NKMJ
Namık Kemal Tıp Dergisi
Namık Kemal Medical Journal

Research Article /Araştırma Makalesi
Doi: https://doi.org/10.37696/nkmj.730698 e-ISSN: 2587-0262

CARDIOVASCULAR SYSTEM FEATURES OF YOUNG ADULTS BORN BY CESAREAN SECTION

Sezaryen ile Doğmuş Genç Erişkinlerin Kardiyovasküler Sistem Özellikleri

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This study was presented as an 'oral presentation' at the 35th Turkish Cardiology Congress with International Participation on 3–6 October 2019 in Antalya, Turkey.

The research was approved by Ethic Committee of Çanakkale Onsekiz Mart University Faculty of Medicine (decision date-no: 17.10.2018-2018/18).

Abstract

Aim: Currently, the prevalence of caesarean section (CS) has been increasing at an alarming rate across the world. In parallel with the increasing rate of CS, it is reported that there is an increasing prevalence of obesity, autoimmune and allergic diseases. The purpose of the present study is to analyse whether the cardiovascular system characteristics of young adults born by CS are different from those of young adults born by vaginal delivery (VD).

Materials and Methods: A total of 112 participants were included in the study (40 CS group vs 82 VD ie control group). Transthoracic echocardiography and carotid Doppler ultrasonography were performed to the participants. In addition, participants were evaluated with a 24-hour ECG recording.

Results: Tricuspid E wave, tricuspid A wave and tricuspid E/A ratio were lower in the CS group compared with the control group (57.6±8.6 vs. 72.4±10.3, p<0.001; 46.7±8.8 vs. 50.6±8.9, p=0.04; 1.2±0.14 vs 1.45±0.88, p<0.001). Epicardial fat tissue thickness were higher in the CS group compared with the control group (4.8±1.3 vs. 3.1±0.8, p<0.001).

Conclusion: The results of this study show that cardiovascular system features of the young adults born by CS are different from those born by VD. Further follow-up studies are needed to understand whether these findings will subsequently result in cardiovascular diseases.

Keywords: Epicardial fat tissue, intima media thickness, heart rate variability, cesarean section.

Öz

Amaç: Günümüzde sezaryen ile doğum (SD) sıklığı dünya genelinde alarm veren düzeyde artmaktadır. Sezaryen sıklığının artmasına paralel olarak obezite, otoimmün ve alerjik hastalıkların yaygınlığının arttığı bildirilmektedir. Bu çalışmanın amacı, SD'li genç erişkinlerin kardiyovasküler sistem özelliklerinin, vajinal yolla doğmuş (VD) genç erişkinlerden farklı olup olmadığını analiz etmektir.

Materyal ve Metot: Çalışmaya toplam 112 katılımcı dahil edildi (40 SD grubu ve 82 VD yani kontrol grubu). Katılımcılara transtorasik ekokardiyografi ve karotis Doppler ultrasonografi yapıldı. Ayrıca, katılımcılar 24 saatlik EKG kaydı ile değerlendirildi.

Bulgular: Triküspit E dalgası, triküspit A dalgası ve triküspit E/A oranı sezaryen grubunda kontrol grubuna göre daha düşüktü (57.6±8.6 ve 72.4±10.3, p<0.001; 46.7±8.8 ve 50.6±8.9, p=0.04; 1.2±0.14 ve 1.45±0.88, p<0.001). Epikardiyal yağ doku kalınlığı sezaryen grubunda kontrol grubuna göre daha yüksekti (4.8±1.3 ve 3.1±0.8, p<0.001).

Sonuç: Bu çalışmanın sonuçları, CS ile doğan genç erişkinlerin kardiyovasküler sistem özelliklerinin VD ile doğanlardan farklı olduğunu göstermektedir. Bu bulguların daha sonra kardiyovasküler hastalıklara yol açıp açmayacağını anlamak için daha ileri takip çalışmalarına ihtiyaç vardır.

Anahtar Kelimeler: Epikardiyal yağ dokusu, intima media kalınlığı, kalp hızı değişkenliği, sezaryen doğum.

