Early Human Development 183 (2023) 105809

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Heart function by M-mode and tissue Doppler in the early neonatal period in neonates with fetal growth restriction

Eirik Nestaas [a,b,*], Lisa Bjarkø [a,c], Torvid Kiserud [d,e], Guttorm Haugen [a,f], Drude Fugelseth [a,c]

[a] Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway
[b] Clinic of Paediatrics and Adolescence, Akershus University Hospital, Lørenskog, Norway
[c] Department of Neonatal Intensive Care, Division of Paediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway
[d] Department of Clinical Science, University of Bergen, Bergen, Norway
[e] Department of Obstetrics and Gynaecology, Haukeland University Hospital, Bergen, Norway
[f] Department of Fetal Medicine, Division of Obstetrics and Gynaecology, Oslo University Hospital, Oslo, Norway

ARTICLE INFO

Keywords:
Echocardiography
Transitional circulation
Preterm birth
Tissue Doppler
Fetal growth restriction

ABSTRACT

Background: Fetal growth restricted (FGR) neonates have increased risk of circulatory compromise due to failure of normal transition of circulation after birth.
Aim: Echocardiographic assessment of heart function in FGR neonates first three days after birth.
Study design: Prospective observational study.
Subjects: FGR- and non-FGR neonates.
Outcome measures: M-mode excursions and pulsed-wave tissue Doppler velocities normalised for heart size and E/e′ of the atrioventricular plane day one, two and three after birth.
Results: Compared with controls (non-FGR of comparable gestational age, n = 41), late-FGR (gestational age ≥ 32 weeks, n = 21) exhibited higher septal excursion (15.9 (0.6) vs. 14.0 (0.4) %, p = 0.021) (mean (SEM)) and left E/e′ (17.3 (1.9) vs.11.5 (1.3), p = 0.019). Relative to day three, indexes on day one were higher for left excursion (21 (6) % higher on day one, p = 0.002), right excursion (12 (5) %, p = 0.025), left e′ (15 (7) %, p = 0.049), right a′ (18 (6) %, p = 0.001), left E/e′ (25 (10) %, p = 0.015) and right E/e′ (17 (7) %, p = 0.013), whereas no index changed from day two to day three. Late-FGR had no impact on changes from day one and two to day three. No measurements differed between early-FGR (n = 7) and late-FGR.
Conclusions: FGR impacted neonatal heart function the early transitional days after birth. Late-FGR hearts had increased septal contraction and reduced left diastolic function compared with controls. The dynamic changes in heart function between first three days were most evident in lateral walls, with similar pattern in late-FGR and non-FGR. Early-FGR and late-FGR exhibited similar heart function.

1. Introduction

Fetal growth restriction (FGR) is one of the major challenges in perinatal care. It is associated with increased risk of neonatal morbidity and mortality, and those born after FGR carry higher risks for metabolic and cardiovascular diseases later in life [1–3]. The contemporary definition of FGR distinguishes between early-FGR and late-FGR and is based on gestational age (GA), growth of the fetus, maternal and fetal blood flow patterns to the placenta, and compensatory changes in fetal haemodynamics [4]. FGR due to placental compromise affects up to 10 % of all pregnancies [5].

During prenatal life, left and right atrial and ventricular pressures are similar [6], but right ventricular output is higher than left [7]. In FGR, however, the fetal heart faces altered haemodynamic demands that include increased afterload and reduced venous return from the placenta. Although maintaining a normal combined cardiac output per kg, their cardiac development reflects an altered morphological and distributional adaptation graded according to the degree of placental compromise [7,8]. I.e., increased afterload primarily affects the left ventricle that responds with a globular morphology, a pattern that also

Abbreviations: a′, peak diastolic tissue Doppler velocity during atrial systole; BW, birth weight; e′, peak early diastolic tissue Doppler velocity; FGR, fetal growth restriction; GA, gestational age; pwTD, pulsed-wave tissue Doppler; s′, peak systolic tissue Doppler velocity.

* Corresponding author at: Faculty of Medicine, Post Office Box 1078, Blindern, 0316 Oslo, Norway.
E-mail address: eirikne@uio.no (E. Nestaas).

https://doi.org/10.1016/j.earlhumdev.2023.105809
Received 5 April 2023; Received in revised form 12 June 2023; Accepted 12 June 2023
Available online 14 June 2023

may develop on the right side in severe cases [9–11]. Simultaneously, an increased fraction of cardiac output is shifted to the more compliant right side increasing the right-left difference according to severity of placental dysfunction. Under extreme conditions, such distributional adaptation tends to break down [7,8].

