Neurological repercussions of changes in cerebral blood flow in neonates undergoing cardiovascular surgery

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Abstract

Introduction: Surgery for congenital heart disease can generate cerebral perfusion-associated alterations with neurological repercussions. **Objective:** To analyze the relationship of peri-surgical cerebrovascular resistance index (RI) with mediate neurological functions after congenital heart disease surgery. **Method:** Prospective cohort study of 34 neonates in whom basilar artery RI, serum oxygen, carbon dioxide and lactate levels were determined before and after palliative or corrective procedures. We related pre-surgical RI with post-surgical ability to initiate the enteral route or to restore unassisted spontaneous breathing. **Results:** Three groups were formed: 79 neonates with high RI (> 0.73), 73 with normal RI (0.63 to 0.73) and eight with low RI (< 0.63). In the former group, high RI persisted in the postoperative period, with persistent hyperlactatemia and hypoxia; in 86 %, the enteral route could not be initiated, and neither could assisted ventilation be withdrawn. In the second group, RI remained within normal values. In the third group, although RI, serum lactate and arterial oxygen pressure tended to normalize, 71 % had severe neurological damage. **Conclusions:** RI changes were common, although neurological damage appears to occur more commonly when RI remains high, possibly associated with low cerebral blood flow.

KEY WORDS: Resistance index. Cardiovascular surgery. Congenital heart disease. Neonate.

Repercusión neurológica por cambios en el flujo sanguíneo cerebral en neonatos sometidos a cirugía cardiovascular

Resumen

Introducción: La cirugía de cardiopatías congénitas puede generar alteraciones perfusorias cerebrales con repercusión neurológica. **Objetivo:** Analizar la relación del índice de resistencia (IR) vascular cerebral perquirúrgico con funciones neurológicas mediatas posteriores a cirugía de cardiopatía congénita. **Método:** Estudio de cohorte prospectivo de 34 neonatos en quienes se determinó IR de la arteria basilar, niveles séricos de oxígeno, dióxido de carbono y lactato, antes y después de procedimientos paliativos o correctivos. Relacionamos el IR prequirúrgico con la capacidad posquirúrgica para iniciar la vía enteral o restablecer la respiración espontánea no asistida. **Resultados:** Se integraron tres grupos: 79 neonatos con IR alto > 0.73 , 73 con IR normal de 0.63 a 0.73 y ocho con IR bajo < 0.63 . En los primeros persistió IR elevado en el posquirúrgico, con hiperlactatemia e hipoxia persistentes; en 86 % no se logró iniciar la vía enteral ni retirar la ventilación asistida. En los segundos, el IR se mantuvo en valores normales. En los terceros, si bien el IR, el lactato sérico y la presión arterial de oxígeno tendieron a normalizarse, 71 % presentó daño neurológico grave. **Conclusiones:** Los cambios en el IR fueron frecuentes, aunque el daño neurológico parece presentarse más cuando el IR se mantiene alto, posiblemente asociado con flujos cerebrales bajos.

PALABRAS CLAVE: Índice de resistencia. Cirugía cardiovascular. Cardiopatía congénita. Neonato.

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Introduction

Therapeutic management, whether palliative or corrective, of neonates with complex congenital heart disease (CCHD) is a challenge due to high mortality and neurological sequelae.^{1,2} The latter are attributed to hypoxic-ischemic events associated with cerebral blood flow variations. Although neurological damage might start since fetal life,^{3,4} the highest risk is usually observed after birth, before or during heart disease corrective or palliative procedures.⁵ Prior to this, neurological damage can be caused by CCHD-inherent chronic hypoxia, recurrent or persistent hypercapnia events or preoperative medications;⁶⁻⁹ during cardiovascular surgery, it can be caused by the use of cardiopulmonary bypass.^{10,11}

One determinant factor against hypoxic-ischemic damage is cerebral blood flow preservation by self-regulation of neuronal metabolic demands.¹² Pre-surgical hypoxia and blood volume variations during surgery can harm these mechanisms and facilitate neurological damage.¹³ An indirect indicator of cerebral blood flow self-regulation functionality is the vascular resistance index (RI),¹⁴ which is measured by transfontanelar Doppler ultrasound in cerebral arteries; among these, the basilar artery provides more information and allows the effect of perfusion to be assessed in basic survival areas.¹⁵

A neonate with CCHD without severe hemodynamic repercussion is expected to maintain a RI of between 0.63 and 0.73,¹⁶ which does not occur if the malformation is not compensatory. In neonates with a history of moderate or severe asphyxia at birth, altered RI has been associated with neurological damage. In neonates with RI < 0.55 at between 36 and 72 hours after birth, greater subsequent neurological deterioration has been observed.¹⁴ This has not been analyzed in neonates with CCHD undergoing cardiovascular surgery. The purpose of this work was to assess the effect of cardiovascular surgery on RI, as well as to analyze whether these changes affect early neurological functionality five days after the operation.