INTRODUCTION

Caesarean section (CS) is a critically important surgical procedure for maternal and neonatal health in cases of complications that may arise during pregnancy[1]. World Health Organization suggested the

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Article History / Makale Geçmişi:

Date Received / Geliş Tarihi: 01.05.2020
Date Accepted / Kabul Tarihi: 27.06.2020

ideal rate for CS procedure be 15% and less considering the benefits and risks of the procedure[2]. The prevalence of caesarean section (CS) has been increasing at an alarming rate across the world[3]. The rate of CS is 55.5% in Brazil, 26.2% in United Kingdom and 53.1% in Turkey[3].

In parallel with the increasing rate of CS, it is reported that there is an increasing prevalence of obesity, autoimmune diseases and allergic diseases[4,5]. Increased prevalence of obesity, autoimmune and allergic diseases in children born by CS is explained with hygiene hypothesis and their gut microbiota flora being different from those born by vaginal delivery (VD)[6,7]. The relationship between cardiovascular system (CVS) diseases and gut microbiota was previously demonstrated[8]. In light of this information, the purpose of this study is to analyze whether the CVS characteristics of young adults born by CS are different from those of young adults born by VD.

MATERIALS AND METHODS

Ethical approval

The study protocol was reviewed and approved by the Çanakkale Onsekiz Mart University Clinical Research Ethics Committee (decision date-no: 17.10.2018-2018/18) in accordance with the Declaration of Helsinki. Verbal and written consents of all participants were obtained prior to the test.

Study population

This study was designed as a case-control study. To rule out factors that may have an effect on CVS (eg eating habits, sleeping patterns and activity levels) to the greatest extent possible, the study population was selected from among people with similar standards of living. To this end, 112 voluntary participants between the ages of 18 and 25 years who were studying at ... Faculty of Medicine between November 2018 and June 2019 were included in the present study. The study population was divided into two groups: CS group of 40 participants and VD ie control group of 82 participants. Those with a history of preterm delivery, low birth weight, those who were elite athletes or had sedentary lifestyle, as well as those with a history of emergency CS were not included in the study. Information concerning their birth weights, delivery week, and period of breastfeeding was recorded based on the information given by the participants themselves and their parents. Their biochemical parameters and hemogram values were obtained from the automation information system of the hospital. Their arterial blood pressure at rest, pulse, height, weight, body mass index (BMI) and waist circumference were measured.

Transthoracic echocardiography assessment

Two cardiologists who were blinded to the study groups performed two-dimensional transthoracic echocardiography on all participants by using a (Vivid 7 Pro, GE, Norway) 2.5-MHz transducer. Pericardial fat tissue (PeFT), epicardial fat tissue (EFT) and paracardial fat tissue (PaFT) thicknesses were measured as previously described in the literature. The hypoechoic cavity between epicardial surface and parietal pericardium gives EFT thickness, and the hypoechoic cavity on the anterior of EFT and parietal pericardium gives PeFT thickness according to the measurements made with the cursor cutting the right ventricle free wall vertically in the parasternal long axis. The total amount of fat tissue on both layers gives PaFT thickness. These measurements were made through three cardiac

cycles and when the ventricle was in end-systolic phase as described by Locobellis et al., and then their mean values were calculated9.

Measuring carotid intima media thickness

Carotid intima media thickness (IMT) was measured as described in a previous study in the literature using the same device (Vivid 7 Pro, 12 L linear probe; GE, Norway)[10]. IMT values of the participants were measured with them in a supine position and with their head positioned at an angle of 45˚ facing forward. IMT was measured in three segments of the carotid arteries on both sides. The measurement was made on the distal wall of common carotid arteries at 1 cm proximal to bifurcation for segment 1; on a 1-cm area of carotid bifurcation for segment 2; and on a 1-cm area of the proximal internal carotid artery for segment 3. The mean value for all of these measurements was calculated to obtain IMT value[10].