At birth, the normal neonates use their early transitional days to establish the postnatal serial configuration of the systemic and pulmonary circulation, with systemic blood flow dependent on the left heart and pulmonary blood flow dependent on the right heart.

FGR neonates, on the other hand, are known to be at risk of circulatory compromise at this stage [12,13]. A better knowledge of how the FGR cardiac morphology and function respond to postnatal demands would help in differentiating and optimising treatment.

The management of circulatory challenges in neonates after FGR will benefit from a deeper and more detailed understanding of how the morphologically altered FGR hearts adapt during the transition. So far, studies investigating the early postnatal cardiovascular effects of FGR classified according to current recommendations [4] are scanty.

This study aimed to assess the effects of FGR on heart function in late premature and term FGR compared with non-FGR neonates during the postnatal circulatory transitional period the first three days after birth, and how GA, birth weight (BW), sex and twin/singleton modify these effects.

2. Methods

2.1. Study population and inclusion criteria

In a prospective observational cohort study at Oslo University Hospital, Norway (April 2017 to October 2018), we included pregnant women and their FGR neonates (GA 30–42 weeks) according to locally modified contemporary published guidelines (Table 1) [4]. The control group was a corresponding cohort within the same range of GA, with prenatal documented normal fetal growth and circulation by ultrasound. We included singleton and dichorionic diamniotic twins, but excluded pregnancies with chromosomal aberrations, severe congenital anomalies, and prenatal infections. We have previously studied the morphological changes in this group [14]. Here we address their heart function.

Table 1
Definition of FGR used in the study, and the number of participants fulfilling each criteria.

	N
Early-FGR	7
Gestational age 30^{+0}–31^{+6} plus one of the following:	
a) AC < 3rd centile	(2)
b) Absent or reversed flow in umbilical artery	(3)
c) AC < 10th centile, combined with PI > 95th centile in umbilical and/or uterine artery	(2)
Late-FGR	21
Gestational age 32^{+0}–42^{+0} plus one of the following:	
a) Two out of three:	(20)
i) AC < 10th centile (n = 20)	
ii) AC crossing two of the following centiles: 2.5, 5, 10, 25, 50, 75, 90, 95 and 97.5) (n = 17)	
iii) CP-ratio < 5th centile or PI >95th centile in the umbilical artery (n = 8)	
b) AC < 3rd centile	(1)

AC: abdominal circumference, CP: cerebroplacental ratio, FGR: fetal growth restriction, PI: pulsatility index. N: Number of participants fulfilling each of the criteria.
Definition used in the study was locally adjusted criteria for FGR, based on published definition by Gordijn et al. [4]. Most important adjustments were that a) deviations in AC was the single criterion for size in the local definition, in contrast to AC and/or estimated fetal weight in the published definition, and b) for Late-FGR a ii), crossing two of the listed centiles fulfilled the local growth-velocity criterion, in contrast to two quartiles in the published definition.

2.2. Ethics

The Hospital's Data Protection Officer and The Regional Ethics Committee of Research, south-east, Norway approved the study (2016/923D). The parents gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki [21].

2.3. Maternal, fetal and neonatal baseline characteristics

We recorded maternal and fetal characteristics as in our study of cardiac morphology in the same cohort [15].

Estimated fetal size was based on percentiles of abdominal circumference [16]. Fetal circulation was assessed by determining the pulsatility index in the umbilical artery [17], the middle cerebral artery [18], ductus venosus [19] and both uterine arteries [20]. Cerebroplacental ratio was the pulsatility index of the middle cerebral artery divided by the pulsatility index of the umbilical artery.

We determined GA using head circumference or femur length [21,22] at a routine ultrasound examination at gestational week 18. In the FGR cohort, the recordings from the last ultrasound examination prior to birth were used as basis for inclusion. The non-FGR cohort had one ultrasound examination as part of the prenatal visits to the outpatient clinic as close to term as feasible.

For baseline neonatal characteristics, we recorded GA, BW, head circumference, sex, twin/singleton and Apgar score at 5 min.

2.4. Postnatal echocardiographic assessment

One neonatologist (LB) performed all the postnatal ultrasound examinations on day one, two and three after birth. Details of the methodology have been previously published [14]. Small insignificant muscular ventricular septal defects did not disqualify from participation.

