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Selective Versus Standard Cerebro-Myocardial Perfusion in Neonates Undergoing Aortic Arch Repair: A Multi-Center Study.

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1 Introduction.

2 Neonatal arch repair either isolated or associated with complex congenital heart lesions carries substantial
3 morbidity, including neurological, cardiac and splanchnic organ complications. In an attempt to mitigate
4 organ injury, perfusion strategies alternative to deep hypothermic circulatory arrest (DHCA) were proposed
5 based on selective antegrade cerebral perfusion (ACP) alone (1), or combined with myocardial, splanchnic
6 or total body district perfusion. Although most studies comparing neuro-protective effects of ACP with
7 DHCA did not show improved clinical outcomes (2, 3, 4), possibly due to multiple, unmodifiable clinical
8 and social confounding variables (5, 6) a trend towards increasing use of ACP during neonatal arch repair
9 was observed (7).

10 Clearly, the burden of perioperative cardiac morbidity, still a leading cause of hospital mortality and of late
11 myocardial dysfunction, in newborn requiring arch repair (8, 9), adds to the risk of neurological injury and
12 of long-term functional disability (6).

13 Prior studies showed the feasibility and safety of combining ACP with myocardial perfusion with the goal
14 of reducing, when not avoiding at all, the duration of myocardial ischemia in a variety of pediatric cardiac
15 surgical scenarios (10, 11, 12, 13). More recently, an alternative and novel strategy for cerebro-myocardial
16 protection was developed, where ACP is associated with controlled and independent coronary perfusion
17 (14). Although early results of this perfusion strategy were satisfactory, supporting its safety, efficacy and
18 versatility (15, 16), potential advantages over standard cerebro-myocardial perfusion (CMP), using an
19 arterial line Y-connector, were not investigated. Aim of the present study was to compare early and mid-
20 term outcomes of selective and independent CMP with standard CMP during neonatal aortic arch surgery.

21 Materials and Methods.

22 Patients.

23 A retrospective study was undertaken in three European Cardiac Units, applying CMP as neurological and
24 myocardial protection during neonatal arch repair. Start of patient enrolment was retrospectively set in May

2008, when all three Units had routinely adopted this perfusion strategy, making consecutive patient selection feasible. Two patient cohorts were identified: newborn having arch repair using selective CMP (Group A) and those using standard CMP (Group B).

Institutional Review Board approval was obtained for the conduct of this study and the board waived the need for specific patient consent. Inclusion criteria were: 1. neonatal age (0-30 days); 2. severe aortic arch hypoplasia (transverse cross-sectional diameter < 50% of arch diameter at origin of innominate artery), with or without coarctation, aortic arch interruption or atresia; 3. diagnoses other than HLHS/HLHC (see Comment).

Between May 2008 to May 2016, 69 consecutive neonates underwent aortic arch repair using CMP. Demographic variables were evenly distributed between groups, except for greater prevalence of males in Group A (Table 1). In this group, a trend toward higher prevalence of univentricular palliation was observed. Distribution of anatomic diagnoses in the two groups was substantially homogeneous, with slight prevalence of more complex associated lesions (TGA, DORV, Taussig-Bing, truncus, single ventricle) in Group A (Table 1).

Operative technique.

The details of selective CMP (Group A) were previously published (14, Figure 1). Via midline sternotomy, an arterial cannula 6-8 Fr was inserted directly into the innominate artery or via interposition of a 3.5 mm polytetrafluoroethylene graft (body weight > 2.5 kg) and connected to the arterial line. A cardioplegia cannula, initially inserted into the ductus and connected to the cardioplegia line, to allow for homogeneous cooling, was relocated into the aortic root after ductus excision. When intracardiac repair was associated, bicaval cannulation was used for venous return, otherwise a single-stage right atrial cannula was used. A left ventricular vent through the right upper pulmonary vein was used. All neonates received blood-based priming solution for bypass to maintain Hb level >8.5 g/dL. An α -stat acid-base management was used for monitoring cerebral protection. Under moderate hypothermia (25°C nasopharyngeal), using low-flow