Ambulatory ECG holter and heart rate variability analysis

All participants were fitted with an electrocardiogram (ECG) Holter monitor (DMS300–4A recorders) for 24 hours, and their records were assessed by two cardiologists who were blinded to the study groups on DMS Cardioscan software. RR intervals were determined based on the ECG Holter records of 24 hours and artifacts were excluded. Heart Rate Variability (HRV) time and frequency domain parameters were analyzed as previously described in the literature11. The time domain analysis of HRV included the following parameters: standard deviation of N–Ns (SDNN), the standard deviation of the 5-min mean values of N–Ns (SDANN), the root mean square successive difference of N–Ns (RMSSD) and the percentage of successive N–N differences >50 ms for each 5-min interval (pNN50). The frequency domain analysis of HRV included the following parameters: low-frequency power (LF), high-frequency power (HF) and the LF/HF ratio.

Statistical analysis

The study data were analyzed using the statistical package program SPSS version 20.0. The numerical, percentile, standard deviation, mean, minimum and maximum values were used to present the data. According to results of the tests assessing normality of distribution, the significance test of the difference between two means was used as the parametric test and Mann–Whitney U test was used as the non-parametric test. To analyze categorical data, Chi-Square Test was used. $p<0.05$ was considered statistically significant.

RESULTS

The CS rate was 32.7% in the present study. There was no difference between the two groups in terms of age, gender, smoking and alcohol use. In addition, there was no significant difference between the two groups in terms of the parameters that may affect CVS characteristics including birth weight, gestational age and breastfeeding. Waist circumference and BMI values were significantly higher in the CS group compared with the control group. Fasting blood glucose (FBG) and triglyceride (TG) levels were also significantly higher in the CS group compared with the control group (Table 1).

Echocardiographic parameters and carotid intima media thickness

Tricuspid E wave, tricuspid A wave and tricuspid E/A ratio were significantly lower in the CS group compared with the control group. Mild tricuspid valve regurgitation was significantly higher in the CS

group compared with the control group. EFT, PeFT and the total value of these two ie PaFT thickness were significantly higher in the CS group compared with the control group. When a comparison was made in terms of carotid IMT, there was no significant difference between the two groups (Table 2).

Table 1. Demographic characteristics and laboratory parameters of study groups

	Control	Caesarean Section	P
Age (years)	22.5±0.72	22.6±0.67	0.85
Gender (male) (n, %)	44(53.7)	18(45.0)	0.37
Smoking (n, %)	26(31.7)	12(30.0)	0.85
Alcohol consumption (n, %)	24(29.3)	11(27.5)	0.84
Birth weight (g)	3442.1±452.7	3564.5±693.8	0.10
Gestational age (weeks)	38.1±1.21	38.2±1.64	0.38
Breast-feeding (n, %)			
≤ 6 mounts	37(45.1)	17(42.5)	0.94
> 6 mounts	45(54.9)	23(57.5)	0.76
Body mass index (kg/m^2)	22.6±3.17	24.2±3.13	**0.03**
Waist circumference (cm)	71.5±7.31	80.0±12.5	**<0.001**
Systolic blood pressure (mmHg)	113.4±10. 62	114.8±10.61	0.53
Diastolic blood pressure (mmHg)	71.1±8.53	71.9±8.37	0.64
Blood glucose (mg/dl)	85.1±8.81	91.8±9.47	**0.02**
Creatinine (mg/dl)	0.79±0.14	0,81±0.16	0.91
Triglyceride (mg/dl)	85.4±45.8	101.3±40.4	**0.04**
High density lipoprotein (mg/dl)	58.6±14.6	57.8±14.2	0.94
Low density lipoprotein (mg/dl)	90.4±27.1	103.9±34.2	0.13*
Thyroid stimulating hormone (mIU/L)	2.29±0.84	2.56±2.59	0.40
Hemoglobin (g/dl)	14.2±1.70	14.1±1.48	0.64

Data are presented as number (percentage), mean ± standard deviation, p: Mann-Whitney U test. *
The significance of differences between two groups was assessed using Student's t-test.