We acquired 1) apical four-chamber M-mode and pulsed-wave tissue Doppler (pwTD) images to assess excursions and velocities of the atrioventricular plane, 2) apical four-chamber grey-scale images to assess the area of the right ventricle and the length of the ventricular septum, 3) apical four-chamber pulsed-wave blood Doppler velocity images to assess the blood velocities of the atrioventricular valves, and 4) parasternal M-mode images to assess the diameter of the left ventricle [23–25]. The pwTD sample volume was 5 mm (default setting). For all recordings we used the default grey-scale frame rate, a pwTD velocity range of $\geq\pm$16 cm/s to avoid aliasing, and simultaneous ECG recordings.

2.5. Off-line echocardiographic analyses

The same physician who performed the neonatal scans (LB), did the off-line analyses using EchoPAC PC SWO analysis software system version 202 (GE, Vingmed, Horten, Norway). The average of the three best images or cycles entered the analysis. To compare hearts of various sizes, we normalised pwTD velocities and excursions by dividing by the septal length at end-diastole, and hence used septal length as a surrogate measure of heart size [26–28]. The septal length was the distance between the apical pericardium and the septal hinge of the mitral valve at onset of systole [29,30].

Atrioventricular plane excursions were the distances between end-systole and end-diastole at the left lateral, septal and right lateral hinges of the atrioventricular valves on M-mode images [23]. Excursion normalised for ventricular length served as a measure of global longitudinal function [24,27].

The left lateral, septal and right lateral atrioventricular plane peak systolic (s′), peak early diastolic (e′) and peak diastolic (a′) velocities during atrial systole were the peaks on the respective pwTD images (Fig. 1). S′ normalised for heart size served as a measure of global longitudinal function during systole. Similarly, diastolic velocities normalised for heart size served as measures of global longitudinal function