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systemic perfusion (40-50 mL/kg/min), brachiocephalic arteries were snared down, ascending and descending aorta were cross-clamped to start selective, controlled and independent cerebral and coronary perfusion, and arch repair was performed. During CMP right radial artery pressure was maintained between 40 and 45 mm Hg, cerebral blood flow rate via the arterial line rotor was regulated at baseline levels of 40–50 mL/kg/min, while myocardial flow was maintained via the cardioplegia line rotor at 15–20 mL/kg/min. Cerebral flow was then tailored to maintain systemic MVO₂ > 70% and cerebral rSO₂ > 45% (NIRS) bilaterally, while myocardial flow was adjusted to preserve sinus rhythm and heart rate faster than 60-70 bpm. Intracardiac repair was performed after arch repair, by switching the aortic root perfusion system to deliver blood cardioplegia. During rewarming, the flow rate was progressively increased (up 150 mL/kg/min). After CPB weaning, modified ultrafiltration was performed to restore fluid balance and pre-bypass Hb level.

Perfusion technique in standard CMP (Group B) differed from selective CMP (Group A) only in the method of myocardial perfusion: the cardioplegia delivery system was linked with a Y-connector to the arterial line. Therefore, the arterial line rotor supported both cerebral and myocardial flows as opposed to selective CMP, where the arterial pump supported cerebral flow and the cardioplegia pump myocardial flow (Figure 1). Consequently, in Group B only total CMP flow was measurable and controllable, but not relative cerebral and myocardial flows.

Threshold for leaving the sternum open and for inserting peritoneal dialysis catheters differed among Institutions, thus were not strictly prompted by hemodynamic instability or reduced urine output during the procedure.

Clinical outcome assessment.

Cross-sectional follow-up analysis of patient population was completed between June and July 2016. No patient was lost to follow up. All neonates underwent preoperative and postoperative head ultrasound and EEG. Follow-up laboratory assessment (EEG, MRI) of patients was tailored in patients with postoperative sequelae.

Study end-points included: hospital mortality and morbidity, survival and freedom from reintervention on the aortic arch. To evaluate impact of myocardial perfusion strategy on early cardiac morbidity, this was defined as presence of one of the following: cardiac death; need for postoperative ECMO support; laboratory evidence of myocardial ischemia (EKG or cardiac troponin I, cTnI, peak greater than 50 ng/mL in first 24 hours)(17); postoperative systemic ventricular dysfunction (ejection fraction less than 30%); high inotropic support (two or more agents, longer than 24 hours).

Statistical analysis.

Continuous variables were expressed as mean $\pm$ SD and categorical variables were reported as numbers and percentage. Univariate analysis tested for between-groups differences in patient preoperative demographics and operative variables (Tables 1 and 2). Categorical variables were analyzed with Fisher exact test. Continuous variables were first examined for normality of distribution: t-test was used for variables with normal distributions and nonparametric Wilcoxon rank-sum test was applied for variables with skewed distributions. In all tests, two-tailed p-values were calculated. Variables showing significant difference between groups were tested by multivariable analysis on the entire patient population to disclose association with end-points. Multivariable stepwise logistic regression was performed to determine whether any significant variable, including CMP perfusion strategy (Group A vs. Group B), was independently associated with cardiac events. Multivariable Cox proportional hazards models were applied after checking for underlying assumptions of

linearity, proportionality, and lack of interactions and OR and 95% CI were reported. Time-dependent events (survival, freedom from arch reintervention) were estimated using the Kaplan-Meier product limit method and compared using the log-rank test. P values less than 0.05 were considered significant. Analysis was performed using PASW/SPSS version 18 (IBM, Inc., Chicago, IL).

Results.

Early Outcome.

