Cardiology in the Young

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Early postnatal metabolic profile in neonates with critical CHDs

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Abstract

Background: Cyanotic CHD is a life-threatening condition that presents with low oxygen saturation in the newborn period. Hypoxemia might cause alterations in the metabolic pathways. In the present study, we aimed to evaluate the early postnatal amino acid and carnitine/acylcarnitine profiles of newborn infants with cyanotic CHD. *Methods:* A single centre case-control study was conducted. Twenty-seven patients with cyanotic CHD and 54 healthy newborn controls were enrolled. As part of the neonatal screening programme, results of amino acid and carnitine/acylcarnitine were recorded and compared between groups. *Results:* Twenty-seven neonates with cyanotic CHD and 54 healthy newborns as controls were enrolled in the study. Cyanotic CHD neonates had higher levels of alanine, phenylalanine, leucine/isoleucine, citrulline, ornithine, C5, C5-OH; but lower levels of C3, C10, C12, C14, C14:1, C16, C16.1, C18, C5-DC, C6-DC, C16-OH, C16:1-OH when compared with the healthy controls. *Conclusion:* This study showed that there are differences between patients with cyanotic CHD and healthy controls in terms of postnatal amino acid and carnitine/acylcarnitine profiles.

CHDs are the most common congenital anomaly seen in children; and cyanotic CHD occurs in 2 to 3 per 1000 births.[1] Cyanotic CHDs are potentially life-threatening conditions that either the systemic or pulmonary circulation is dependent on a patent ductus arteriosus and requires intervention in the neonatal period. Recent advances in neonatal care and early diagnosis of cyanotic CHD have improved outcomes and survival rates.[2]

Fetus has low oxygen saturation in intrauterine period; after the delivery, transition to postnatal life begins and oxygen saturation gradually increases within the first minutes of life.[3,4] However, cyanotic CHD lead to low levels of oxygen saturation, volume and pressure overload, and pulmonary hypertension which may adversely affect these vulnerable infants. Neonates with cyanotic CHD have to survive with rather low oxygen saturation until the interventional procedures including surgery or catheterisation are being performed. In the fetal life, primarily glucose and lactate are the preferred sources for fetal heart. After the delivery, contribution of fatty acid oxidation to overall energy production increases and becomes the major substrate for the neonatal heart where cardiac energy metabolism shifts from glycolytic to oxidative pathway in postnatal life.[5] Metabolic remodelling is an integral part of the pathogenesis of heart disease. However, acute and chronic hypoxemia might cause alterations in these metabolic pathways.[6–11] There is insufficient information about the changes of amino acid, fatty acid, and carnitine metabolism in CHD in paediatric patients.

Dried blood spots for expanded newborn screening programme are taken between postnatal 24th and 48th hours in every newborn regardless of infant's primary diagnosis like cyanotic CHD. Metabolic profile based on amino acid and carnitine-acylcarnitine profile studies with liquid chromatography–tandem mass spectrometry (LC–MS/MS) may give clues about early postnatal metabolic status of neonates with cyanotic CHD who have to live with rather low oxygen saturation.

The present study aimed to compare the early postnatal amino acid and carnitine/acylcarnitine profiles of newborns with cyanotic CHD and healthy controls.

Materials and methods

Study design

This case-control study was conducted by recruiting the patients with cyanotic CHD and matched with the healthy controls between January, 2016 to December, 2018 in a tertiary care

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hospital, Acıbadem University, İstanbul, Turkey. The study was approved by the Acibadem Mehmet Ali Aydinlar University Ethics Committee (ATADEK 2018-19/19). The study was retrospective and did not involve interventions; thus, informed consent from the parents and patients was not obtained. Consent waiver for this study was obtained from the ethics committee.

Study population

During the study period, term infants (gestational age above 37 weeks) with cyanotic CHD and as a control group inborn infants without cyanotic CHD (gender, birth weight, gestational age, and birth date appropriate) in the first 24–48 hours (h) of life were included in the study. Data were collected from hospital medical records of all patients. Demographic and clinical data including gender, gestational age, birth weight and mortality, and amino acids and acyl carnitine results were recorded. Patients with inborn metabolic diseases detected by expanded newborn screening programme ENSP were excluded. Additionally, infants born to mothers with gestational diabetes, preeclampsia, infections; multiple gestations; and preterm infants (gestational age below 370/7 weeks) were excluded from the study to avoid its confounding effects.

