Assessing Cardiac Functions in Large for Gestational Age Infants using Tissue Doppler Imaging

Gestasyonel Yaşa Göre İri Bebeklerde Kardiyak Fonksiyonların Doku Doppler Ekokardiyografi ile Değerlendirilmesi

Ayse Simsek[1], Suzan Sahin[2]

[1]Izmir Demokrasi University, Faculty of Medicine, Buca Seyfi Demirsoy Training and Research Hospital, Department of Pediatrics, Division of Pediatric Cardiology, Izmir, Turkey
[2]Izmir Demokrasi University, Faculty of Medicine, Buca Seyfi Demirsoy Training and Research Hospital, Department of Pediatrics, Division of Neonatology, Izmir, Turkey

ABSTRACT

Objective: To assess cardiac functions of large for gestational age (LGA) infants with no maternal gestational diabetes mellitus using tissue Doppler imaging (TDI).
Methods: LGA infants of nondiabetic mothers and appropriate for gestational age (AGA) infants were included in this study. Conventional echocardiography and tissue Doppler echocardiography were performed in all patients.
Results Totally 78 neonates, of these, 37 term LGA infants were in study group and 41 gestational-age matched AGA infants constituted the control group. The mean birth weight of LGA infants was 4175 ±249.4 g; AGA infants was 3317±183.9 g (p <0.001). Among left and right ventricle tissue Doppler parameters; Left ventricular Am velocity was significantly higher and Em/Am ratio was lower in LGA infants and right ventricular Em/Am ratio and Em velocity was significantly lower in LGA infants compared to control group. Among tissue Doppler myocardial performance index parameters, LGA infants had significantly higher values than controls regarding left ventricular (p<.001), and right ventricular (p<.001) myocardial performance indices.
Conclusion The results of our study suggest that term LGA infants may have a predisposition for cardiac structural changes and diastolic dysfunction. TDI is a feasible technique in neonates that provides direct information on the myocardium, allowing analysis of both systolic and diastolic functions in one waveform. The addition of TDI to standard neonatal echocardiography may provide additional information on cardiac functions of LGA infants

Keywords: Large for gestational age, macrosomia, tissue Doppler imaging, cardiac function .

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ÖZET

Amaç: Diyabetik olmayan anneden doğan, gestasyonel yaşına göre iri yenidoğan bebeklerde kardiyak fonksiyonları doku Doppler ekokardiyografi yöntemi ile değerlendirmektir.
Yöntem: Çalışmamıza diyabetik olmayan anneden doğan, gestasyonel yaşına göre iri bebekler (Large for gestational age: LGA) ile gestasyonel yaşına göre gelişimi yaşına uygun (appropriate for gestational age: AGA) bebekler dahil edildi. Tüm bebeklere konvansiyonel ve doku Doppler ekokardiyografik görüntüleme yapıldı.
Bulgular: Diyabetik anne bebeği olmayan LGA tanılı 37 term bebek ve gestasyonel yaşına uygun gelişim gösteren 41 term bebek çalışmamıza dahil edildi. LGA tanılı bebeklerin ortalama doğum ağırlığı 4175 ±249,4 g; AGA'lı bebeklerin 3317±183.9 g idi (p<0.001). Sol ve sağ ventrikül doku Doppler parametreleri arasında; LGA'lı bebeklerde sol ventrikül Am velositesi anlamlı olarak daha yüksek, Em/Am oranı daha düşüktü. LGA'lı bebeklerde sağ ventrikül Em/Am oranı ve Em velositesi kontrol grubuna göre anlamlı olarak daha düşüktü. Doku Doppler miyokardiyal performans indeksi (MPI) karşılaştırıldığında, sol ventrikül (p<.001) ve sağ ventrikül (p< 001) MPI değerleri LGA'lı bebeklerde AGA'lı bebeklere göre yüksekti.
Sonuç: Bizim çalışmamızın sonucu göstermektedir ki LGA'lı bebeklerde kardiyak yapısal değişiklikler ve diyastolik disfonksiyon gelişebilmektedir. Doku Doppler ekokardiyografik görüntüleme, yenidoğanlarda güvenle kullanılabilen ve konvansiyonel ekokardiyografik incelemeye ek bilgiler sağlayan, hem sistolik hem de diyastolik fonksiyonlar hakkında bilgi elde edebildiğimiz bir yöntemdir. LGA'lı bebeklerde kardiyak disfonksiyon ile ilgili risk faktörlerinin erken tespit edilmesi gelişebilecek komplikasyonların engellenmesi açısından önemlidir.

