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Original Research Paper

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UMBILICAL CORD BLOOD ACID-BASE STATUS IN NEWBORNS WITH CONGENITAL HEART DISEASE IN A CARDIOVASCULAR REFERRAL CENTER IN COLOMBIA

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ABSTRACT **Introduction:** Congenital heart diseases (CHD) represent the most frequent group of congenital disorders, with an incidence of 8 to 10 per 1000 live births. The aim of this study was assess the correlation between the presence of CHD and the acid base status of the umbilical cord blood at the Fundación Cardiovascular de Colombia during the period 2007-2018. **Materials And Methods:** Retrospective descriptive study in FCV, prior to authorization of the ethics committee, medical records were reviewed and with ICD10 codes the patients with CHD were identified everyone with prenatal echocardiography, CHD incompatible with life or incomplete records were excluded, It took a sample of arterial blood from the umbilical cord, the sample was processed in a gases machine (i-STAT300F), the data was collected in Excel, the heart diseases were classified according to the cardiopathophysiological classification, the association measure was -X2 **Results:** we met 111 patients with CHD, 56.7% men, in total 367 specific defects, grouped into 4 groups (IPB, DBPF, OBNSD and NSBC) with 157, 50, 77 and 58 respectively. The pH, HCO3, Pco2, Po2 in general without alterations. However, when we compare DPBF, it had an increase in the incidence of acidosis and mortality statistically significant p = 0.005. **Conclusions:** according to the findings, we can affirm that there are specific heart diseases such as DPBF, which predispose worse results, including acidosis and perinatal asphyxia. It also means that the changes in acid-base state in patients with CHD are not simply physiological variations, but are indicators of pathology and mortality, just as in patients without CHD.

KEYWORDS : Umbilical cord blood, Congenital Heart Disease, Acid-base status

INTRODUCTION:

Congenital heart diseases (CHD) represent the most frequent group of congenital disorders, with an incidence of 8 to 10 per 1000 live births, of which about 80% will need cardiac surgery, being half of them operated in the first year of life (1,2). These are defects with a multifactorial origin in which both genetic and environmental factors play critical roles in their development. Due to its increasing importance, in recent years, there have been improvements in diagnostic methods that have allowed more precise identification of these defects in utero (2,3,4). These antenatal diagnostic methods have opened the door to study the impact of these malformations on the fetal cardiovascular physiology, finding a potential negative impact in the fetus by several mechanisms e.g. the almost total mixture of oxygenated and un oxygenated blood could increase the risk of pathological processes (5,6). However, to our knowledge, no studies in Latin America have demonstrated the impact of CHD in specific alterations of the acid-base and oxygenation state that characterizes perinatal asphyxia. The aim of this study was to assess the correlation between the presence of fetal CHD and the acid-base status of the umbilical cord blood at birth in individuals born at the Fundación Cardiovascular de Colombia during the period 2007-2018.Our aimed as well to elucidate whether changes in the acid-base status in this population had truly deleterious effect on the newborn health, or if it only represented physiologic variations of a distinct homeostasis.

METHODS:

Study design

Retrospective descriptive study, conducted in the neonatal unit of the Fundación Cardiovascular de Colombia (FCV), Bucaramanga, Colombia, a high complexity referral center for patients with a wide variety of cardiac diseases at a national and international level. The neonates born at this center during the period between 2007-2018 with a diagnosis of Congenital Heart Disease (CHD) made by echocardiography were included. Newborns with malformations incompatible with life and the records with incomplete information were excluded.

Summary of the clinical practice

The samples were collected according to standardized institutional protocols in line with recommendation from the National Health Ministry. Delayed umbilical cord clamping (2-4 minutes after birth) was performed according to the institutional protocol, then the umbilical cord was cut between the first two clamps and local asepsis of the isolated cord segment was performed immediately, later a sample is taken directly from the umbilical artery by direct puncture with a previously heparinized syringe needle of 1 cm (sample size), and lastly the sample was immediately delivered to the assistant nurse of the ward, who proceeded to bring the sample directly to the blood gas analyzer (i-STAT300F, Abbott Point of Care Inc., Abbott Park, IL, USA) arranged in the corridor of the surgery rooms. The sample was processed in less than 3 minutes after obtaining it. The results were then immediately evaluated by the neonatologist and the perinatologist.