Method

Once approval of the local Research and Ethics Committee was obtained, with registration R 2015-3603-32, as well as informed consent of the children's parents, 34 patients attended to from October 2015 to May 2016 were recruited at the Pediatric Hospital of

the National Medical Center *Siglo XXI*, Mexican Institute of Social Security, Mexico City. Neonates (< 28 days of life) with CCHD, scheduled for palliative or corrective cardiovascular surgery, were included. Children with multiple extracardiac malformations, children scheduled for therapeutic catheterization or without ultrasound record prior to surgery were excluded. Children who died during surgery were censored from the final analysis.

Pre-surgical medical treatments and scheduled surgery were decided by a group of neonatologists, cardiologists and cardiovascular surgeons, although the final surgical decision was determined based on trans-operative findings. Postoperative management was independent of the ultrasound study results and was based on the consensus of the doctors responsible for the child.

With pulsatile Doppler ultrasound (Hewlett Packard Sonos 5500® model with 8-MHz transducer), cerebral coronal sections were made in the anterior fontanelle until the basilar artery flow was located. The RI was obtained with the (systole-diastole)/systole formula, with the most acceptable pulse wave being measured and the maximum systolic peak velocity and end-diastolic peak velocity being obtained. The final value consisted of the average of three measurements made in 30 seconds. The measurements were always performed by a single trained evaluator and within a period not exceeding 45 minutes prior to the start of surgery. Two subsequent measurements were made, the first one at the conclusion of surgery and with at least 30 minutes of hemodynamic stability during intensive care unit stay; the second, at 18 hours. In addition, partial pressure of oxygen (pO₂), partial pressure of carbon dioxide (pCO₂) and serum lactate (mmol/L) were determined at each time-point. Data on gestational age, birth weight, type of heart disease, age at the procedure, pre-surgical weight, RASCH-1,¹⁷ use of analgesia or preload sedation, ventilatory support and enteral feeding were obtained from each patient. Regarding the performed procedure, data on cardiopulmonary bypass time, vascular clamping time and delayed or non-delayed closure of the sternum were recorded.¹⁸

To assess neurological functional condition after surgery, we recorded whether or not it allowed ventilatory support withdrawal and/or feeding initiation within the first five days following surgery. The decision on assisted ventilation withdrawal and feeding initiation was determined by the medical team based on clinical criteria (respiratory automatism, acid-base balance, soft abdomen with peristalsis and evidence

Figure 1. Flow chart of the selection of neonates with complex congenital heart disease included in the study.

of intestinal transit), regardless of the RI report and of researchers. Finally, survival to this admission period was determined.

Patients were grouped according to pre-surgical RI: normal, 0.63 to 0.73; low, < 0.63; high, > 0.73. Simple frequencies and percentages were obtained for categorical variables and medians with interquartile ranges for quantitative variables, given their abnormal distribution. To determine differences in the results at three specified time points, a non-parametric Wilcoxon test or the chi-square test was used. All analyses were performed with the statistical program SPSS, version 24. A p-value < 0.05 was considered to be statistically significant.

Results

As shown in Figure 1, 115 patients with CCHD were admitted, out of which 51 (42.8 %) met the selection criteria. Pre-surgical measurements were obtained in 34, and only in 28 were all three measurements available.

Demographic and clinical pre-surgery characteristics

Data are summarized in Table 1. Most neonates were males and full-term, with a median weight of

2900 g and 10 days of age at surgery. The most common heart disease was transposition of the large arteries, followed by abnormal connection of the pulmonary vessels. In nine, surgery was palliative, and in the rest, corrective; arterial switch was the most common (12/34; 35.2 %); 75 % of neonates received assisted ventilation, 50 % received sedative medication and 67 % were fasted. Adjusted surgical risk (RASCH-1) ranged from 1 to 6, and 61.7 % had a score of 3.

According to pre-surgical RI, seven patients (20.5 %) had normal values, eight (23.5 %) low and 19 (55.8 %) high.

Post-surgery evolution

Owing to their decease, six patients were not measured at all three scheduled time-points: four (11.7 %) died during cardiopulmonary bypass (two with high RI, one with normal RI and one with low RI), and two (5.8 %) in the immediate postoperative period, both with low RI, during the first hour of exiting cardiopulmonary bypass.

