Chapter 4

Impact of Modified Ultrafiltration in Congenital Heart Disease Patients Treated with Cardiopulmonary Bypass

Pedro José Curi-Curi, Elizabeth Aguilar Alanis,

Juan Calderón-Colmenero,

Jorge Luis Cervantes-Salazar,

Rodrigo Reyes Pavón and

Samuel Ramírez-Marroquín

Additional information is available at the end of the chapter

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Abstract

Modified ultrafiltration is used in cardiac surgery with cardiopulmonary bypass in order to diminish systemic inflammatory response syndrome. We aimed to show its utility for removing pro-inflammatory agents in operated pediatric patients with congenital heart disease and its impact at operative care. A clinical case control trial was designed, including patients with simple congenital heart disease operated on with cardiopulmonary bypass in a 1-year period. We randomized them to a problematic group (with modified ultrafiltration, n = 15) and a control group (without it, n = 16), and blood samples to measure interleukins (6 and 10), 3d and 4d complement fraction concentrations were taken at the following times: baseline, before cardiopulmonary bypass, after it, after modified ultrafiltration, and from the ultrafiltration concentrate. Operative clinical end points of success were defined as hemodynamic stability, absence of morbidity, and lack of mortality. We observed a higher significant interleukin six concentration in the problematic group patients at baseline, as well as a higher removal of this pro-inflammatory agent at the ultrafiltration concentrate. Modified ultrafiltration has a positive impact over simple congenital heart disease surgery with cardiopulmonary bypass because of removing interleukin 6. We recommend its routinely use when hemodynamic conditions are favorable.

Keywords: cardiopulmonary bypass, congenital heart disease, interleukin

1. Introduction

Cardiopulmonary bypass (CPB) allowed the correction of several congenital heart diseases such as intracardiac malformations, but it is well known that this is not a harmless procedure because it can lead to a systemic inflammatory response syndrome (SIRS), with activation of complement, cytokines, coagulation, and fibrinolysis pathways. Factors that contribute to the development of SIRS include blood contact with the synthetic surface of cardiopulmonary bypass components, as well as leukocyte and endothelial activation after tissue ischemia and reperfusion [1–5]. If there is a severe inflammatory response, it could also develop a multiorgan dysfunction syndrome that increases morbidity and mortality of the patients at pediatric intensive care units (PICUs). Some of the methods used to quantify the magnitude of SRIS due to the use of CPB include measurement of blood cytokine concentrations (interleukins 1 and 6), complement activation products (C3d and C4d), and also coagulation activated factors (Von Willebrand, fibrinogen, and factor VIII) [6].

There are several operative strategies for diminishing SRIS and its clinical repercussion, such as the use of steroids, modified tubular surfaces for CPB, and ultrafiltration. Despite the single or combined use of these strategies [7–12], ultrafiltration is the one that probably removes a larger amount of pro-inflammatory agents, as well as water (volume) [13]. The two ultrafiltration technique modalities widely accepted for pediatric cardiac surgery are conventional ultrafiltration (CUF) and modified ultrafiltration (MUF). CUF is applied in CPB during the heart re-warming period and MUF right after ending CPB.

Currently, there is no enough evidence that favor routinely use of MUF [14–19], and we can still find some controversies regarding the benefits of this technique [20–22]. Additionally, most reports of the literature are focalized in adult cohorts of patients, and there is few information provided for pediatric population that shows the real impact of MUF in the remotion of pro-inflammatory agents due to CPB use. Therefore, we aimed to study the real utility of MUF for remotion of pro-inflammatory agents induced by CPB in operated pediatric patients with simple congenital heart disease. We made a special emphasis in hemodynamic variables, morbidity and mortality at the operative period.

2. Material and methods

2.1. Study design

A prospective, randomized, analytic, clinical case-control trial was designed at the Department of Pediatric Cardiac and Congenital Heart Surgery of a single center during a 1-year period of time. Inclusion criteria were: age ≤ 18 years and simple congenital heart disease that required elective surgical treatment with CPB use for at least 30 minutes. Exclusion criteria were preoperative renal failure, preoperative cardiogenic shock requiring the use of inotropes, preoperative sepsis, preoperative mechanical ventilatory support ≤48 hours, preoperative lactate concentration ≥ 3 mmol/L, and cardiac reoperation. Patients were randomized in two study

groups: problematic group (with MUF) and control group (without MUF). With the use of an electronic URNA software, a statistical person randomized the patients and told the perfusionist who was the only surgical team person informed about the results of randomization. All patients included in this study were operated on with informed consent signed by their parents or tutors. The study was also approved by our institutional research and ethics committee.