Anahtar Sözcükler: Gestasyonel yaşa göre iri bebek, makrozomi, doku Doppler ekokardiyografi, kardiyak fonksiyon

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ORCID IDs. A.Ş.0000-0001-6387-4926,S.Ş.0000-0002-2599-3075

Address for Correspondence / Yazışma Adresi: Ayse Simsek, MD Pediatric Cardiology Unit, Izmir Democracy University, Buca Seyfi Demirsoy Training and Research Hospital, Ataturk Mh. Hoca Ahmet Yesevi Cd. No:42-44 PC: 35390 Buca,Izmir, Turkey. E-mail: draysesimsek@hotmail.com

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INTRODUCTION

Large for gestational age (LGA) infants are defined as those having a birthweight above the 90th percentile, adjusted for sex and the gestational week at delivery (1). Macrosomia, another commonly used definition, refers to infants who is born much larger than average for their gestational age (2). Main risk factors for neonatal macrosomia include genetic predisposition, environmental, constitutional factors and metabolic disorders, particularly maternal diabetes mellitus (3). Currently, the estimated incidence of LGA in all pregnancies vary between 1% and 10% (2).

Tissue Doppler imaging (TDI) is a noninvasive cardiac imaging technique, relatively independent on the cardiac loading conditions, allowing more accurate and direct measurement of regional myocardial velocities and myocardial motility. Thus, TDI provides a sensitive marker of mild systolic and diastolic dysfunction. Other factors that make tissue Doppler a preferred technique for assessing heart function in neonates include the good time-resolution and ability to evaluate left and right cardiac function (4). The recently introduced myocardial performance index (MPI or Tei index) to be utilized with tissue Doppler technique is an indicator of global ventricular function and can also be used to evaluate both systolic and diastolic functions (5).

In the neonatal period infants with LGA or macrosomia are known to have an increased risk of complications such as hypoglycemia, brachial plexus injury, perinatal asphyxia, and prolonged hospital stay (6). There are various studies in the literature on cardiac structural changes in infants with LGA. However, to the best of our knowledge, no previous studies have investigated left and right ventricular myocardial velocity and MPI in LGA infants of non-diabetic mothers (INDMs) born at term. Early identification of risk factors in these infants could allow preventive measures to be taken to avoid adverse outcomes. Thus, in this study we aimed to assess cardiac functions using TDI in term LGA infants with no history of maternal gestational diabetes.

MATERIALS and METHODS

Study population

LGA-infants of nondiabetic mothers (INDMs) born in our unit between January 2018 and December 2020 were included in the study. The control group consisted of term appropriate for gestational age (AGA) infants with no underlying pathology.

LGA infants included in the study were born at the ≥ 37 gestational week with a birthweight of > 90th percentile from a mother with normal oral glucose tolerance test (OGTT) result. Control subjects were AGA infants born with normal birthweight percentile (between 10th and 90th) from mothers with similar characteristics and referred to pediatric cardiology department for evaluation of cardiac murmur who were subsequently found to have no cardiac pathology.

Birthweight, gestational week, gender, 5th min APGAR score, mode of delivery, maternal weight, HbA1c values were recorded in both groups.

Exclusion criteria were; prematurity, presence of at least one of the diagnoses of maternal pregestational/gestational diabetes mellitus, hypertension, preeclampsia or any other systemic diseases needing medication, neonatal syndromic appearance and findings, underlying congenital heart disease (except for patent foramen ovale), history of perinatal asphyxia and/or need for admission to neonatal intensive care unit for any reason.