DATA COLLECTION

After authorization of the Ethical Review Board, electronic medical records were reviewed from January 1st of 2007 to December 31st of 2018 to identify ICD-10 codes for CHD and related disorders. Given the wide variety of CHD, a pathophysiological classification was used (1),allowing clustering of individual cardiac defects into groups sharing key features. Several variables were also identified for multivariate analysis including possible cofounding factors, that could contribute to acid-base alterations, being the following: maternal parity, maternal age, maternal comorbidities, maternal ICU need, prenatal CHD diagnosis,

maternal hemoglobin, leukocyte and platelet count, gestational age at born, type of delivery, type of anesthesia, weight, height, APGAR at the first minute and at the fifth minute, umbilical cord blood acid-base status (pH, PCO2 (mmHg), PO2 (mmHg), Base/excess (mmol / L), HCO3 (mmol / L), Lactate (mmol / L), perinatal asphyxia diagnosis, postnatal echocardiography result, total days of inpatient care and death. Relevant clinical data was collected in a pre-designed data collection instrument in the Excel© program and then stored in a password protected registry.

Ethics in research

This study was approved by the Ethical Review Board of the FCV (Record number 418 of March 21, 2017) following the guidelines stated in the Declaration of Helsinki of the World Medical Association and in the Resolution 8430 of 1993 of the Ministry of Health of Colombia, classifying as an investigation with minimal risk to participants.

Statistical Analysis

Due to the type of study, the association measure that we used was X^2 to find statistical significance. We individually compared each group of congenital heart disease with patients without congenital heart disease and the association with the presence or absence of acidosis in a blood sample of the umbilical cord with a significance level of 99% with a degree of freedom of 1 limit value of X^2 7,879, less than that, the alternative hypothesis is rejected and the null hypothesis is accepted, therefore there is no association, if on the contrary it is greater than 7.879, the null hypothesis is rejected and the alternative hypothesis is accepted.

RESULTS

Sociodemographic features, obstetrics history, and hemogram

The median motherly age in our sample was 27 years old (IQR 22-32). The median number of gestations were two (IQR 1-3), and the median number of previous parturitions was one (IQR 1- 3). Amongst women who had children from previous gestations, they delivered via labor more frequently than via cesarean section (63% via labor, 37% via cesarean section). 23% of women had a history of abortion from passed pregnancies, while none of them had ectopic pregnancies before.

Regarding laboratory data, the median value for maternal hemoglobin was 12.5 g/dl (IQR 11.4-13.7), for white blood cell count was 9,500 cells/mcl (IQR 7,880 – 11,320) and for platelet count 228,000 plt/mcl (IQR 193,000 – 270,000).

Gestational age, diagnosis status, delivery, and newborn conditions

The median gestational age for delivery in our sample was 38 weeks (IQR 37-38.5). In 10% of cases, newborns did not have prenatal congenital heart disease (CHD) diagnosis. Cesarean section was the delivery choice in 93% of cases, being regional anesthesia, the most common anesthetic procedure (95%). Male newborns accounted for 56.7% of our patients. The median weight was 2,960 g (IQR 2,740 – 3,240), and median height 49 cm (IQR 47 – 51). Median Apgar at one, five, and 10 minutes were 8, 9 and 9, respectively. As regards to umbilical cord blood gases, median pH was 7.3 (IQR 7.25 – 7.36), pCO2 43.4 mm Hg (IQR 35.7 – 53.2), pO2 29 mm Hg (IQR 21 – 38.8) and median lactate level was 2.6 mmol/L (IQR 2 – 3.8). Among the six patients with a pH value equal or lower than 7.15 CHD diagnoses were heterogeneous, highlighting single morphology ventricle (3), Ebstein anomaly (2), hypoplastic left heart (1) and anomalous venous drainage (1). These patients were more commonly males (83%), with gestational ages at delivery that ranged from 30,5 to 38,8 weeks (median 34,5 weeks).

Congenital heart disease incidence

From the 111 patients with CHD, 367 specific heart defects were found. According to the pathophysiological classification of CHD (**Table 1**), the IBPF group of CHDs accounted for the largest number of defects among other groups (157 defects), while only four entities from the SUAA group were encountered. The number of defects for the DBPF, OBNSD, and NSBC groups was 50, 77, and 58, respectively. The most common conditions were patent ductus arteriosus (57 cases) and interatrial communication (49 cases). There was also a predominance for left heart hypoplastic defects in comparison with the right heart side, having found 25 cases of hypoplastic left heart syndrome in contrast with only 8 cases of hypoplastic right heart syndrome; similarly, hypoplastic aortic arch was seen in 22 patients, whereas hypoplastic pulmonary artery in 3 cases. There were also 2 cases of left isomerism, while none of right isomerism.