2.2. Modified ultrafiltration (MUF) technique

Patients randomized to problematic group (with MUF), when informed to the perfusionist, were prepared for CPB with an additional MUF set. Once CPB was ended and hemodynamic stability of the patient was provided, the surgeon was told not to remove the venous cannula, and the venous line was clamped just before its connection to the reservoir. Arterial and venous line pathways were released in order to begin MUF with a 10–20 ml/kg/min flow. MUF continuous flow was achieved pumping the venous residual reservoir volume by means of the arterial line to the patient. A 150–200 mmHg venous vacuum was applied when needed. MUF lasted 10–20 minutes in order to reach a desired hematocrit level and obtain a suitable volume and electrolyte balance. MUF was stopped in case of hemodynamic instability. Once ended, MUF volume was restored to the patient from the hemofilter and venous cannula, allowing the surgeon for decannulation of the patient.

2.3. Biochemical and clinical operative analysis

Biochemical and clinical results were compared between the two study groups at the operative period. Biochemical results were the concentration of cytokine (interleukin 6 and 10) and complement activated products (C3d and C4d). These concentrations were measured from blood samples at the following times: T0 (baseline, at the beginning of anesthesia induction), T1 (before CPB), T2 (immediately after CPB), and T3 (immediately after MUF, in the problem group). The same agents were measured in the MUF fluid concentrate of the problematic group after the procedure (T4). Clinical operative results were evaluated in terms of hemodynamic instability (>20% post-CPB variation respect to previous CPB values of at least three of the following five hemodynamic variables: heart rate, systolic, diastolic and mean blood pressure, and central venous pressure), operative morbidity, and mortality. Operative clinical end points of success were defined as hemodynamic stability, absence of morbidity, and lack of mortality.

2.4. Laboratory analysis of the fluid samples

All patient samples were obtained from central or peripheral blood and collected in tubes without heparin (vacutainer, Becton Dickinson). A 3-ml blood sample was obtained for each of the study times (T0, T1, T2, and T3). The same volume of T4 samples were obtained from the ultrafiltration fluid concentrate. All of the samples were centrifugated at 3000 rpm during 15 minutes, 4°C, and cryopreserved in aliquots of 1.5 ml at –75°C. Interleukin concentrations (IL-6 and IL-10) were measured by means of an ELISA sandwich technique with the use of monoclonal antibodies (PeproTech, New Jersey, EUA). Complement activation products (C3d and C4d) were measured with the same technique, using commercial kits (Bachem, San

Carlos, CA, EUA). Optical density was determined at 450 nm in the ELISA plate detector. Concentrations of IL-6, IL-10 (pg/ml) as well as C3d and C4d (ng/ml) were calculated by means of a GraphPad Software v. 4.2.

2.5. Statistical analysis

Information was registered in evaluation sheets, stored in an electronic Excel page, and analyzed by means of a Prisma Graphics v 3.1 statistical software. Continuous variables are presented as a mean, standard deviation, and variability ranges (minimum and maximum). Categorical data are presented by means of frequency and percentages in relation to the population at risk. Comparison between the two study groups was made by means of a Student t test for continuous variables. A chi-square (χ^2) test was used for comparing categorical variables with a 95% confidence interval (CI). A p value < 0.05 was considered as statistically significant.

3. Results

A total of 31 patients were enrolled and randomized to this trial: 15 to the problematic group (with MUF) and 16 to the control group (without MUF).

3.1. Preoperative characteristics

Table 1 shows the type of congenital disease that was operated by means of CPB in both groups of study. There are no differences in the total number of congenital heart disease in the studied groups, but control group (without MUF) showed more patients with AV channel than the problematic group (with MUF).