Conventional M-mode and tissue Doppler imaging evaluations were performed for all patients between 2 to 5 days of age, using a Vivid S5 N (General Electric, Horten, Norway) ultrasound system with a 6S probe, as per standard imaging technique. Cardiac structures and function parameters were evaluated with echocardiography by the same experienced pediatric cardiologist. Measurements were determined using the M-Mode method at the parasternal long axis position near papillary muscle level: the interventricular septum end diastolic thickness (IVSTd) was measured and the ejection fraction (EF), fractional shortening (FS) were calculated. Tricuspid regurgitation jet was used to assess pulmoner pressure in conventional echocardiography. The pressure difference between the right ventricle and the right atrium was measured using a tricuspid regurgitation jet, and the estimated right atrial pressure of 5 mmHg was added to obtain the systolic pulmonary artery pressure (sPAP).

Tissue Doppler imaging

Myocardial velocities were obtained using an apical four chamber view. A Pulse wave Doppler (PWD) sample gate was positioned at the lateral mitral annuli and lateral tricuspid annuli to acquire right and left ventricular velocities, respectively.

Early myocardial peak velocity or early diastolic (Em), atrial systolic peak velocity or late diastolic (Am), and their ratio Em/Am, myocardial peak systolic velocity (Sm), isovolumic contraction time (IVCTm), isovolumic relaxation time (IVRTm), and myocardial contraction time (CTm) were measured by TDI. Myocardial Performance Index (MPI) was calculated using the following formula: (IVCTm+IVRTm)/CTm.

Isovolumic contraction time was defined as the time duration between the beginning of QRS complex in the electrocardiogram to the beginning of S' wave. The isovolumic relaxation time was defined as the interval between the end of S' wave and the beginning of the E' wave of the next cardiac cycle. In tissue Doppler examinations; Systolic wave (Sm) corresponds to ventricular ejection and E'-wave reflects ventricular relaxation (elongation), while A'-wave reflects atrial contraction and late ventricular filling. This study has been approved by the institutional committees (approval no:2022/03-76).

Statistical Analysis

Statistical Package for the Social Sciences version 23 (SPSS Inc, Chicago,IL) was used for data analysis. The Shapiro-Wilk test was used to test for normality. Data with normal distribution were examined using the independent T-Test, while parameters without normal distribution were examined with the Mann-Whitney U test. Pearson chi-square test was used to compare categorical variables. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Totally 78 neonates were included in our study. Of these, 37 term LGA infants were included in the study group and 41 term gestational-age matched AGA infants constituted the control group.

There were 16 female and 21 male infants with LGA, 19 female and 22 male infants in the control group. Demographic characteristics were similar in between the two groups except for the birth weight. The average maternal HbA1c was 5.03 ± 0.45 (range: 4.2-6) in the LGA group. LGA infants had significantly higher maternal weight as compared to controls (71±11.7; 66±7.7 p:0.02).

The mean birth weight of LGA infants was 4175 ±249.4 grams and AGA infants was 3317±183.9 grams ($p < 0.001$). There were no differences in the mean gestational age at delivery between the two groups.

Interventricular septal dimension (IVSTd) was significantly higher in LGA infants compared to controls (5.45±0.098 vs. 3.8±0.74, respectively; $p<0.001$), while no significant differences were found in left ventricular EF and FS. There were significant differences sPAP measurements between the two groups. Demographic characteristics and conventional echocardiography findings of the two groups are shown in Table 1.

Table 1. Demographic characteristics and conventional echocardiography findings

	LGA (n: 37)	AGA (n: 41)	P value
Gestational age (week)	39.5±0.6	39.9±0.7	0.27
Maternal weight,(kg)	71±11.7	66±7.7	**0.02**
Gender,male n (%)	21 (57%)	22 (54%)	0.78
Birth weight,(g)	4175 ± 249.4	3317±183.9	**< 0.001**
APGAR 5th min	9 (8-10)	9 (8-10)	0.24
Mode of delivery, Cesarean section rate	19 (51.4%)	19 (46.3%)	0.82
EF	73.56±3.07	72.14±3.78	0.07
FS	40.81±2.34	39.97±2.79	0.15
Interventricular septum thickness (mm)	5.45±0.098 (min 4- max 8)	3.8±0.74 (min 3- max 6)	**< 0.001**
Interventricular septum Z- score	3.14(1.95- 4.5)	0.54 (0.47- 0.95)	**<0.001**
sPAP (mmHg)	23.7±4.4	15.1±4.1	**<0.001**

Data presented as mean ±SD, and median with quartiles (25-75) or count (percentages) EF: Ejection fraction, FS: fractional shortening, sPAP systolic pulmonary artery pressure.