Operative variables differed between groups (Table 2). Duration of CPB was comparable, but more Group B patients had concomitant intra-cardiac repair during cardioplegic myocardial arrest. Duration of cardiac arrest in patients having intra-cardiac repair, however, was longer in Group A patients, in line with greater complexity of anatomy in this group (Table 1). Duration of splanchnic arrest, corresponding to duration of CMP required to complete arch repair, was comparable between groups. Finally, CMP flows were higher among Group A patients, in whom an additional, independent myocardial flow was added to a baseline cerebral flow identical to Group B patients (Table 2). Overall hospital survival was 97.1%, with two (2.9%) early deaths, one in each group, due to sepsis (Group A) and multisystem organ failure (Group B). High inotropic support had similar prevalence in the two groups (1/34 vs. 4/35, Group A vs. B, p=0.2). Delayed sternal closure was significantly more frequent in Group A. Duration of mechanical ventilation and ICU stay were comparable between groups. Non-fatal complications showed similar distribution, except for cardiac complications less common in Group A. In Group A, one patient required prolonged high-dose inotropic support for worsening single ventricle and common AV valve function, while in Group B, 7 patients experienced reversible cardiac events, including 6 with evidence of post-operative myocardial ischemia (peak cTNI above threshold) and 1 requiring post-

operative V-A ECMO support. All patients survived to discharge. No permanent neurological injury was diagnosed. Only one Group A patient had postoperative seizures, with unremarkable brain MRI findings and EEG at discharge. Peak serum creatinine levels in the first 24 hours were lower in Group A patients, although not translating into higher prevalence of peritoneal dialysis. Peak serum ALT levels in the first 24 hours were comparable, as it was prevalence of sepsis (Table 3).

Mid-Term Outcome.

During a mean follow-up of 3.2 ± 2.4 years (0.3-7.3 years), there were 5 (7.4%) late deaths among 67 hospital survivors: 2 (6.1%) late deaths in Group A (cardiac, neurological) and 3 (8.8%) in Group B (cardiac, sepsis, multiple organ failure) with comparable 5-year survival (Figure 2). Aortic arch reintervention, transcatheter or surgical, was required in 9 (13.4%) late survivors: 4 (12.1%) arch procedures in Group A and 5 (14.7%) in Group B, with similar 5-year freedom reintervention (Figure 3).

Predictors of Cardiac Morbidity.

Univariate analysis showed no association between cardiac events ($n=8$) and prevalence of female gender (5/34 female vs. 3/35 male, $p=0.6$) and of cardioplegic arrest (4/36 in patients with arrest vs. 4/33 without, $p=0.4$). Unexpectedly, duration of cardioplegic arrest was shorter in newborn with events (46 ± 11 vs. 62 ± 16 min, $p=0.06$) of cardioplegic arrest. In contrast, CMP flows were lower in patients suffering cardiac events (31 ± 7 ml/kg/min vs. 46 ± 24 ml/kg/min, $p=0.035$). In addition, standard CMP technique (Group B) was associated with higher prevalence of cardiac events (7/8 versus 28/61, $p=0.02$). At multivariable analysis, likelihood to experience early cardiac events was three-fold greater (OR 3.7, CI 1.87-5.95, $p=0.04$) in neonates having CMP flows less than 50 ml/kg/min and five-fold greater (OR=5.2, CI 3.3-6.8, $p=0.001$) in neonates having standard CMP (Group B).

Discussion.

The primary finding of the largest study to date on cerebral and myocardial protection during neonatal aortic arch repair using CMP is that it affords excellent survival and satisfactory freedom from recurrent aortic arch obstruction. Furthermore, selective and independent CMP, using two separate pump rotors and

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higher perfusion flows, is associated with lower cardiac morbidity, when compared to standard CMP, using a single pump rotor.