Delayed closure of the sternum was required by 21 (61 %) patients who survived the surgical procedure (Table 1). Two patients were operated on two occasions: in one case, pulmonary artery cerclage

Table 1. Clinical and demographic data of 34 neonates with complex congenital heart disease

Variable	Median	1, 3 quartile
Age at surgery (days)	10	2, 44
	Median	Min-max
Weight in grams at surgery	2900	1430-3835
	n	%
Male gender	22	64.7
Gestational age at birth		
< 37 weeks	4	11.8
≥ 37 weeks	30	88.3
Type of cardiovascular anomaly		
Transposition of large arteries	11	32.4
TLA + aortic coarctation/hypoplasia	2	5.9
Anomalous pulmonary venous connection	9	26.5
Aortic interruption/coarctation	3	8.8
Hypoplastic left ventricle syndrome	3	8.8
Pulmonary atresia	3	8.8
Single atrium and single ventricle	1	2.9
Ebstein anomaly	1	2.9
Atrioventricular canal	1	2.9
Pre-surgical management		
Analgesia	8	23.5
Sedation	17	50.0
Ventilatory support	25	73.5
Enteral nutrition	12	35.3
Performed surgeries		
Arterial switch	12	35.3
Systemic pulmonary fistula	8	23.5
Pulmonary vessels total repair	7	20.5
Aortic plasty	2	5.9
Norwood procedure	2	5.9
Pulmonary artery banding + aortic repair	1	2.9
Pulmonary artery banding	1	2.9
PVTR + ARP	1	2.9
RASCH-1 score		
1	1	2.9
3	21	61.8
4	10	29.4
6	2	5.9
Cardiopulmonary bypass time		
< 90 minutes	3	8.0
≥ 90 minutes	18	52.9
Clamping time		
< 60 minutes	8	23.5
≥ 60 minutes	13	38.2
Deferred sternal closure	21	61.8

TLA = transposition of large arteries, PVTR = pulmonary vessels total repair, ARP = aortic repair.

was initially performed and then corrective arterial switch, and in the other, initial aortic plasty and subsequent arterial switch (Fig. 1).

Post-surgery resistance index evolution

Figure 2 shows postoperative RI by groups. In patients with normal RI, there were no differences between their initial values (30 minutes) and 18 hours later ($p = 0.223$), in addition, the figures remained between 0.63 and 0.73 at all times. In children with low pre-surgical RI, it was normalized in the postoperative period: 0.65 at 30 minutes and 0.68 at 18 hours (Wilcoxon test $p = 0.09$). In neonates with high pre-surgical RI, it remained high: 0.82 at 30 minutes and 0.81 at 18 hours, $p = 0.204$.

O₂, CO₂ and serum lactate modifications in the post-surgical period

In all children, an increase in oxygen saturation was observed after cardiovascular surgery. The increase was more noticeable and constant in the group with low pre-surgical RI: 35, 45 and 65 mmHg in the measurements at baseline, at 30 minutes and at 18 hours ($p = 0.007$). The change was minimal in neonates with normal RI: 40, 61 and 57 mmHg for the same measurements ($p = 0.738$), as in those with high IR as well: 30, 46 and 50 mmHg ($p = 0.014$) (Fig. 3).

paCO₂ in neonates with low and high RI was reduced 30 minutes after surgery and was normalized at 18 hours: in children with low RI, measurements at baseline, at 30 minutes and at 18 hours were 36, 32 and 35 mmHg ($p = 0.692$); in those with high RI, 36, 32 and 36 mmHg, respectively ($p = 0.19$). The group with normal RI showed no changes: baseline, 36 mmHg, and at 30 minutes and 18 hours, 41 mmHg ($p = 0.26$) (Fig. 4).

Serum lactate was elevated since pre-surgical measurement in all patients. In those with normal RI, it did not change during the postoperative period: 3 mmol/L in the pre-surgical measurements and at 30 minutes, and 2.5 mmol/L at 18 hours ($p = 0.554$). In patients with low RI, it did increase at 30 minutes (2 to 4 mmol/L), and it remained high at 18 hours (4 mmol/L, $p = 0.247$). In the group with high RI, it increased from 2.5 mmol/L to 5.5 mmol/L at 30 minutes; at 18 hours, it dropped close to pre-surgical values (3.5 mmol/L, $p < 0.0001$).

Postsurgical clinical evolution

Postoperative neurological functionality was assessed in 28 patients (82.3 %). In 60.7 % (17/28), it was

Figure 2. Changes in resistance indices (RI) after surgery (30 minutes and 18 hours) according to pre-surgical values (normal RI, $n = 5$; low RI, $n = 6$; high RI, $n = 17$). The squares, circles and diamonds correspond to the medians, and the 'whiskers', to the 1-3 interquartile range. With Wilcoxon test, $p = 0.091$ was obtained for low RI, $p = 0.223$ for normal RI and $p = 0.204$ for high RI.

Figure 3. Levels of arterial blood oxygen tension before and after the surgical procedure, according to the resistance index: normal, $n = 5$; low, $n = 6$; high, $n = 17$). The squares, circles and diamonds correspond to the medians, and the 'whiskers', to the 1-3 interquartile range. With Wilcoxon test, $p = 0.007$ was obtained for low RI, $p = 0.74$ for normal RI and $p = 0.01$ for high IR.

unfavorable and did not allow enteral feeding initiation or assisted ventilation withdrawal within the first five postsurgical days (Table 2). A statistically significant

difference between the groups could not be demonstrated. Only four patients in the high RI group (23.5 %) achieved complete neurological functionality.