Table 2. Echocardiographic parameters and carotid intima media thickness of study groups

	Control	Caesarean Section	P
Aortic root diameter (mm)	22.5 (2.0)	22.1 (1.6)	0.38
Ascendant aorta diameter (mm)	27.7 (2.6)	27.4 (2.4)	0.59
Sol atrium diameter (mm)	31.3 (3.8)	31.9 (3.1)	0.48
Interventricular septum thickness (mm)	8.41 (1.1)	8.18 (1.0)	0.27
Left ventricular end-diastolic diameter (mm)	42.5 (2.9)	42.6 (2.6)	0.71
Left ventricular end-systolic diameter (mm)	27.6 (2.5)	28.0 (2.4)	0.54
Left ventricular ejection fraction (%)	63.7±3.0	63.4±2.8	0.79
Mitral E/A ratio	1.4±0.14	1.38±0.12	0.63
Right atrium end-diastolic diameter (mm)	39.7 (2.4)	40.3 (1.8)	0.12
Right ventricle end-diastolic diameter (mm)	38.0 (2.8)	38.8 (1.8)	0.25
Tricuspid annular plane systolic excursion (mm)	21.0±1.9	20.6±2.0	0.29
Systolic pulmonary artery pressure (mmHg)	24.1±5.8	25.1±5.7	0.40
Tricuspid E wave (cm/sn)	72.4±10.3	57.6±8.6	**<0.001**
Tricuspid A wave (cm/sn)	50.6±8.9	46.7±8.8	**0.04**
Tricuspid E/A ratio	1.45±0.88	1.2±0.14	**<0.001**
Tricuspid deceleration time (ms)	142.0±8.0	159.4±15.1	**<0.001** *
Epicardial fat tissue thickness (mm)	3.1±0.8	4.8±1.3	**<0.001**
Pericardial fat tissue thickness (mm)	2.7±0.7	5.3±1.2	**<0.001**
Pericardial fat tissue thickness (mm)	5.6±1.4	10.0±2.5	**<0.001**
Mild mitral valve regurgitation (n, %)	11(13.4)	5(12.5)	0.89
Mild aortic valve regurgitation (n, %)	1(1.2)	0(0.0)	0.49
Mild tricuspid valve regurgitation (n, %)	9(11)	16(40)	**<0.001**
Mild pulmonary valve regurgitation (n, %)	2(2.4)	3(7.5)	0.19
Carotid intima media thickness (mm)	0.46±0.11	0.48±0.13	0.84

Data are presented as number (percentage), mean ± standard deviation, p: Mann-Whitney U test. * The significance of differences between two groups was assessed using Student's t-test

Ambulatory ECG Holter and heart rate variability parameters

There was no significant difference between the two groups in terms of average heart rate. Although the LF value was lower in the CS group compared with the control group, the difference was not high enough to be statistically significant (table 3).

Table 3. Ambulatory ECG recording and heart rate variability parameters of study groups

	Control	Caesarean Section	p value
Average heart rate	77.2±10.1	77.5±10.9	0.92*
SDNN-24 hours	152.8±33.2	152.9±38.9	0.99*
SDANN index	136.3±33.6	139.6±37.1	0.98
RMSSD	42.8±14.9	38.6±13.3	0.25
PNN 50	18.8±12.3	15.5±9.8	0.29
LF	1200.3±405.1	1014.7±471.7	0.06
HF	571.3±320.2	479. 7±305.3	0.28
LF/HF ratio	2.57±1.19	2.46±0.87	0.95

Data are presented as number (percentage), mean ± standard deviation, p: Mann-Whitney U test. * The significance of differences between two groups was assessed using Student's t-test. HF, high-frequency power; LF, low-frequency power; pNN50, percentage difference between adjacent normal RR intervals >50 msec; RMSSD, squared differences between adjacent normal NN intervals; SDANN, standard deviation of 5-min mean NN intervals; SDNN, standard deviation of normal RR intervals