Cyanotic CHDs with low arterial saturation include tetralogy of Fallot, transposition of the great arteries, pulmonary atresia with intact ventricular septum or ventricular septal defect, tricuspid atresia, hypoplastic left heart syndrome, Ebstein's anomaly, total abnormal pulmonary venous return, double outlet right ventricle, persistent truncus arteriosus, and single ventricle.[12]

Sample preparation and LC-MS/MS analysis

Dried blood spots quality control materials for amino acids and acylcarnitines were obtained from the Centers for Disease Control and Prevention (CDC, Atlanta, GA, USA, Newborn Screening Quality Assurance Programme [NSQAP]). Analysis of amino acids and acylcarnitines in DBS sample by flow injection analysis were performed by Shimadzu LCMS-8040 Liquid Chromatograph Triple Quadrupole Mass Spectrometer (Shimadzu Corporation, Kyoto, Japan). High-performance liquid chromatography column was not used in this method. The ion abundances were quantified by calculating the signal intensity ratio of the compound to its internal standard. All data has been collected and evaluated in terms of multiple reaction monitoring for amino acids and acylcarnitines by using Shimadzu's LabSolutions LCMS Version 5.60 SP2 (Shimadzu Corporation, Kyoto, Japan). The Neonatal Solution (Neonatal Mass Screening Software) was used to calculate the concentration of amino acid/acylcarnitines.

The results of amino acids, including alanine [reference value (RV): 90–900 µmol/L], methionine (RV: 9.0–65 µmol/L), phenylalanine (RV: 22.9–120 µmol/L), tyrosine (RV: 26.9–275 µmol/L), leucine-isoleucine ratio (RV: 43.4–373 µmol/L), valine (RV: 52.8–250 µmol/L), arginine (RV: 0.0–50 µmol/L), citrulline (RV: 2.0–65 µmol/L), glycine (RV: 105–1100 µmol/L), ornithine (RV: 19.7–300 µmol/L), arginino-succinic acid (RV: 0.0–0.66 µmol/L), glutamic acid (RV: 0.0–704 µmol/L), and also carnitine/acylcarnitine profile including free carnitine (C0) (RV: 8.6–90.0 µmol/L), acetyl carnitine (C2) (RV: 5.0–73.4 µmol/L), propionyl carnitine (C3) (RV: 0.0–6.8 µmol/L), butyryl carnitine (C4) (RV: 0.0–1.2 µmol/L), isovaleryl carnitine (C5) (RV: 0.0–0.6 µmol/L), tiglyl carnitine (C5:1) (RV: 0.0–0.13 µmol/L), hexonyl carnitine (C6) (RV: 0.0–0.21 µmol/L), octanoyl carnitine (C8) (RV: 0.0–0.32 µmol/L), decanoyl carnitine (C10) (RV: 0.0–0.48 µmol/L), decenoyl carnitine (C10:1) (RV: 0.0–0.28 µmol/L), dodecanoyl carnitine (C12) (RV: 0.0–0.69 µmol/L), tetradecanoyl carnitine (C14) (RV: 0.0–0.8 µmol/L), tetradecenoyl carnitine (C14:1) (RV: 0.0–0.6 µmol/L), tetradecadienoyl carnitine (C14:2) (RV: 0.0–0.25 µmol/L), palmitoyl carnitine (C16) (RV: 0.0–8.70 µmol/L), palmitoleyl carnitine (C16:1) (RV: 0.0–1.04 µmol/L), stearyl carnitine (C18) (RV: 0.0–2.24 µmol/L), oleyl carnitine (C18:1) (RV: 0.0–2.8 µmol/L), linolenoyl carnitine (C18:2) (RV: 0.0–0.9 µmol/L), glutaryl carnitine (C5-DC) (RV: 0.0–0.21 µmol/L), methylglutaryl carnitine (C6-DC) (RV: 0.0–0.20 µmol/L), 3-OH butyryl carnitine (C4-OH) (RV: 0.0–0.48 µmol/L), 3-OH isovaleryl carnitine (C5-OH) (RV: 0.0–0.80 µmol/L), 3-OH tetradecanoyl carnitine (C14-OH) (RV: 0–0.12 µmol/L), 3-OH palmitoyl carnitine (C16-OH) (RV: 0.0–0.1 µmol/L), 3-OH palmitoleyl carnitine (C16:1-OH) (RV: 0.0–0.18 µmol/L), 3-OH oleyl carnitine (C18:1-OH) (RV: 0.0–0.1 µmol/L), and 3-OH linonenoyl carnitine (C18:2-OH) (RV: 0.0 0.1 µmol/L) with LC-MS/MS were compared in each group. The sum of all carnitine and acylcarnitines was presented as total carnitine.