Congenital heart disease type	**Total series (n = 31)** **n (%)**	**Problematic group (With MUF) (n = 15)** **n (%)**	**Control group (Without MUF) (n = 16)** **n (%)**	**P** **OR (95% CI)**
Ventricular septal defect	13 (42%)	8 (52%)	5 (31%)	NS
Balanced AV channel	8 (26%)	1 (7%)	7 (44%)	0.0373 0.09 (0.0096 – 0.8770)
Congenital mitral valve disease	4 (13%)	3 (20%)	1 (6%)	NS
Sub aortic membrane	3 (10%)	1 (7%)	2 (13%)	NS
Right ventricular outflow tract obstruction	1 (3%)	1 (7%)	0 (0%)	NS
Double chamber right ventricle	1 (3%)	1 (7%)	0 (0%)	NS
Atrial septal defect	1 (3%)	0 (0%)	1 (6%)	NS
TOTAL	**31 (100%)**	**15 (100%)**	**16 (100%)**	**NS**

Table 1. Congenital heart disease type in the studied groups.

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Variable	Total series n (%) or mean ± SD (range)	Problematic group (with MUF) n (%) or mean ± SD (range)	Control group (without MUF) n (%) or mean ± SD (range)	p
Age (years)	4.26 ± 4.11 (0.38–17.18)	37 ± 14 (18–76)	31 ± 11 (18–56)	NS
Gender				
Male	12 (39%)	8 (53%)	4 (25%)	NS
Female	19 (61%)	7 (47%)	12 (75%)	NS
Anthropometric data				
Weight (kg)	14.9 ± 10.8 (4–47)	14.1 ± 10.4 (4–38.3)	15.9 ± 11.6 (5.3–47)	NS
Height (cm)	90 ± 31.1 (12–159)	94.2 ± 31.2 (55–158)	86 ± 31.5 (12–159)	NS
Body surface area (m^2)	0.56 ± 0.27 (0.25–1.32)	0.58 ± 0.31 (0.25–1.32)	0.53 ± 0.18 (0.28–0.78)	NS
Circulating blood volume (ml)	1032 ± 627 (343–2660)	1164 ± 756 (343–2660)	867 ± 385 (452–1560)	NS
Cardiovascular background				
Previous surgery	0 (0%)	0 (0%)	0 (0%)	NS
Previous catheterization	2 (6%)	0 (0%)	2 (6%)	NS
Pathologic background				
Pre-operative infection	1 (3%)	0 (0%)	1 (6%)	NS
Pulmonary artery hypertension	4 (13%)	0 (0%)	4 (25%)	NS
None	26 (84%)	15 (100%)	11 (69%)	NS
Syndromes				
Down's syndrome	3 (10%)	0 (0%)	3 (19%)	NS
None	28 (90%)	15 (100%)	13 (81%)	NS
NYHA/Ross pre-operative functional class				
I	8 (26%)	4 (27%)	4 (25%)	NS
II	21 (68%)	9 (60%)	12 (75%)	NS
III	2 (6%)	2 (13%)	0 (0%)	NS
Operative risk				
RACHS-1 score	2.4 ± 0.5 (1–3)	2.4 ± 0.5 (2–3)	2.4 ± 0.6 (1–3)	NS
Basic Aristoteles	7.2 ± 1.5 (3–9)	7 ± 1.2 (6–9)	7.4 ± 1.9 (3–9)	NS
Complete Aristoteles	8.1 ± 1.8 (4–11)	7.8 ± 1.5 (6–10)	8.4 ± 2.1 (4–11)	NS
Preoperative morbidity				
Mechanic ventilation	0 (0%)	0 (0%)	0 (0%)	NS
Pre-operative inotropic support	0 (0%)	0 (0%)	0 (0%)	NS
Pre-operative infection	1 (3%)	0 (0%)	1(6%)	NS
None	30 (97%)	15 (100%)	15 (94%)	NS
Pre-operative laboratory exams				
Lactate	1.2 ± 0.3 (0.6–1.7)	1.2 ± 0.3 (0.7–1.7)	1.1 ± 0.3 (0.6–1.5)	NS