DISCUSSION

In this study, the CS group was found to have higher levels of FBG, TG, EFT, PeFT and PaFT thickness in parallel with the higher BMI and waist circumference. Goldani et al., reported in their cohort study that CS increases obesity risk by 58% in young adults and speculated that the increasing prevalence of CS may have played a role in obesity that has become an epidemic across the world[12]. In another study that included only 21,051 men in Denmark, it was found out that CS increases the risk for obesity 1.35 times in young male adults[13]. A cohort study reported that CS was associated with central obesity and hypertension but not with metabolic syndrome in early and middle childhood[14]. The BMI and waist circumference values were higher in the CS group in our study, but there was no statistically significant difference between the two groups in terms of systolic and diastolic blood pressure. The echocardiography performed as part of the present study revealed that EFT, PeFT and PaFT thickness values were increased in the CS group compared with the control group in parallel with the increase in BMI and waist circumference. A meta-analysis reported that CS increased type I diabetes mellitus by 20% during childhood and associated this effect with the changes in gut microbiota and the immune functions[15]. FBG and TG levels were found to be higher in the CS group, although they were within normal range in our study.

Studies showed that almost no *Bifidobacterium* spp. were detected in the stool samples of infants born by CS[5,16]. *Bifidobacterium* spp. populations are negatively correlated with the levels of serum TG and non-HDL cholesterol, autoantibodies against oxidized LDL and atherosclerosis lesion size[17]. Kalliomaki et al. reported that there were less species of *Bifidobacterium* in the microbiota of overweight children at the age of 7[18]. As part of a study conducted in Finland investigating the effects of probiotics on allergic diseases, pregnant women in the last month of pregnancy and the newborns for the first 6 months after their birth were given probiotics (lactobacilli, bifidobacteria and propionibacteria). The results obtained at the end of a 5-year follow-up period showed that the prevalence of allergic diseases was similar in the probiotic group and the placebo group; however, that the children born by CS had a lower risk of allergic diseases because of probiotics[19]. It is known that right ventricular diastolic functions are diminished in cases of allergic diseases such as asthma and

autoimmune diseases such as rheumatoid arthritis[20,21]. Although they were within normal range in our study, tricuspid E wave, tricuspid A wave and E/A ratio were found to be smaller in the CS group, whereas the tricuspid deceleration time was longer. Out of all valves, only tricuspid regurgitation was higher in the CS group compared with the control group at a statistically significant level.

In a cohort study, 17,423 infants were followed up for ~5 years, and the children born by CS had higher rates of anemia[22]. There was no difference between the two groups in terms of hemoglobin values in our study. The study by Vida et al. found that levels of asymmetric dimethylarginine were increased in the samples taken from the umbilical vein and artery and from peripheral vein on day 30, with an associated decrease in the production and bioavailability of nitric oxide, and concluded that CS may cause endothelial dysfunction as a result of this, highlighting the need for further studies concerning this issue[23]. It was reported that systemic endothelial function is more closely correlated with the progression of preclinical carotid artery disease, and endothelial function is more closely correlated with carotid IMT than with conventional risk factors[24]. In our study there was no significant difference between the two groups in terms of carotid IMT. In a study that investigated the HRV parameter in newborns, cardiovagal modulation was higher because of higher levels of HF band levels in infants born by VD, and this effect was observed to be less in infants born by CS[25]. In our study, there was no significant difference between the two groups in terms of HRV.

The present study has some limitations to be mentioned. The major limitation of our study is that community-based study could not be performed. Only medical students were included in our study. As the purpose of the present study was to investigate the effect of the delivery method on CVS by means of eliminating factors that may have an effect on CVS to the greatest extent possible, some of the individuals in this community could not be included in the study. CS prevalence may therefore be misleading based on the delivery methods included in the present study. Although the differences in CVS characteristics of the two groups were associated with their different gut microbiota floras, the gut microbiota floras of the participants were not analyzed and compared.

CONCLUSION

The results of this study show that cardiovascular system features of the young adults born by CS are different from those born by VD. Further follow-up studies are needed to understand whether these findings will subsequently result in cardiovascular diseases.

Conflict of interest: None declared.

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