Table 1. Demographic characteristics of the study population

	CCHD *n = 27*	Control *n = 54*	p
GW (wk), mean ± SD	37.4 ± 1.4	37.6 ± 1.2	0.73
Girls, n (%)	10 (39%)	21 (40%)	0.92
BW (g), mean ± SD	2891 ± 528	3082 ± 605	0.20
BW SDS, mean ± SD	−0.21 ± 1.11	0.13 ± 1.28	0.16

CCHD = cyanotic congenital heart disease; GW = gestational week; BW = body weight.

Statistical analysis

Statistical Package for the Social Sciences software (SPSS version 16.0, Inc. Chicago, Illinois, USA) was used to analyse the data. The numerical variables were presented as median and interquartile range and the categorical data as rates. The suitability of normal distribution of the quantitative data was tested by Kolmogorov Smirnof test and graphical analysis. Student's t-test was used for comparisons of normally distributed quantitative variables between two groups, and Mann–Whitney U test was used for comparisons of not normally distributed quantitative variables between the two groups. Pearson Chi-Square test and Fisher–Freeman–Halton test were used for comparison of qualitative data. Pearson Chi-Square test and Fisher–Freeman–Halton test were used for comparison of qualitative data. All the hypotheses were constructed as two-tailed and an alpha critical value of 0.05 was accepted as significant.

Results

Twenty-seven neonates with cyanotic CHDs and 54 healthy newborn as controls were enrolled into the study. According to the cardiac pathology, 27 patients had cyanotic CHD. Six patients were diagnosed with hypoplastic left heart syndrome, six patients were being followed up with the diagnosis of tetralogy of Fallot, five patients were diagnosed with transposition of the great arteries, four of them had ventricular septal defect - pulmonary atresia, four had intact ventricular septum with pulmonary atresia, one had critical pulmonary stenosis, one patient was diagnosed with Ebstein's anomaly - pulmonary atresia. The study groups did not differ in terms of gender ($p = 0.92$), gestational age (37.4 ± 1.4 versus 37.6 ± 1.2; $p = 0.73$), and birth weight (2891 ± 528 g versus 3082 ± 605 g; $p = 0.20$) (Table 1).

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Table 2. Comparison of amino-acids levels

Amino acid, µmol/L (median, IQR)	CCHD *n* = 27	Control *n* = 54	p
Alanine	282.08 (227.13-358.78)	173.28 (145.27-237.49)	**0.001**
Methionine	21.26 (17.16-27.83)	20.00 (16.56-23.91)	0.342
Phenylalanine	59.09 (47.47-68.21)	47.16 (41.09-56.93)	**0.006**
Tyrosine	65.92 (55.74-82.80)	69.05 (52.89-85.84)	0.595
Leucine/Isoleucine (Ile)	119.22 (104.52-153.00)	89.03 (79.41-102.40)	**0.001**
Valine	98.58 (80.64-118.47)	83.13 (74.51-105.08)	0.078
Arginine	10.58 (6.20-14.58)	8.35 (5.54-11.34)	0.128
Citrulline	12.89 (10.04-17.86)	9.85 (8.50-11.95)	**0.002**
Glycine	308.72 (244.44-393.43)	284.06 (240.32-373.72)	0.504
Ornithine	83.20 (55.42-107.70)	52.53 (42.14-70.52)	**0.001**
Arginino-succinic acid	0.01 (0.00-0.02)	0.02 (0.00-0.04)	0.240
Glutamic acid	247.84 (210.42-285.43)	262.96 (232.10-301.36)	0.269

CCHD = cyanotic congenital heart disease.

Amino acids

Neonates with cyanotic CHD had higher levels of alanine (282.08 versus 173.28; p = 0.001) phenylalanine (59.09 versus 47.16; p = 0.006), leucine–isoleucine (119.22 versus 89.03; p = 0.001), citrulline (12.89 versus 9.85; p = 0.002), and ornithine (83.20 versus 52.53; p = 0.001) when compared to healthy controls (Table 2).

