a control group of pigs [16]. We still lack enough scientific evidence about the unsafe period of LBCA with SA closure at 32°C and the permissible periods of LBCA at 37°C, 32°C and 28°C with SA closure to build a reliable estimation [6, 7].

ATAAD surgery is technically demanding, and it is still associated with high mortality and morbidity. A cardiothoracic surgeon's caseload is often low, especially in the Nordic countries [17, 18]. Therefore, the surgeon's main focus should be on making the procedure as simple as possible by repairing the entry tear (ET), because there is no long-term outcome without a short-term outcome. Surprisingly, ATAAD repair limited only to the parts that involved the ET was associated with survival and reoperation rates comparable to those in large centres utilizing a more aggressive surgical strategy [17].

Reflecting on the current European Association for Cardio-Thoracic Surgery guidelines, the FET technique has a IIa-level C recommendation to close the primary ET in patients with ATAAD with a primary ET in the distal aortic arch or in the proximal half of the descending aorta to treat associated malperfusion syndrome or to avoid its postoperative development [8]. This recommendation should be followed also in low-volume centres because the standard hemiarch/total arch does not provide acceptable survival. A slightly lower IIb-level C recommendation indicated that the FET procedure might be considered for use in patients undergoing surgery for ATAAD to prevent mid-term aneurysmal formation in the downstream aorta [8]. However, the performance of this method by low-volume surgeons at low-volume centre could lead to excess mortality and morbidity by complicating the surgical operation and therefore prolonging LBCA.

Limitations

A limitation of this study is the relatively small group sizes, which could lead to a type II statistical error. However, we have been conservative in our conclusions, especially those based on the Tarlov and neurobehavioural scores, because most of the pigs were lost to follow-up. High early mortality is also a confounding factor in the present study because it weakened the reliability of our histopathological analyses as well as the aforementioned neurological evaluation. There are also minor differences in spinal cord vasculature between pigs and humans [19]. In the clinical setting, these patients would have been in the ICU much longer than our patients were, where they would have had adequate monitoring, medication and the possibility for dialysis. Current commercially available FET grafts in Europe cover the thoracic aorta 10–16 cm distal to the left subclavian artery, depending on the product [8]. In comparison, in the present study, the coverage was 15–20 cm, which simulates an aggressive surgical strategy.

CONCLUSION

The present study demonstrated that the ischaemic tolerance of the viscera and spinal cord is significantly lower than what might have been anticipated. Therefore, before doing an FET procedure, careful consideration must be given to using mild to moderate temperatures during SCP and LBCA. Larger animal studies are still needed to confirm these findings.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

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Author contributions

Hannu-Pekka Honkanen: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing—original draft; Writing—review & editing. **Caius Mustonen:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing—original draft; Writing—review & editing. **Hannu Tuominen:** Data curation; Formal analysis; Methodology; Resources. **Kai Kiviluoma:** Project administration; Resources; Supervision; Writing—review & editing. **Vesa Anttila:** Project administration; Resources; Supervision; Writing—review & editing. **Tatu Juvonen:** Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Writing—review & editing.

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