Selective ACP is the most common strategy for cerebral protection during aortic arch repair in infants and children (7), in spite of inability of multiple studies, including randomized trials, to confirm its superiority over DHCA (2, 3, 4). Several reasons explain this apparent paradox, including: more recent adoption of ACP, thus greater variability among methods; role of non-modifiable demographic factors (genetics, gestational age/maturity, prenatal circulatory physiology, preoperative brain lesions); socio-economic factors (5, 6, 18). Furthermore, even randomized trials which ruled out superiority of ACP over DHCA, excluded newborn with complex arch pathology requiring prolonged repair and assigned them to DHCA instead (4).

Regardless of strategy to protect the brain, neonatal arch repair carries the additional burden of perioperative cardiac morbidity, inherent with the complexity of congenital heart pathology, which may in turn aggravate neurological and other end-organ injuries (6, 8, 9).

In order to focus on strategies to protect the heart during ACP, neonates with HLHS/HLHC undergoing first stage palliation were excluded from the current study, as these continue to account for the vast majority of hospital deaths to date. This observation is consistent both in series of ACP, where myocardial protection is achieved by cardioplegic arrest (2, 3, 4, 9, 18, 19), as well as for those entailing simultaneous CMP (11, 12), all reporting hospital mortality between 10% and 25%. Accordingly, hospital mortality in the present series (2.9%) is expectedly lower than the ones reported in studies including HLHS/HLHC. However, it also favorably compares with series on arch repair in newborn with biventricular cardiac physiology (8), the latter focusing on lower risk neonates than the ones herein. The ability of CMP to achieve very low hospital mortality in neonates with arch pathology in the context of complex cardiac malformations is the first observation of this study. We speculate that the possibility to reduce duration of myocardial ischemia by CMP, when not avoid it at all, was instrumental in obtaining this result.

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6 164 Prior evidence on CMP in neonatal arch surgery is limited. Kostelka (10) showed that CMP, albeit with
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8 165 great variability in perfusion flows and temperatures, was associated with no hospital mortality in a select
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10 166 series of 19 neonates having biventricular repair. Later work by Oppido (11) observed significant mortality
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12 167 (13%) in 39 neonates having arch repair CMP using standardized flows (10-20 ml/kg/min) and temperature
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14 168 (25°C). Whether the substantial difference in perfusion flows (10-20 vs. 40-60 ml/kg/min) may explain the
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16 169 difference in hospital survival with the present study remains speculative. Interestingly, longer ischemic
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18 170 time was associated with hospital mortality (11), highlighting the importance of myocardial protection in
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20 171 this population. In a study by Lim (12) on 67 neonates having arch surgery using CMP, all in the context
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22 172 of biventricular repair, hospital mortality was comparable to the one herein (3% versus 2.9%). While unable
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24 173 to demonstrate that CMP was superior to ACP alone in terms of mortality, Lim found shorter ICU and
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26 174 hospital stay and lower inotropic requirements (12). Of note, CMP flows were significantly higher than in
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28 175 prior works (10, 11) and similar to the ones herein (50-70 vs. 40-60 ml/kg/min), when corrected for
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30 176 difference in perfusion temperature (28°C vs. 25°C).
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33 177 Overall hospital morbidity in the present study was in line with prior observations on neonatal arch repair,
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35 178 when not lower (2, 3, 4, 8, 9, 10, 11, 12, 13, 20). Furthermore, cardiac morbidity was significantly lower in
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37 179 patients having selective CMP. Definition of cardiac events related to adequacy of myocardial protection
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39 180 is difficult in neonates having arch repair, as it is influenced by complexity and heterogeneity of underlying
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41 181 congenital lesion. In addition to gross clinical end-points (mortality, post-cardiotomy ECMO), entity and
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43 182 duration of inotropic support, as reported in most series (9, 10, 11, 12), worsening ventricular function and
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45 183 laboratory evidence of myocardial ischemia were all considered herein. The latter was responsible for most
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47 184 of cardiac morbidity in newborn having standard CMP. Although the biomarker cut-off value, including
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49 185 cTnI, indicative of myocardial ischemia in neonates is controversial, we applied a restrictive definition by
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51 186 including only patients with peak values in the first 24 hours ten-fold or higher than the maximum reported
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53 187 range (17). At univariate analysis, neither prevalence nor duration of cardioplegic cardiac arrest were
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55 188 associated with cardiac morbidity in standard CMP group. On the contrary, higher CMP flow (greater than
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189 50 ml/kg/min), a variable strictly correlated with the different perfusion protocols in Group A and B, was
190 associated with lower morbidity. The present study, therefore, cannot exclude that if patients undergoing
191 standard CMP had received average flows identical to patients having selective CMP they would not have
192 experienced comparable cardiac morbidity. The importance of keeping generous perfusion flows was
193 underscored by the excellent outcomes obtained by Lim (12) using standard CMP, where average flows in
194 patients having myocardial perfusion (67-70 ml/kg/min) were significantly higher than in patients with only
195 ACP (57-60 ml/kg/min). The present study suggests that by using a selective and independent CMP set-up
196 both cerebral and myocardial flows can be finely titrated to intra-operative monitoring thereby allowing to
197 extend the results reported by Lim (12) to a subset of more complex neonates, including those with
198 univentricular physiology. We infer that when starting CMP, either by selective and independent or by
199 standard technique, combined perfusion flow should not be lower than 50 ml/kg/min at 25°C, as
200 demonstrated herein, or 70 ml/kg/min at 28°C, as observed by Lim (12).