Variable	Total series n (%) or mean ± SD (range)	Problematic group (with MUF) n (%) or mean ± SD (range)	Control group (without MUF) n (%) or mean ± SD (range)	p
Creatinine	0.4 ± 0.1 (0.2–0.7)	0.4 ± 0.1 (0.2–0.7)	0.4 ± 0.1 (0.3–0.5)	NS
Perfusion variables				
Oxygenator type				
Baby Rx	14 (52%)	7 (47%)	7 (58%)	NS
Terumo SX10	6 (22%)	4 (27%)	2 (17%)	NS
Terumo SX18	1 (4%)	1 (7%)	0 (0%)	NS
Mini max	5 (19%)	2 (13%)	3 (25%)	NS
Safe Mini	1 (4%)	1 (7%)	0 (0%)	NS
Arterial filter use	18 (67%)	12 (80%)	6 (50%)	NS
Surgical variables				
CPB time (min)	81.9 ± 26.9 (40–131)	76.5 ± 23.7 (40–122)	87 ± 29.4 (41–131)	NS
Aortic cross clamp time (min)	53.7 ± 23.6 (12–96)	49.5 ± 21.8 (18–90)	57.6 ± 25.2 (12–96)	NS
Temperature (°C)	27 ± 1.6 (24–30)	27 ± 1.5 (24–29)	27.3 ± 1.8 (24–30)	NS
Anterograde cardioplegia	29 (94%)	14 (93%)	15 (94%)	NS
Blood cardioplegia	29 (94%)	14 (93%)	15 (94%)	NS

Table 2. Pre-operative characteristics of the studied groups.

Table 2 shows the rest of preoperative characteristics in both studied groups. Note that there are no statistical differences in all variables analyzed between the two groups.

Although more random patients with AV channel in the control group, the rest of the preoperative data showed that both groups are absolutely comparable.

3.2. Biochemical operative results

Table 3 compares the concentration of pro-inflammatory agents between groups before surgical correction (T0). Note a baseline elevated concentration of IL-6 in the problematic group (with MUF), without differences in both groups for the rest of pro-inflammatory agents (IL-10, C3d, and C4d).

On the other hand, **Table 4** shows a lack of statistical significant difference in the concentrations of pro-inflammatory agents at the control group before surgical correction (T0) and after CPB (T2).

Finally, **Table 5** shows the comparison between concentration of pro-inflammatory agents in the problematic group before surgical correction (T0) and after MUF (T4). There is a statistically significant removal of IL-6, but no difference in the concentrations of the rest pro-inflammatory agents analyzed (IL-10, C3d, and C4d).

Pro-inflammatory agent	T0 problematic group (with MUF) n = 15 Mean ± DE	T0 control group (without MUF) n = 16 Mean ± DE	p
C3d (ng/ml)	368.66 ± 331.87	413.248 ± 316.804	NS
C4d (ng/ml)	199.57 ± 201.56	213.89 ± 116.72	NS
IL-6 (pg/ml)	**672.249 ± 433.186**	**246.874 ± 365.69**	**0.0061**
IL-10 (pg/ml)	239.698 ± 381.517	299.618 ± 370.148	NS

Table 3. Comparison between concentrations of pro-inflammatory agents in both groups of study (with and without MUF) at baseline (T0).

Pro-inflammatory agent	T0 control group (without MUF) n = 16 Mean ± SD	T2 control group (without MUF) n = 16 Mean ± SD	p
C3d (ng/ml)	413.248 ± 316.804	264.33 ± 198.12	NS
C4d (ng/ml)	213.89 ± 116.72	210.65 ± 141.13	NS
IL-6 (pg/ml)	246.874 ± 365.69	289.499 ± 301.913	NS
IL-10 (pg/ml)	299.618 ± 370.148	387.26 ± 306.07	NS

Table 4. Comparison between concentrations of pro-inflammatory agents at T0 (baseline) and T2 (after CPB) for the control group (without MUF).

3.3. Clinical operative results

Table 6 summarizes the comparison of clinical end point variables in both groups of study (with and without MUF). There is a statistically significant decrease of hemoglobin (Hb) in the problematic group after MUF compared with the baseline level, which is not observed in the control group.

Both groups show an increase in lactate levels and heart rate after surgery when comparing these values with the baseline ones before CPB. Control group (without MUF) showed a

Pro-inflammatory agent	T0 problematic group (with MUF) n = 15 Mean ± SD	T4 problematic group (without MUF) n = 15 Mean ± SD	p
C3d (ng/ml)	368.66 ± 331.87	379.99 ± 264.64	NS
C4d (ng/ml)	199.57 ± 201.56	172.89 ± 139.64	NS
IL-6 (pg/ml)	**672.249 ± 433.186**	**366.31 ± 280.25**	**0.0293**
IL-10 (pg/ml)	239.698 ± 381.517	230.453 ± 352.27	NS

Table 5. Comparison between concentrations of pro-inflammatory agents at baseline (T0) and after MUF (T4) for the problematic group (with MUF).