Among left ventricle tissue Doppler parameters, left ventricular Em velocity did not significantly differ between the two groups while Am velocity was significantly higher and Em/Am ratio was lower in LGA infants compared to control group. Peak systolic myocardial velocity Sm values did not differ significantly, although these measurements were slightly lower in the LGA group.

Among right ventricle tissue Doppler parameters, infants with LGA had significantly lower values of Em/Am ratio and Em velocity, while there was no significant difference regarding Am and Sm velocity values.

Among tissue Doppler MPI parameters, infants had significantly higher values than controls regarding left ventricular (p<.001), and right ventricular (p<.001) myocardial performance indices. Tissue Doppler imaging results shown in table 2.

Table 2. Myocardial velocities obtained using tissue Doppler imaging

	LGA (n:37)	AGA (n:41)	P value
Left ventricle			
Em (cm/s)	6,89±0.80	7.14±0.85	0.18
Am (cm/s)	6.67±0.66	6.04±0.83	**< 0.001**
Em/Am ratio	1.04±0.17	1.18±0.12	**< 0.001**
Sm (cm/s)	5.64±0.67	5.87±0.78	0.16
MPI	0.48±0.02	0,46±0.02	**0.001**
Right ventricle			
Em (cm/s)	6.89±0.65	7.60±0.58	**<0.001**
Am (cm/s)	10.13±0.75	9.82±0.83	0.09
Em/Am ratio	0.67±0.09	0.77±0.10	**<0.001**
Sm (cm/s)	7.13±0.97	7.36±1.17	0.34
MPI	0.49±0.02	0.45±0.01	**<0.001**

Data presented as mean ±SD, Em:Em wave velocity, Am:Am wave velocity , Sm: Sm wave velocity MPI: myocardial performance index

DISCUSSION

Large for gestational age infants are known to have an increased predisposition to neonatal complications such as hypoglycemia, respiratory distress, perinatal asphyxia etc.(1, 6, 7). Maternal diabetes mellitus represents a major risk factor for LGA infants. Several studies examining the cardiac functions among LGA infants born to mothers with gestational and pregestational diabetes mellitus have been published (8). However, to the best of our knowledge, no previous studies have investigated left and right ventricular myocardial velocity and MPI in LGA infants of non-diabetic mothers.

Our findings indicate significant differences between LGA infants and controls in terms of left and right ventricular diastolic function as assessed by the Em/Am ratio in TDI. According to our observations, infants with LGA are more likely to have diastolic dysfunction than appropriately grown infants (AGA). Olander et al conducted a study evaluating left ventricular functions of infants with LGA, small for gestational age (SGA) and AGA. In this study, it was reported that the E/Em ratio, which indicates diastolic dysfunction, was found to be the highest in infants with LGA (9). In another study, LGA infants of mothers with pregestational diabetes, gestational diabetes and non-diabetic mothers were evaluated regarding N- terminal pro-brain natriuretic peptide (NT-ProBNP), troponin T values and these parameters were found to be higher in these three groups compared to controls (10) . As stated in this and other similar studies, in order to prevent cardiomyopathy, natriuretic peptides are secreted starting from the fetal period in response to increasing pressure and volume (10, 11). It is also stated that there is a correlation between NT-proBNP and diastolic function parameters and it is an important biomarker for diastolic dysfunction (12). Although NT-ProBNP levels were not measured in the current study, our findings are consistent with other studies that reported both right and left ventricular diastolic dysfunction in LGA infants.