Tables

Table 1. Pathophysiological classification of Congenital Heart Diseases

Category	Acronym	CHD
CHD with increased pulmonary blood flow	IPBF	-Partial anomalous pulmonary venous drainage -Atrial septum defects (ASD) -AV septum defects -Ventricular septum defects (VSD) -Persistent truncus arteriosus -Patent ductus arteriosus
CHD with decreased pulmonary flow	DPBF	-Pulmonary valve stenosis with ASD -Pulmonary stenosis with VSD (Tetralogy of Fallot) -Tricuspid atresia -Ebstein anomaly of the tricuspid valve -Single ventricle with pulmonary stenosis
CHD with obstruction to blood progression and no septal defects	OBNSD	-Pulmonary stenosis -Aortic stenosis -Coarctation of the aorta
CHD so severe as to be incompatible with postnatal blood circulation	NCBC	-Pulmonary atresia -Aortic/Mitral atresia -Complete transposition of the great arteries -Total anomalous pulmonary venous drainage
CHD silent until adult age	SUAA	- Bicuspid aortic valve -Congenital anomalies of coronary arteries -Wolff-Parkinson-White Syndrome -Congenitally corrected transposition of the great arteries

Table 2. Congenital Heart Disease Diagnoses

CHD diagnosis	N	%
PAD	57	16,14
ASD	49	13,88
VSD	30	8,49
Hypoplastic Left Heart Syndrome	25	7,08
Aortic Arch Hypoplasia	22	6,23
Single ventricle CHD	20	5,66
AV Septum Defect	15	4,24
Pulmonary Valve Stenosis	12	3,39
Pulmonary Valve Atresia	10	2,83
Ebstein Anomaly	9	2,54

Tricuspid Valve Atresia	8	2,26
Mitral Valve Atresia	8	2,26
Hypoplastic Right Heart Syndrome	8	2,26
Right Ventricle Double Outlet	8	2,26
Aortic Coarctation	8	2,26
Aortic Valve Stenosis	7	1,98
Large Vessel Transposition	7	1,98
Aortic Valve Atresia	6	1,69
Persistent arterious trunk	5	1,41
Anomalous venous drainage	5	1,41
Tetralogy of Fallot	4	1,13
Single atrium	4	1,13
Inferior Venae Cavae Interruption	4	1,13
Ambiguous situs	3	0,84
Pulmonary Artery Hypoplasia	3	0,84
Right Aortic Arch	3	0,84
Left Isomerism	2	0,56
Dextrocardia	2	0,56
Complete AV Block	2	0,56
Cantrell Pentalogy	2	0,56
Anomalous pulmonary venous return	1	0,28
Situs Inversus	1	0,28
Hypertrophic Cardiomyopathy	1	0,28
Bicuspid aortic valve	1	0,28
Otros	1	0,28

Table 3. Demographic Variables and Umbilical Cord Blood Acid-base Status by CHD Group

Variable	IPBF n = 81	DPBF n = 43	OBNSD n = 54	NCBC n = 37	SUAA n = 4
Gestational Age (Weeks)	**38 (IQR 37 - 38.5)**	**38 (IQR 36.2 -38.1)**	**38 (IQR 37 - 38.5)**	**38.75 (IQR 38 - 39)**	**37 (IQR 37 - 37)**
Males	36 (44.4%)	22 (51.16 %)	25 (46.3 %)	16 (43.24%)	2 (50%)
Weight (Grams)	2935 (IQR 2700 - 3255)	3000 (IQR 2700 -3240)	2900 (IQR 2700 -3130)	3020 (IQR 2730 -3130)	3020 (IQR 2770 - 3670)
pH	7.29 (IQR 7.2 - 7.36)	7.29 (IQR 7.22 - 7.36)	7.3 (IQR 7.26 - 7.37)	7.29 (IQR 7.24 -7.36)	7.36 (IQR 7.32 - 7.37)
PCO2 (mm Hg)	42.5 (IQR 35.1 - 53.2)	40.65 (IQR 33.3 – 53.2)	42.2 (IQR 36.3 – 53.2)	46.45 (IQR 40.3 – 54.6)	40.6 (IQR 39.3 – 50.3)
PO2 (mm Hg)	33 (IQR 23 - 46)	31.25 (IQR 26 – 39.8)	29 (IQR 22 – 37.1)	27.25 (IQR 19.69 - 35)	19.69 (IQR 18.4 – 27.8)
Base excess (mEq/L)	(-) 3.6 [IQR (-)6.4 - (-) 2.5]	(-) 3.55 [IQR()8.1 - (-) 2.55]	(-) 3.5 [IQR (-)6.3 - (-) 2.5]	- 3 (IQR (-)4.7- (-)2.2)	- 3 [IQR(-)4.3- (-)2.6]
HCO3 (mEq/L)	22.65 (IQR 19.5 - 24.5)	22.3 (IQR 17 - 23.6)	22.7 (IQR 20.45 - 24.35)	22.9 (IQR 21.5 -24.3)	22.3 (IQR 20.1 – 22.7)
Lactate (mmol/L)	2.55 (IQR 2.1 - 4.1)	3 (IQR 2 – 4.1)	2.35 (IQR 1.75 – 3.55)	2.4 (IQR 2 - 3.4)	2.4 (IQR 1.3 – 2.9)