	Problematic group (with MUF)			Control group (without MUF)			Problem vs control groups (with vs without MUF)		
Operative clinical end point variable	Control group	Problematic group	p	Control group	Problematic group	p	Problematic group	Control group	P
	Before CPB	After MUF		Before CPB	After MUF		After MUF	After CPB	
	n/total n (%) or	n/total n (%) or		n/total n (%) or	n/total n (%) or		n/total n (%) or	n/total n (%) or	
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Laboratory exams									
Hematocrit (%)	38 ± 7	34 ± 6	NS	37 ± 5	34 ± 7	NS	34 ± 6	34 ± 7	NS
Hemoglobin (g/dl)	**14 ± 5**	**11 ± 2**	**0.0344**	12 ± 2	11 ± 2	NS	11 ± 2	11 ± 2	NS
CPB hematocrit (%)							26 ± 5*	24 ± 4*	NS
Lactate (mmol/L)	**1.2 ± 0.3**	**3.5 ± 1.4**	**0.0001**	**1.1 ± 0.3**	**3.3 ± 1.2**	**0.0001**	3.5 ± 1.4	3.3 ± 1.2	NS
Hemodynamic variables									
Heart rate (beats per minute)	**97 ± 15**	**113 ± 18**	**0.012**	**97 ± 16**	**112 ± 15**	**0.0116**	113 ± 18	112 ± 15	NS
Systolic blood pressure (mmHg)	85 ± 16	89 ± 12	NS	83 ± 10	90 ± 20	NS	89 ± 12	90 ± 20	NS
Diastolic blood pressure (mmHg)	53 ± 15	52 ± 12	NS	49 ± 7	49 ± 12	NS	52 ± 12	49 ± 12	NS
Mean blood pressure (mmHg)	64 ± 18	61 ± 12	NS	64 ± 13	64 ± 17	NS	61 ± 12	64 ± 17	NS
Central venous pressure (mmHg)	10 ± 8	12 ± 7	NS	**8 ± 1**	**10 ± 3**	**0.0203**	12 ± 7	10 ± 3	NS
Operative morbidity and mortality									
Morbidity						3 (20%)	1 (6%)		NS
Mortality						0 (0%)	0 (0%)		NS

*CPB measured values (due to hemodilution).

Table 6. Comparison between operative clinical end point variables in both groups of study (with and without MUF).

statistically significant increase in central venous pressure after CPB compared with the ones before CPB. There were no differences before and after CPB in the other hemodynamic variables (systolic, diastolic, and mean blood pressures), nor inoperative morbidity and mortality. Successful clinical operative endpoints were archived in both groups of study.

4. Discussion

Cardiopulmonary bypass (CPB) is able to trigger a systemic inflammatory response syndrome (SRIS) due to several factors that include: (1) cell activation secondary to contact with CPB synthetic surfaces, (2) mechanic stress, (3) tissue ischemia and reperfusion, (4) hypotension, (5) non-pulsatile flow, (6) hemodilution relative anemia, (7) blood and blood products transfusion, (8) heparin and protamine administration, and (9) hypothermic effects. CPB activates the vessels endothelium and releases pro-inflammatory agents such as tumoral necrosis factor α (TNF-α), interleukins, and endotoxins. These agents also activate the intracellular transcription factor that increases endothelial pro-inflammatory cytokines and the molecular expression of leukocyte adhesion.

It is well known the fact that younger age increases even more the inflammatory effects of CPB. Some reasons include increased metabolic demand in these patients, hyperactivity of their pulmonary vessels, immaturity of their organs/systems, and altered homeostasis. The risk is particularly high in neonates and young infants due to mismatch between CPB and patient's size, with CPB circuit volume usually 200–300% higher than that of the patient. Additionally, an increased metabolic demand requires elevated pump flow up to 200 ml/kg^{-1}/min^{-1} in neonates. Combining a relative major size of CPB with an increased perfusion rate leads to a greater blood exposure to synthetic surfaces of the circuit components [23]. In our series, there was no age difference between the studied groups, and it is important to highlight that none of the groups included neonate patients for the reasons already discussed.