Figure 4. Levels of arterial blood carbon dioxide tension before and after the surgical procedure, according to the resistance index (normal, $n = 5$; low, $n = 6$; high, $n = 17$). The squares, circles and diamonds correspond to the medians, and the 'whiskers', to the 1-3 interquartile range. With Wilcoxon test, $p = 0.69$ was obtained for low RI, $p = 0.26$ for normal RI and $p = 0.13$ for high RI.

Table 2. Post-surgery neurological capabilities according to pre-surgery resistance index in 28 neonates with complex congenital heart disease

Neurological capability	Normal RI (n = 6)		Low RI (n = 5)		High RI (n = 17)		Total (n = 28)	p*
	n	%	n	%	n	%		
Not achieved for starting enteral nutrition or spontaneous breathing	4	57.1	4	50	9	47.3	17	0.35
Only start of enteral nutrition or spontaneous breathing	2	33.3	1	20	4	23.5	7	
Both enteral nutrition and spontaneous breathing achieved	0	0	0	0	4	23.5	4	
Death	2	28.5	4	50	5	26.3	11	

RI = vascular resistance index. normal RI, 0.63-0.73; low RI, ≤ 0.63 ; high RI, ≥ 0.73 .

*Pearson's test, contingency coefficient = 0.34.

Discussion

An initial finding was that most patients (79 %) had a low or high RI prior to surgery, which implies a high prevalence of neonates with altered cerebral blood flow, possibly due to hemodynamic changes since the fetal stage and related to the heart defects.¹⁹ It is possible that, with cardiovascular surgery, flows are redistributed and thereby the RI changes to normal levels within 18 hours after surgery, as it occurred in most patients. When cerebral blood flow is not normalized, there can potentially be neurological damage.²⁰

On the other hand, due to the establishment of three different groups according to pre-surgical RI, it was possible to assess differential patterns in the vasculocerebral behavior secondary to the hemodynamic challenge a complex surgery implies. In the neonates with normal pre-surgical RI, a preserved cerebral vasomotor response was observed, with a slight increase in the RI at the conclusion of the surgical intervention, possibly owing to volume changes due to reperfusion after cardiopulmonary bypass withdrawal,¹¹ but which returned to normal value once the patient was stabilized at 18 hours.

In the group with a high presurgical RI, eight of the 19 patients had transposition of the large arteries or chronic hypoxic right heart failure, which are conditions that induce a RI increase; in these patients, despite a correction of the defect with an increase in partial pressure of oxygen, there was no vasodilation consistent with a substantial RI reduction, which can be explained by alterations in regional oxygen saturation.²⁰

Contrary to our hypothesis that immediate postoperative period would be favorable in children with RI normalization, this only occurred in one patient with a previously elevated RI. Three other neonates with high pre-surgery IR also had a favorable postoperative period, but the RI values continued to be high. In the rest, it was difficult to decannulate or starting the enteral route or both.

Due to the small number of patients and the interaction of multiple factors, mainly the types of heart disease, it is difficult to analyze the conditions that affected neurological evolution. Particularly in neonates with low RI, although the values did increase during the postoperative period, subsequent evolution was very poor: three died and the others did not achieve respiratory and enteral autonomy. These findings are consistent with those observed by Ilves²¹ in patients with severe asphyxia and explained as damage due to vasoparalysis secondary to delayed hyperperfusion. Perhaps in patients with high RI, cerebral self-regulation maintained better compensation for the changes in cerebral perfusion pressure.¹⁵ When this self-regulation is impaired, efficacy depends exclusively on external factors such as blood pressure and blood volume, among others. We do not doubt that these mechanisms might have been abolished in the patients, with the conditions of surgical and anesthetic treatment contributing to it.²²

Another contributing factor in several patients was the need to perform a delayed sternum closure. During the wait, they were under sedation, analgesia and intubation, which are high-risk conditions for new hypoxic-ischemic episodes.

Two important limitations of this study should be considered: one is the sample size, and the second, the follow-up period. Although it is difficult to reproduce the study due to the characteristics of the patients, a multicenter study will be necessary. Furthermore, vascular magnetic resonance imaging has been suggested as another option for peri-surgical assessment,²³ as well as analyzing other factors involved.²⁴

Conclusions

A high proportion of patients with CCHD show cerebral RI alteration before the cardiovascular procedure, and although cardiovascular surgery appears to favor RI normalization, neurological repercussions could be already determined. In most patients, it was difficult to withdraw respiratory assistance or start enteral feeding due to inadequate central neurological control.

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