However, for other defects aside from hypoplastic and isomerism syndromes, we found that defects affecting right side structures were more common, as can be seen with tricuspid insufficiency (6 patients), pulmonary valve stenosis (12 cases), tricuspid atresia (8 patients), pulmonary artery atresia (10 patients), when they are compared with their left side structures counterparts: mitral insufficiency (1 patient), aortic valve stenosis (7 patients), mitral atresia (8 patients) and aortic atresia (6 patients) **(table 2)**.

More complex syndromes incidence was, as expected, lower, and an extensive comparison between these entities was not possible. The most frequent of these conditions was the single ventricle morphology in 19 cases (right or left morphology not specified), followed by the Ebstein anomaly in 9 cases, double outlet right ventricle (8 cases), aortic coarctation (8 cases) and transposition of great arteries (7 cases). Other worth noting CHD were persistent truncus arteriosus (5 cases), anomalous venous return (5 cases), tetralogy of Fallot (4 cases), interrupted inferior vena cava (4 cases), single atrium (4 cases) and single (double inlet) ventricle with pulmonary stenosis (3 cases).Respecting the CHD severity classification proposed by the American Heart Association, there were no cases in the Simple Heart Disease group (Group 1). In the Medium congenital heart disease group (Group 2), 40.5% of patients had a single defect of this severity, 10.8% had two defects, 13.5% had three defects, 5.4% had four defects, and 1.8% had five defects. Similarly, in regards to Group 3 (Congenital heart defects of high severity), 37.8% had one defect from this group, 12.6% had two defects, 1.8% had three defects, and only one patient (0.9%) had five defects.

Newborn and perinatal outcomes

Newborn ICU was required in 89% of births, and the median length of hospitalization was 13 days (IQR 4 – 43). Only eight patients (7.2%) had a reported perinatal asphyxia diagnosis, either due to excess base, pH or APGAR (7). while perinatal death occurred in 23.4% of cases. Importantly, from the group with a pH value under (7.15) the mortality rate was 83% (five of six patients).

DISCUSSION

Congenital heart diseases (CHD) have been identified, as a risk factor for metabolic acidosis due to perinatal asphyxia, however data supporting this relation is scarce. Therefore, we intended to objectively describe the contribution from cardiopathies to acid-base disorders and perinatal asphyxia. We wanted also to establish if there was place for the so-called "normal variatons in acid-base state" that reflected only a different homeostasis in fetuses that have been growing with a CHD for months in the womb. According to our findings, newborns with CHD had in general an acid-base status similar to the values established as normal in healthy newborns (Table 3). However, in the subgroup analysis, the DPBF group showed an increased incidence of acidosis (pH < 7,15) (1-22), in comparison with the other groups, a difference that was statisticallysignificant ($p < 0.005$) after addressing cofounding factors. Furthermore, the presence of acidosis in this group resulted in higher mortality risk, a difference that was statistically significant as well ($p = 0.005$). These relations suggest, that there are specific cardiopathies, i.e. those that have a decreased pulmonary blood flow (PDBF), that predispose to worse outcomes, including acidosis and perinatal asphyxia. It also means, that changes in acid-base status in patients with CHD are not merely physiologic variations, but are indicators of pathology and even mortality, just like in patients without CHD.

Our study has several limitations. First, this was a single-center retrospective review that incorporates any inherent limitations of data collection and review. Second, the sample size limits our results. Third, there were no control patients, and thus the normal values for the acid-base state that we took for comparison, did not come from our own population, but from the literature. Fourth, many patients had several CHD that corresponded to different groups of the pathophysiological classification; nonetheless, extensive consensus for every patient were made, in order to correctly classify each case. For all these reasons, this article invites the scientific community to carry out a prospective study with a larger sample size to improve our knowledge of CHD and its

outcomes in the neonatal population, and thus take additional actions in order to benefit these patients.

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