Acylcarnitine profiles

Neonates with cyanotic CHDs had higher levels of C5 (0.14 versus 0.10; p = 0.003) and C5-OH (0.13 versus 0.10; p = 0.01) whereas C3 (1.54 versus 2.25; p = 0.001), C10 (0.05 versus 0.070; p = 0.03), C12 (0.06 versus 0.09; p = 0.001), C14 (0.14 versus 0.21; p = 0.001), C14:1 (0.05 versus 0.12; p = 0.001), C16 (1.86 versus 2.85; p = 0.001), C16.1 (0.15 versus 0.23; p = 0.001), C18 (0.55 versus 0.84; p = 0.001), C5-DC (0.05 versus 0.07; p = 0.004), C6-DC (0.02 versus 0.03; p = 0.02), C16-OH (0.02 versus 0.03; p = 0.05), C16:1-OH (0.020 versus 0.026; p = 0.003) levels were lower when compared to healthy neonates (Table 3).

Discussion

Metabolomics is an analytical profile technique for evaluating different molecules in the human body and generating knowledge about diagnostic and prognostic biomarkers for various diseases.[13] It has been reported that acylcarnitine and amino acid concentrations vary, depending on gestational age and birth weight.[14] These circulating metabolomes may also provide important information about energy metabolism.

In a recent study, intraoperative cardiac biopsies of cyanotic and acyanotic patients were evaluated by LC-MS/MS and significant differences were found in terms of the Krebs cycle, amino acid metabolism, and glycometabolism[15]. Therefore, LC-MS/MS for ENSP may also provide important clues for the metabolism of cyanotic CHD patients.[13,16]

Amino acids play a central role in cardiac metabolism; it is known that they are cardioprotective substrates against ischaemia and hypoxia. Amino acids may be used as metabolic substrates, especially in cases where tissue perfusion is insufficient.[17] The changes that emerge in the amino acid metabolism with CHDs are not fully understood. In our study, differences in the amino acid and carnitine-acylcarnitine levels of patients with cyanotic CHD were identified.

Alanine is produced and secreted by the heart in cases of hypoxia and ischaemia.[17] Modi et al found that, only alanine concentration in cyanotic heart patients, were found to be higher compared with patients with acyanotic heart diseases.[9] Apart from this study, we also found differences in amino acids in addition to alanine including phenylalananine, citrulline, leucine/isoleucine, and ornitihine. In an adult study, patients with cardiac insufficiency had increased blood phenylalanine levels and recovery from cardiac insufficiency was associated with decreased phenylalanine levels.[18]

Branched-chain amino acids (valine, leucine, and isoleucine) increase in catabolic states.[11,19] Similar to studies in literature[8,9], we identified that our patients with cyanotic CHD had high blood levels of leucine/isoleucine. In an animal study, increased levels of branched-chain amino acids was shown to have a favourable effect on the cardiac functions.[20] Prospective studies are needed to understand whether the increase in branched-chain amino acids is a result of hypoxia and catabolic state or is a protective adaptive mechanism.

Arginine is precursor of nitric oxide and may decrease in children undergoing surgery with cardiopulmonary bypass as a result of arginase increase.[21] On the other hand arginine was increased in patients with myocardial infarction.[22] Arginine levels may vary due to different mechanisms in cyanotic CHD patients. In our study, we did not find differences between arginine levels due to the heterogeneity of study population.

Carnitine is involved in the metabolism of fatty acids, hence in energy generation. Changes in the level of acylcarnitine indicate a disturbance of fatty acid oxidation metabolism. Carnitine deficiency can also be observed in different situations such as cardiac insufficiency.[23] In our study, C5 and C5-OH levels were found to be significantly high in cyanotic CHD patients, the C3, C10, C12, C14, C14:1, C16, C16:1, C18, C5-DC, C6-DC, C16-OH, and

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Table 3. Comparsion of acylcarnitine levels