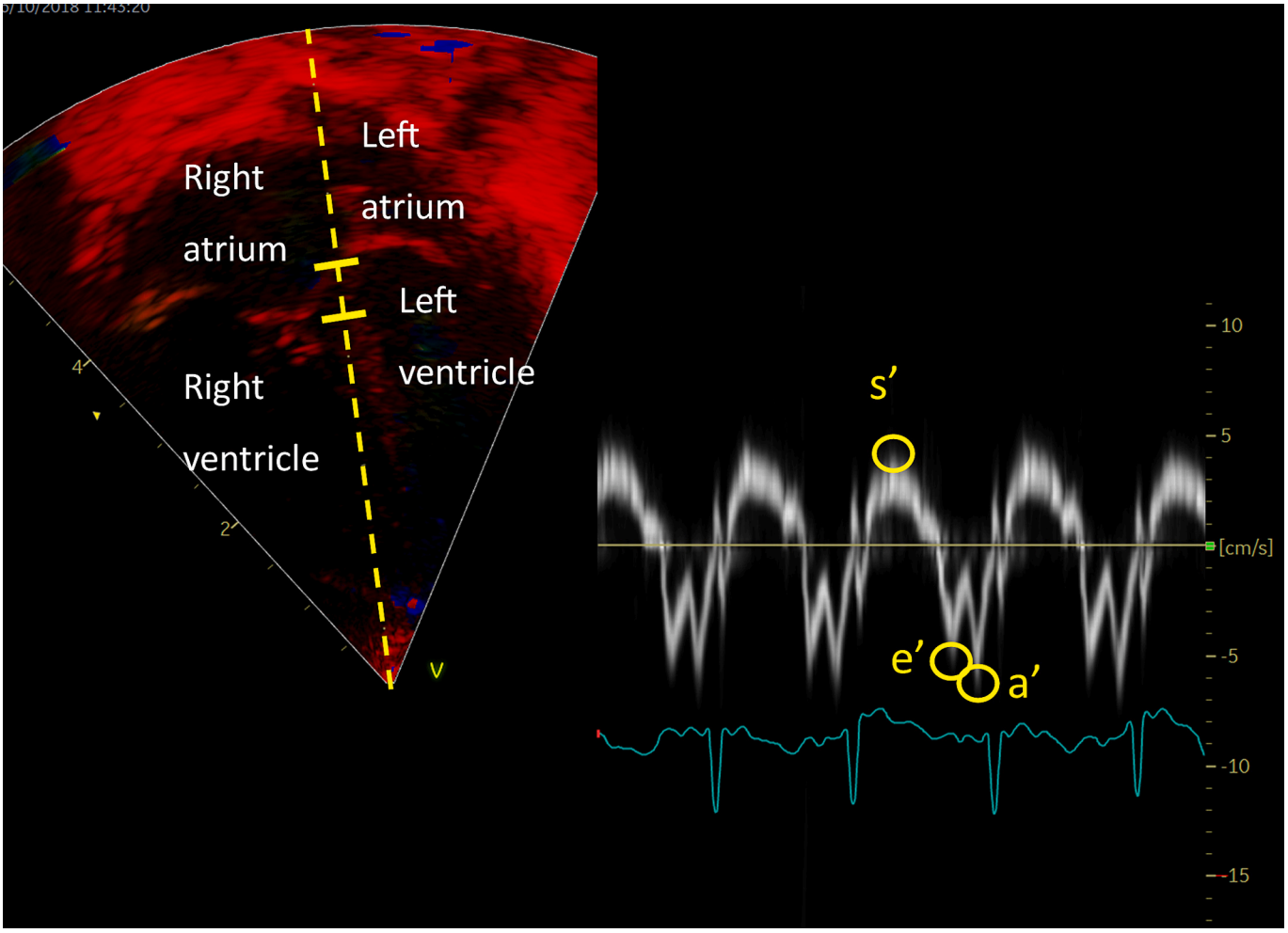


Fig. 1. Tissue Doppler analysis from an FGR infant. Image shows analysis of a pulsed-wave tissue Doppler image from the septal wall.
Left panel: Apical four-chamber Tissue Doppler image. Pulsed-wave velocities are sampled along the dotted yellow line (indicating the direction of the ultrasound beam) between the two yellow solid lines. Right panel: The white curve shows the velocities recorded throughout cardiac cycles. Yellow circles at the s′, e′ and a′ peak velocities in systole and in early and late diastole, respectively. Velocities were normalised for heart size by dividing by the septal length at end of diastole. See chapter 2 section 2.5 Off-line echocardiographic analyses for details. X-axis: Time. Y-axis: tissue velocity (cm/s). Cyan curve shows the ECG signal. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

[24] during diastole.

The early diastolic blood velocities of the tricuspid and mitral valves were the early diastolic peak from the respective pulsed-wave blood Doppler velocity images. The right and left E/e′ were the peak early diastolic blood Doppler velocity of the tricuspid and mitral valves, divided by the right and left lateral early peak diastolic pwTD velocity.

The fractional area change of the right ventricle was the relative change in area from end-diastole to end-systole, and the fractional shortening of the left ventricle was the relative change in diameter from end-diastole to end-systole [23].

2.6. Statistical analysis

FGR neonates were divided into early- and late-FGR according to the inclusion criteria. Within the allocated study period, it turned out to be no inclusions below 34 weeks in the non-FGR cohort justifying comparison with the early-FGR. The analysis strategy was therefore shifted to make two separate sets of analyses. One set comparing the late-FGR with the non-FGR cohort, and one set comparing the early and late-FGR cohorts.

When planning the study, we deemed ten percent relative difference in echocardiographic variables as an arbitrary clinically relevant difference between groups. Based on previous studies [29,30], power calculations showed that a sample size of 25–30 in each group would provide 80 percent statistical power for detecting such differences with two-sided five percent p-values.

We used *t*-test, chi square test and independent samples Mann-Whitney *U* test for analyses of independent variables, and mixed-effects linear regression models for analyses of repeated continuous variables. All mixed-effects models included intercepts and FGR as an independent categorical fixed effect. We assessed effects of FGR on measurements in one model assessing the unadjusted effect of FGR and a second model assessing the adjusted effects of FGR by taking GA, BW, sex, and twin/singleton into the model as fixed-effects covariates. For transitional changes, we used measurements on day three as reference and assessed changes during transition as percentage differences in indices on day one and day two in a model where day of assessment was a covariate in addition to GA, BW, sex, and twin/singleton. In a model assessing impact from heart rate on heart function, heart rate was a fixed-effects covariate in addition to GA, BW, sex, and twin/singleton.

Our approach allowed for detailed adjustment of the effects of GA and BW and accounted for consecutive examinations in the participants. As the GA and BW correlated at a higher level (0.91) than our pre-selected threshold for collinearity (0.75), we were unable to assess the separate effects of BW and GA on the measurements.

We present heart function variables as Estimated Marginal Means.

The software calculated the Estimated Marginal Means in the adjusted models by use of the average values for each of the continuous fixed-effects covariates (GA and BW), and therefore used GA 38 weeks and BW 2.8 kg in the comparisons between late-FGR and non-FGR, and 35 weeks and 1.9 kg in the comparisons between early-FGR and late-FGR. Estimated Marginal Means hence represents expected values for a neonate with the average GA and BW.

We used two-sided tests, 95 percent confidence intervals and five percent p-values for all tests, and IBM SPSS Statistics for Windows, version 28.0 (IBM Corp., Armonk, N.Y., USA) for all analyses.