201 Postoperative recovery in terms of duration of inotropic support, mechanical ventilation and ICU stay were
202 comparable in the two groups and in line with most series on neonatal arch repair using ACP (2, 3, 4, 8, 9,
203 10, 11, 12, 13, 19). Splanchnic morbidity was limited herein, supporting prior evidence by Algra (20) on
204 sufficient collateral flow during ACP with splanchnic circulatory arrest. The greater peak values of
205 creatinine in patients with standard CMP, possibly reflective of lower total perfusion flows, did not translate
206 into greater prevalence of acute renal failure requiring dialysis. Although combination of ACP with
207 splanchnic perfusion via descending aortic cannulation showed benefits in terms of reduced incidence of
208 acute renal failure, as reported by Hammel (19), its role is difficult to separate from duration of myocardial
209 ischemia (9), lending further support to the importance of adequately protecting the myocardium of
210 newborn having arch repair.

211 Finally, neonatal arch repair is challenging also for the high rate of reintervention due to recoarctation,
212 particularly in neonates weighing less than 2.5 kg (21). In spite of more than ¼ of patients (18/69) being
213 less than 2.5 kg at repair, freedom from recurrent arch obstruction proved satisfactory in this series and

214 identical in the two groups, perhaps related to possibility of taking the time to perform an accurate arch
215 repair during CMP.

216 **Limitations:**

217 Like any retrospective study, the current presents some bias, as reflected by heterogeneity, albeit limited,
218 in demographic and operative variables. Furthermore, although the two perfusion protocols only differed
219 by the method of CMP, the possibility exists that other institutional factors may account for some of the
220 differences between groups. Nonetheless, it is the largest study on neonatal aortic arch repair using CMP
221 and the only one comparing two patient cohorts. By design, it is impossible to separate the beneficial effects
222 of higher CMP flows from the one of using two separate and independent pump rotors. Clearly, combining
223 flows greater than 50 mL/kg/min at 25°C with independent perfusion during arch repair would seem rational,
224 particularly in neonates in whom a lengthy procedure is anticipated (TGA, DORV, truncus).

225 In conclusion, both standard and selective CMP are associated with satisfactory early and late outcomes in
226 neonatal arch surgery. Selective and independent CMP with higher flows is associated with lower cardiac
227 morbidity and may thus be ideally suited in complex arch repairs.

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289 Table 1. Demography.