One of the most involved cytokines in SRIS development is, indeed, IL-6. Increased concentrations of IL-6 have been reported in patients with postoperative complications, and a correlation with posterior left ventricular wall dyskinesia detected by means of transesophageal echocardiography has been established. IL-6 is also an endogenous pyrogen agent that activates acute phase reactant proteins. Concentration of IL-6 increases independently of the oxygenator type, degree of hypothermia, or heparin use in the CPB circuit surfaces [24, 25]. Although in our study IL-6 concentrations were significantly higher before surgery in the problematic group than in the control group, this agent is also the one that is significantly more removed by MUF. This is probably the most relevant fact of our study because it shows that the benefit of MUF in congenital heart disease surgery is the removal of IL-6, an important pro-inflammatory agent, particularly in patients that SRIS is enhanced because of the immaturity of their immune system. Another effect that is important to discuss is the fact that, if MUF benefits patients with simple congenital heart disease surgery as were the ones included in our study, it would indeed improve operative outcomes in those operated on for complex congenital heart disease [26]. This single fact justifies the routine use of MUF in all patients with congenital heart disease that is operated on with CPB.

There are several additional methods, despite ultrafiltration, that had been developed in order to diminish SRIS secondary to CPB at surgical correction of congenital heart disease in pediatric population. Some of them are steroids (e.g., dexamethasone 10–30 mg/kg 6–12 hours before CPB) and modified tubular synthetic surfaces in the CPB circuit. However, none of these methods is as such as useful for this purpose as MUF, which is established right after ending the CPB and before decannulation of the patient [27]. Since 1973, different types of hemofilters have been developed in order to remove priming volume (water) following the principle of pressure gradient, particularly those made of polycarbonate. These filters have been replaced by the ones made out of polysulfonate in 1986 and later by the current generation of polyamide hemofilters. These are the most practical ones because of its greater biocompatibility, reduced surface, and more ultrafiltration effectiveness due to a less than physiological pressure.

The effectiveness of ultrafiltration for removing pro-inflammatory agents depends also on the type of hemofilter and on the modality of ultrafiltration procedure used. Kosik et al comments Berdat´s study on the effectiveness of polysulfonate filters vs polyamide ones in the two ultrafiltration modalities for the removal of pro-inflammatory agents such as IL-6, IL-10, and TNFα [3]. They prove that IL-6 was better removed by conventional ultrafiltration (CUF) with poliariletersulfonate filter, while TNFα was better removed by modified ultrafiltration (MUF) and poliariletersulfonate filter. The rest of the pro-inflammatory agents was not modified neither for the ultrafiltration modality nor for the hemofilter type. Therefore, it seems that MUF with poliariletersulfonate hemofilter is the better strategy for removing pro-inflammatory agents in pediatric patients with congenital heart surgery. Our results are based on the ultrafiltration modality rather than the type of filter, since the material of hemofilters that we used was variable.

It has been reported that MUF is not only useful for removing extracellular fluid excess, but also cytokines and other inflammatory agents triggered by CPB and surgical trauma. There is some controversy in the literature regarding the efficacy of filters in the removal of cytokines, as well as in the differences between the two ultrafiltration modalities [28]. Additionally, the comparative results between both ultrafiltration modalities are difficult to interpret due to variations in the ultrafiltration technique, equipment, definitions and objectives, and measurements of cytokines. Finally, it is still not known if the clinical benefits of MUF are due to the removal of cytokines and other inflammatory agents, or to the isolated reduction of tissue edema [29–33].

5. Conclusion

Based on the results of this study [34], we can say that although the baseline concentrations of IL-6 in the patients of the problematic group were higher in relation to those of the control group, the removal of this pro-inflammatory agent by MUF was statistically significant. This indicates that MUF is a procedure that can benefit pediatric patients with congenital heart disease undergoing CPB because it is able to decrease the concentration of IL-6. Therefore, we consider that the use of MUF in pediatric patients should be routinely recommended as long as hemodynamic conditions allow it.

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Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship or publication of this manuscript.

Author details

Pedro José Curi-Curi[1]*, Elizabeth Aguilar Alanis[1], Juan Calderón-Colmenero[2], Jorge Luis Cervantes-Salazar[1], Rodrigo Reyes Pavón[1] and Samuel Ramírez-Marroquín[1]

*Address all correspondence to: pcuricuri001@gmail.com

1 Department of Congenital Heart Disease and Pediatric Cardiac Surgery, "Ignacio Chávez" National Cardiology Institute, Mexico City, Mexico

2 Department of Pediatric Cardiology, "Ignacio Chávez" National Cardiology Institute, Mexico City, Mexico

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