3. Results

The 62 women gave birth to 69 neonates: 28 FGR (7 early- and 21 late-FGR) and 41 non-FGR. The number of days from the last prenatal ultrasound examination to delivery was median (interquartile range) 6 (2–21); early-FGR 3 (0–4), late-FGR 2 (1–4) and non-FGR 18 (7–29). Table 1 shows the number of FGR neonates fulfilling each of the FGR criteria. Nearly 50 % had signs of prenatal circulatory compromise, five in the early (71 %) and eight in the late FGR (38 %) group.

3.1. Clinical and baseline characteristics

Clinical and baseline characteristics has been reported previously [14] and are shown in Table 2. We assigned a mother of twins as FGR if at least one twin was FGR. Mean time from delivery to the first echocardiography was 25 (standard deviation 8) hours, to the second 47 (7) and to the third 71 (8).

FGR neonates had lower GA, BW, and head circumference than non-FGR neonates (Table 2) ($p < 0.05$). Sex and Apgar score at 5 min were similar. Rates of caesarean section were higher in both FGR cohorts than in the non-FGR cohort ($p < 0.05$). Only neonates who were either premature or suffered from FGR needed admission to the Neonatal Intensive Care Unit. All neonates admitted to the Neonatal Intensive Care Unit survived to discharge and none of them were at any time critically ill. Only one participant needed ventilatory support, a preterm FGR neonate received CPAP the first two days after birth.

3.2. Heart function

We conducted 60 postnatal ultrasound examinations on day one, 66 on day two and 63 on day three after birth. Eighteen examinations were missing due to logistical reasons. Except for small, haemodynamically insignificant ventricular septal defects in two participants, all neonates had structurally normal hearts.

Neonates exposed to late-FGR had higher septal excursion, higher right a′, and higher left E/e′ than non-FGR in unadjusted and adjusted analyses (Table 3). Right s′ was higher in unadjusted analyses. All other measurements were similar between the two cohorts. Changes during transition were similar in late-FGR and non-FGR. Left- and right lateral excursions, left e′ and right a′, and both left- and right E/e′ were significantly higher on day one than on day three (Fig. 2). No index changed significantly from day two to day three.

An increase of 10 beats per minute was associated with an increase of 0.04 (0.02)/s, $p = 0.039$ (mean and standard error of the mean) in in right s′. Heart rate had no significant impact on other systolic velocities, excursions, E/e′, left ventricular fractional shortening or right ventricular fractional area change. For diastolic velocities, an increase of 10 beats per minute was associated with increases in septal e′ (0.04 (0.02)/s, $p = 0.014$), septal a′ (0.04 (0.02)/s, $p = 0.049$) and right a′ (0.11 (0.03)/s, $p = 0.004$). There were no changes for left e′, left a′ or right e′.

Early-FGR neonates had higher left s′ and heart rate than late-FGR in unadjusted analyses. Other measurements were similar in unadjusted analyses, and all measurement were similar in the adjusted analyses (Table 4).

Table 2
Clinical and baseline characteristics.

Maternal characteristics n = 62	Early-FGR n = 7	Late-FGR n = 19	Non-FGR n = 36
Age, years	36 (6)	35 (5)	34 (5)
Height, cm	163 (4)	166 (7)	166 (6)
Pre-pregnancy weight, kg	67 (12)	63 (15)	63 (9)
Pre-pregnancy BMI, kg/m^2	23 (4)	22 (4)	22 (3)
Higher education	6/7 (86 %)	12/18 (67 %)	28/35 (80 %)
Non-smoking during pregnancy	6/7 (86 %)	18/19 (95 %)	35/36 (97 %)
No alcohol during pregnancy	6/7 (86 %)	15/26 (79 %)	30/36 (83 %)
Pre-pregnancy and pregnancy related medical condition	4/7 (57 %)	8/19 (42 %)	16/36 (46 %)
Preeclampsia	4/7 (57 %)	4/19 (21 %)	0/36 (0 %)
Antihypertensive medication	4/6 (66 %)	2/17 (12 %)	2/34 (6 %)
Maternal blood pressure (mm Hg)			
- Early systolic	126 (15)	108 (9)	111 (9)
- Early diastolic	79 (15)	69 (9)	70 (9)
- Late systolic	136 (21)	121 (23)	112 (12)
- Late diastolic	82 (7)	77 (13)	73 (9)