Acylcarnitines, μmol/L (median, IQR)	CCHD *n = 27*	Control *n = 54*	p
Free carnitine (C0)	24.68 (20.62-38.66)	24.85 (17.62-29.63)	0.141
Total carnitine	52.54 (44.38-81.37)	57.07 (41.34-73.25)	0.802
Short-chain acylcarnitines			
Acetyl carnitine (C2)	19.85 (15.56-29.50)	23.72 (17.00-31.56)	0.264
Propionyl carnitine (C3)	1.54 (0.92-1.96)	2.25 (1.71-3.16)	**0.001**
Butyryl carnitine (C4)	0.30 (0.19-0.47)	0.26 (0.18-0.35)	0.304
Isovaleryl carnitine (C5)	0.14 (0.11-0.20)	0.10 (0.08-0.13)	**0.003**
Tiglyl carnitine (C5:1)	0.012 (0.011-0.019)	0.013 (0.010-0.019)	0.730
Medium-chain acylcarnitines			
Hexonyl carnitine (C6)	0.05 (0.04-0.10)	0.05 (0.03-0.06)	0.154
Octanoyl carnitine (C8)	0.05 (0.03-0.07)	0.05 (0.03-0.06)	0.814
Decanoyl carnitine (C10)	0.05 (0.04-0.07)	0.07 (0.04-0.09)	**0.039**
Decenoyl carnitine (C10:1)	0.03 (0.02-0.05)	0.03 (0.02-0.04)	0.190
Dodecanoyl carnitine (C12)	0.06 (0.05-0.07)	0.09 (0.07-0.13)	**0.001**
Long-chain acylcarnitines			
Tetradecanoyl carnitine (C14)	0.14 (0.11-0.17)	0.21 (0.15-0.28)	**0.001**
Tetradecenoyl carnitine (C14:1)	0.05 (0.04-0.07)	0.12 (0.08-0.17)	**0.001**
Tetradecadienoyl carnitine (C14:2)	0.02 (0.01-0.03)	0.02 (0.01 (0.03)	0.278
Palmitoyl carnitine (C16)	1.86 (1.15-2.46)	2.85 (2.08-3.47)	**0.001**
Palmitoleyl carnitine (C16:1)	0.15 (0.09-0.22)	0.23 (0.17-0.30)	**0.001**
Stearyl carnitine (C18)	0.55 (0.32-0.85)	0.84 (0.64-0.98)	**0.001**
Oleyl carnitine (C18:1)	0.88 (0.51-1.25)	0.80 (0.61-1.04)	0.913
Linolenoyl carnitine (C18:2)	0.22 (0.16-0.36)	0.18 (0.12-0.26)	**0.034**
Acylcarnitine esters derived from dicarboxylic acids-DC			
Glutaryl carnitine (C5-DC)	0.05 (0.04-0.07)	0.07 (0.05-0.09)	**0.004**

C16:1-OH levels were identified to be low. Cardiac metabolism is a high-oxygen-consuming process, showing a preference for fatty acids as the fuel source under physiological conditions. While energy metabolism is in a catabolic state in the first days of life, an anabolic state emerges in normal babies in the process of adapting to extrauterine life. It is considered that this result is due to a decreased use of fatty acids in the heart and that the energy pathway switched from the oxidative side to the glycolytic side.

The aetiology of CHDs is known to be multifactorial. This makes it difficult to conduct studies on these diseases. This study is not without limitations. First, the lack of metabolomic values of these patients during follow-up; therefore, the post-operative progress of metabolic profile and the effect of diet could not be determined. Second, since this is a retrospective study, the other metabolomes in the energy pathways were not studied. Hence, we do not have enough data to interpret these changes. Additionally, the oxygen saturation, lactate value, or tissue oxygenation at the time of heel lance were not recorded. Unfortunately, the effect of these variables could not be determined. For that reason, prospective follow-up studies with the inclusion of more patients are needed. In this way, the reason why these metabolomes changed can be understood and can be ensured that they are used as biomarkers in our clinical practice.

Conclusion

This study showed that patients with cyanotic CHD differ in terms of some amino acids and carnitine/acylcarnitine metabolomites when compared with the healthy controls. But at this time, these changes will not be of benefit in clinical use or in patient management. There are no studies on this subject in humans or mice. However, further studies with more detailed parameters are needed to reveal the reasons for these difference

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Conflict of interest. None.

Ethical standards. The study was approved by the local ethics committee of Acibadem University (No: ATADEK 2018-19/19). This article does not contain any studies with human participants or animals performed by any of the authors.

Data sharing statement. All data used in this network meta-analysis are available in the main article and supplementary materials. All authors have full access to the raw data files used in this study.

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