In our study, we did not find a significant difference between systolic cardiac function parameters like; EF, FS and Sm of infants with LGA and the control group. Olander et al. suggest that there is no impact of abnormal body size on left ventricular ejection fraction (9). On the other hand, Doni D. et al. examining cardiac hemodynamic alterations in healthy term newborns using ultrasonic cardiac output monitoring, reported that birthweight could influence blood pressure, stroke volume, cardiac output, and cardiac index. Particularly, a transient increase in cardiac index, cardiac output and stroke volume up to 24 h of life was observed in LGA infants, as opposed to AGA and SGA infants. After this period, while these parameters remained stable in SGA and AGA infants, a reduction was observed in LGA infants (13) . In our study, echocardiographic assessments were performed after 48 h of life, which may be one of the reasons for the absence of difference in systolic functions between LGA and control infants. Similarly, another study found no difference in EF and FS among AGA infants, macrosomic infants of non-diabetic mothers, and infants of diabetic mothers (14). In tissue Doppler examinations, left and right ventricular Sm values represent a good indicator of systolic function, due to their ability to directly reflect the motility of the cardiac muscle. Some studies using TDI even claimed that left ventricular Sm may actually represent a more sensitive indicator of systolic functions as compared to EF, FS, and stroke volume measurements (15). Although right and left ventricular Sm did not differ significantly in our study, there was a tendency toward slightly lower values of this parameter among LGA infants.

The MPI is used to evaluate global ventricle systolic and diastolic function (16) . In our analysis, LGA infants had higher left and right ventricular MPI than controls. In Mert MK et al.'s study comparing left ventricle-MPI (LV-MPI) in LGA INDMs and healthy controls, it is found that LGA- INDMs had lower values for these parameters. However, these authors also expressed their challenge when trying to account for these findings, and suggested that their observation may be associated with the fact that free wall assessment was performed in LV. Also, these authors only examined LV- MPI (10). In our study both right and left ventricular MPI were evaluated. To the best of our knowledge, right ventricular MPI has never been studied before in LGA infants.

Although myocardial hypertrophy and especially septal hypertrophy is one of the most common cardiac problems in infants of diabetic mothers (17, 18), recent studies have also reported certain cardiac structural changes, also in LGA -INDMs (19, 20). In one study involving LGA born to diabetic mothers, LGA-INDMs and controls, in diabetic group elevated septal thickness was found, although septal thickness was also higher in LGA- INDMs as compared to controls (21). Demirören K. et al observed increased IVS and IVS/PW ratio in LGA- INDMs as compared to controls, although the difference was insignificant (14). Again, in our study LGA infants had increased septal thickness compared to controls.

Two other potential complications in macrosomic and/or LGA infants are perinatal asphyxia and pulmonary hypertension. Diaz et al. investigating risk factors for persistent pulmonary hypertension (PPHN) found an increased risk of PPHN in infants with a birthweight > 90^{th} percentile (22). Maternal obesity and insulin resistance are known to induce endothelial dysfunction and inflammation and might therefore have a direct impact on fetal lung development (23) . In our study, we found that the weights of mothers of LGA infants were more than the weights of mothers of the control group infants, and the sPAP values were within the normal limits in LGA infants. but when compared, sPAP values were significantly higher than the control group. One of the limitations of our study is that we only evaluated the cross-sectional measurement of cardiac functions in infants diagnosed with LGA, with no long-term follow up. We believe that further studies may elucidate whether initial echocardiographic alterations may improve with time. Another limitation is the limited number of cases included in the study, as in a study conducted with a larger population, normative values for these parameters may be determined. In addition, we did not perform speckle-tracking echocardiography as the echocardiography device used in the study did not have speckle-tracking echocardiography option.

CONCLUSION

The results of our study suggest that term LGA infants may have a predisposition for cardiac structural changes and diastolic dysfunction. Cardiac function in LGA infants should be assessed during the postnatal period even in the absence of need for intensive care unit admission, and clinicians should be alert about possible need for monitoring and further intervention in these patients. Monitorization of cardiac functions is particularly important during the neonatal adaptation period of especially LGA infants. In this regard, TDI is a feasible technique in neonates that provides direct information on the myocardium, allowing analysis of both systolic and diastolic functions in one waveform. Conventional echocardiography may be insufficient to show functional cardiac pathologies from time to time. The addition of TDI to standard neonatal echocardiography may provide additional information on cardiac functions. We believe that, performing TDI for especially high risk neonatal groups like LGA infants will reveal hidden pathologies and improve neonatal care in our neonatal intensive care units and obstetrics wards during their maternal bedside follow-up.

Conflict of interest

No conflict of interest was declared by the authors.

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