Neonatal characteristics n = 69	Early-FGR n = 7	Late-FGR n = 21	Non-FGR n = 41
Gestational age, weeks	31.0 (0.7)	36.7 (2.2)	39.0 (2.5)
Prematurity, 30–37 weeks	7/7 (100 %)	12/21 (57 %)	12/41 (29 %)
Birth weight, kg	1.1 (0.2)	2.2 (0.5)	3.2 (0.7)
Head circumference, cm	27.3 (1.3)	30.3 (2.4)	31.3 (1.7)
Sex, girls	5/7 (71 %)	11/21 (52 %)	21/41 (51 %)
Caesarean section	7/7 (100 %)	13/21 (62 %)	11/41 (27 %)
Apgar, 5 min	8 (2)	9 (2)	10 (1)
Ponderal Index	23 (1)	24 (3)	27 (3)
Admission to NICU	7/7 (100 %)	7/21 (33 %)	6/41 (15 %)

Values are mean (SD) or fractions (per cent). FGR – fetal growth restriction. The number of maternal and neonatal characters differs because of seven included twin pregnancies. Early-FGR defined as gestational age 30^{+0}–31^{+6}. Late-FGR defined as ≥32 weeks. Non-FGR were all ≥32 weeks. BMI - Body mass index. Higher education was defined as >15 years. Pre-pregnancy and pregnancy related medical conditions for all cohorts combined were: allergy (28/62), asthma (6/62), hypertension (8/62), gestational diabetes (3/62), gynaecological (6/62), or other pre-existing medical conditions (19/62). NICU - Neonatal Intensive Care Unit.

4. Discussion

Our main findings were that late-FGR hearts in neonates without clinical signs of any circulatory compromise after birth exhibited increased septal contraction and reduced left diastolic function compared with non-FGR the first three days after birth. Late-FGR had no impact on the dynamic changes in heart function between the first three days after birth, and these changes during transition were most evident for excursions and diastolic measurements in the lateral walls. Heart rate had minor influence on systolic heart function measurements, whereas several diastolic measurements increased with heart rate. Early-FGR had similar heart function as late-FGR when adjusted for GA and BW.

4.1. Late-FGR effects on excursions

Excursion normalised for heart size was higher in late-FGR than in non-FGR. Changes in ventricular wall lengths during systole are usually lower in septum than in left lateral wall [29–31]. In contrast, we found similar changes in septum and left lateral wall in late-FGR due to a high excursion in late-FGR. Many studies of heart function following FGR have assessed excursions in lateral walls [32,33]. The present study adds that FGR was associated with higher septal excursion during postnatal

Table 3
Heart function measurements in late-FGR and non-FGR without adjustments (left columns) and adjusted for sex, twin/singleton, gestational age, and birth weight (right columns). Values are Estimated Marginal Means (standard error of the mean) by use of gestational age 38 weeks and birth weight 2.8 kg. Excursions and velocities were normalised for heart size by dividing by the length of the left ventricular septum.

	Unadjusted			Adjusted		
	Late-FGR	Non-FGR	p	Late-FGR	Non-FGR	p
Excursion of atrioventricular plane normalised for septum length (%)						
Left	15.6 (0.7)	15.4 (0.5)	0.887	16.6 (1.0)	15.6 (0.7)	0.459
Septal	15.1 (0.5)	13.9 (0.3)	0.044	15.9 (0.6)	14.0 (0.4)	0.021
Right	26.0 (1.0)	26.0 (0.7)	0.985	28.7 (1.3)	26.0 (0.9)	0.101
Peak systolic tissue velocity normalised for septum length (/s)						
Left	1.21 (0.05)	1.22 (0.04)	0.966	1.21 (0.08)	1.20 (0.05)	0.904
Septal	1.26 (0.04)	1.24 (0.03)	0.688	1.32 (0.05)	1.25 (0.04)	0.277
Right	2.10 (0.07)	1.90 (0.05)	0.017	2.09 (0.09)	1.89 (0.06)	0.089
Peak early diastolic tissue velocity normalised for septum length (/s)						
Left	1.33 (0.09)	1.53 (0.06)	0.071	1.30 (0.12)	1.59 (0.08)	0.061
Septal	1.41 (0.06)	1.42 (0.04)	0.907	1.50 (0.08)	1.48 (0.05)	0.905
Right	2.17 (0.08)	2.01 (0.11)	0.232	2.33 (0.15)	2.03 (0.10)	0.107
Peak diastolic tissue velocity during atrial systole normalised for septum length (/s)						
Left	1.39 (0.1)	1.45 (0.1)	0.534	1.50 (0.12)	1.42 (0.08)	0.564
Septal	1.69 (0.07)	1.55 (0.05)	0.119	1.69 (0.08)	1.59 (0.06)	0.356
Right	2.83 (0.12)	2.44 (0.08)	0.008	2.93 (0.16)	2.48 (0.11)	0.028
E/e′						
Left	17.5 (1.3)	12.1 (0.9)	0.002	17.3 (1.9)	11.5 (1.3)	0.019
Right	7.2 (0.4)	7.5 (0.3)	0.541	6.5 (0.5)	7.6 (0.4)	0.110
Other indices						
Heart rate (/min)	128 (3)	122 (2)	0.110	130 (3)	121 (2)	0.052
FS (%)	31 (1)	33 (1)	0.263	34 (1)	33 (1)	0.604
FAC (%)	28 (3)	24 (2)	0.207	28 (4)	26 (3)	0.648