Variable	Group A (n=34)	Group B (n=35)	p
Gender (M/F)	21/13	14/21	0.01
Mean age (days)	19±10	10±6	0.7
Mean weight (kg)	3.1±1.1	2.8±0.9	0.2
BSA (m ²)	0.20±0.05	0.19±0.03	0.1
Single stage biventricular repair	20	23	0.9
Staged biventricular repair	8	10	0.7
Univentricular palliation	6	2	0.7
Diagnoses:			
CoAo and Arch hypoplasia/VSD	10	13	
IAA/isolated or VSD	8	9	
CoAo and Arch hypoplasia	6	7	
CoAo and Arch hypoplasia in UVH with TGA/DORV	6	2	
IAA/Arch hypoplasia/DORV Taussig-Bing	3	4	
IAA/Truncus arteriosus	1	-	

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 291 N, number; M, male; F, female; BSA, body surface area; CoAo, aortic coarctation; VSD, ventricular septal
 292 defect; IAA, interrupted aortic arch; UVH, univentricular heart; TGA, transposition of great arteries; DORV,
 293 double outlet right ventricle.
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Table 2. Operative variables.

Variable	Group A (n=34)	Group B (n=35)	p
CPB duration (min)	119±55	104±28	0.07
Cardiac arrest (n)	13	23	0.03
Cardiac arrest duration (min)	64±41	44±14	0.04
Splanchnic arrest duration (min)	27±8	28±7	0.9
CMP flow (ml/kg/min)	57±27	39±19	0.01
End-side/patch augmentation arch repair (n)	25/9	35/0	0.04

N, number; CPB, cardiopulmonary bypass; CMP, cerebro-myocardial perfusion.

Table 3. Postoperative Results.

Variable	Group A (n=34)	Group B (n=35)	p
Hospital mortality (n)	1	1	0.9
High inotropic support (n)	1	4	0.3
Delayed sternal closure (n)	13	3	0.03
Mechanical ventilation (days)	6.2±4.8	5.4±14.3	0.7
ICU stay (days)	8.1±6.1	7.2±14.6	0.7
Cardiac morbidity (n)	1	7	0.02
Neurologic morbidity (n)	1	-	0.8
Peak serum creatinine (μmol/L)	46.1±15.9	74.0±36.0	0.01
Peritoneal dialysis (n)	4	1	0.06
Peak serum ALT (U/L)	37.1±32.6	25.2±15.0	0.4
Sepsis (n)	8	5	0.7

N, number; ICU, intensive care unit; ALT, alanine transaminase.

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Figure Legends.

Figure 1. Schematic showing cardiopulmonary bypass set-up for selective and independent cerebro-myocardial perfusion. Two independent pump rotors are used: the arterial pump rotor is used to provide selective antegrade cerebral perfusion; the blood cardioplegia rotor is used to provide myocardial perfusion.

Figure 2. Actuarial survival after neonatal arch repair using selective CMP, Group A, (broken line) and standard CMP, Group B (solid line). Patients at risk are shown over the y-axis.

Figure 3. Actuarial freedom from aortic arch reintervention (FFR) after neonatal arch repair using selective CMP, Group A, (broken line) and standard CMP, Group B (solid line). Patients at risk are shown over the y-axis.

Schematic showing cardiopulmonary bypass set-up for selective and independent cerebro-myocardial perfusion. Two independent pump rotors are used: the arterial pump rotor is used to provide selective antegrade cerebral perfusion; the blood cardioplegia rotor is used to provide myocardial perfusion.

254x190mm (72 x 72 DPI)

Actuarial survival after neonatal arch repair using selective CMP, Group A, (broken line) and standard CMP, Group B (solid line). Patients at risk are shown over the y-axis.

254x190mm (72 x 72 DPI)

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Actuarial freedom from aortic arch reintervention (FFR) after neonatal arch repair using selective CMP, Group A, (broken line) and standard CMP, Group B (solid line). Patients at risk are shown over the y-axis.

254x190mm (72 x 72 DPI)