E/e′: Peak early diastolic blood velocity of the mitral (left) and tricuspid (right) valves, divided by the left and right lateral early peak diastolic tissue velocity.
FS: Fractional shortening, relative change in left ventricular diameter during systole.
FAC: Fractional area change, relative change in right ventricular area during systole.

transition. This corroborates our previous study [14] showing a shorter septal length in late-FGR, which could explain the higher relative change. Previous studies commonly show higher relative changes in the right lateral wall than in other walls which is in line with the present results, although our findings seem more pronounced [31,34].

4.2. Late-FGR effects on tissue Doppler velocities and E/e′

The higher right a′ in late-FGR suggest increased atrial and ventricular contraction or increased ventricular filling. The lack of significant difference in E/e′ might suggest that the higher right lateral a′ was more related to increased atrial or systolic contraction in the right lateral wall rather than differences in diastolic function, although impact from diastolic function cannot be ruled out.

Septal and left lateral pwTD velocities were similar between late-FGR and non-FGR. This indicates similar heart function in these cohorts, whereas the significantly higher left E/e′ in late-FGR may indicate a relatively stiffer and less compliant left ventricle, or a relatively higher left preload. Of note is the relatively large difference between right and left E/e′. Others have found bilaterally increased E/e′ but less relative increase than in our study [34–36]. We found differences between late-FGR and non-FGR only for the left side, others have found significant differences on both sides [34]. The high left E/e′ could be due to left lateral diastolic dysfunction and hence indicate that the normal transition was more challenging for the left than right heart.

4.3. Changes during transition in late-FGR and non-FGR

Changes during transition observed longitudinally day one, two and three showed the same pattern in late-FGR and non-FGR in our study. In contrast, others have found different changes during transition between FGR and non-FGR term neonates in myocardial performance index between day two and five [34], with changes from day one to day two more prominent on the right than left side [35,36] indicating that FGR hearts adapted differently from non-FGR hearts [37]. The higher excursion, similar systolic velocities and higher diastolic velocities and E/e′ on day one than day three suggest bilaterally higher preload and filling pressure in both ventricles at unchanged contractility on day one. Most transitional changes seem to occur shortly after birth, as we found no differences from day two to day three. In contrast to the changes between days shown in our study, several studies report only minor changes in longitudinal excursions over the first days after birth [26,29,35,36].

4.4. Effect of heart rate on heart function

The force-frequency relationship [38] is the positive correlation between heart rate and contractility, considered mediated via neurohumoral mechanisms. Except for a minor impact on right lateral s′, we found no effect from heart rate on measurements in systole, indicating no or only weak relation between heart rate and contractility. We also found a weak but positive association between heart rate and a′ in the septal and right lateral walls. The latter could indicate a higher level of atrial or ventricular systolic function or augmented ventricular filling at higher heart rate.

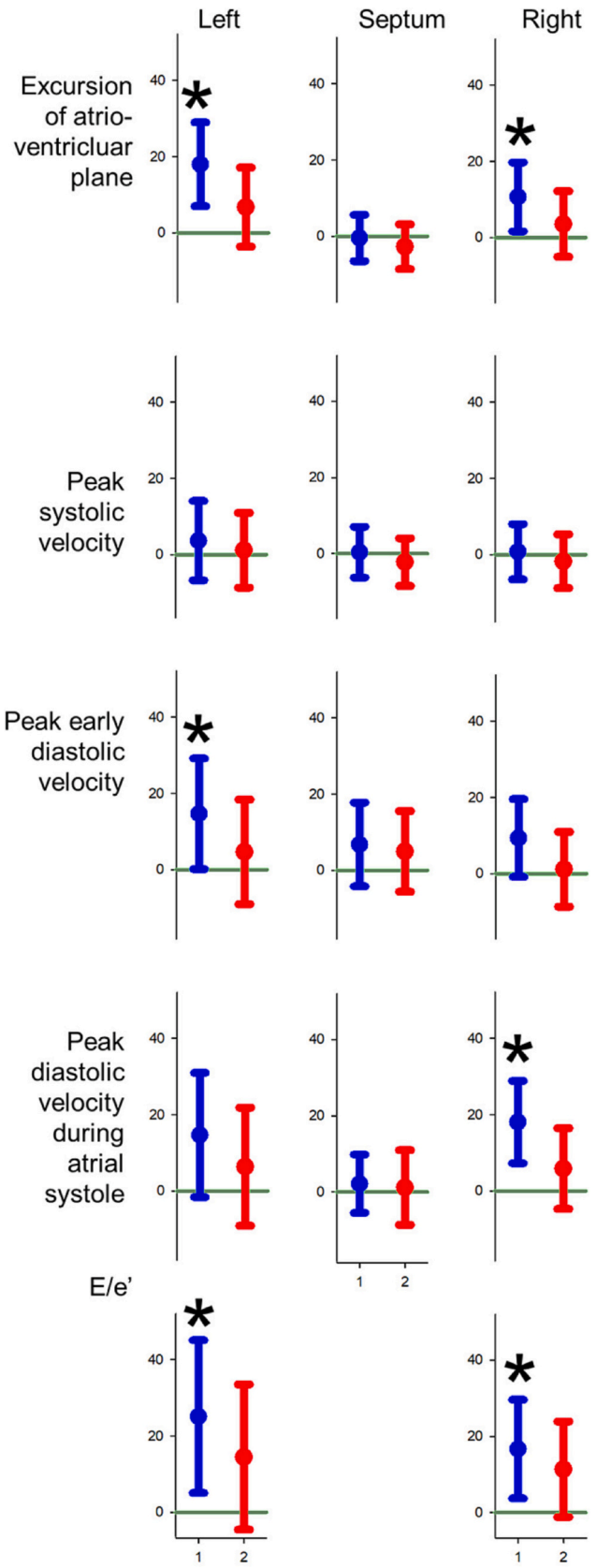
4.5. Heart function in early-FGR vs. late-FGR

Between early- and late-FGR, the presence of differences in unadjusted analyses and lack of differences in adjusted analyses indicated that GA and BW were stronger determinants for heart function than early- versus late-FGR per se and underscored the importance of adjustments when comparing cohorts with large spans in GA and BW.

4.6. Strengths and limitations

Studies have compared FGR and non-FGR by use of analyses adjusted for GA, size and other factors [34] and by use of unadjusted analyses [33], and others have presented analyses both with and without adjustments [32]. As FGR impacts weight and several heart function measurements vary with size, BW could be regarded as a mediator, collider or confounder in the statistical models assessing the effects from FGR. There are hence arguments for presenting unadjusted results and for presenting adjusted results. We therefore present results both of unadjusted and adjusted analyses in our study.

As excursions and pwTD velocities vary with heart size, adjusting these indices for heart size seems plausible, and this approach has been



(caption on next column)

Fig. 2. Changes during transition, data from non-FGR and late-FGR neonates combined. Relative difference in per cent for values on day one (blue bars) and two (red bars) by use of value on day three as reference. Excursions and velocities are normalised for heart size by dividing by the length of the left ventricular septum. Green horizontal lines denote zero percent change, i.e. the day three value. Late-FGR had no impact on changes during transition. Bars are mean with 95 percent confidence intervals. X-axis: day after birth. Y-axis: Percent difference from values on day three. *: Values significantly different from day-three values ($p < 0.05$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

used previously [27,34] and suggested in guidelines [24]. Others have reported heart function indices unadjusted for heart size [33]. Although diastolic tissue Doppler velocities are regarded as measurements of diastolic function, they are influenced by many factors including restoring forces, myocardial wall stiffness, preload and, for the peak diastolic velocity during atrial systole (a′), the quality of the atrial systolic contraction and the quality of the ventricular systolic function [39–41].

Among challenges interpreting FGR literature are the variations in the definitions of FGR [42,43], that FGR neonates can respond differently to drugs and treatments after birth [44], and that they may have various degrees of pulmonary vascular maldevelopment [45] with potential impact on the heart. Strengths in our study were that we based our definition of FGR on contemporary criteria by use of fetal assessment [4] and that the non-FGR cohort had verified normal prenatal growth and circulation. Sometimes FGR and small for GA are used interchangeably [46], and studies have often used definitions based solely on estimated fetal centiles [47] or confirmed BW [33], probably contributing to the heterogeneity of findings in this field. Another factor that could contribute to the heterogeneity is that the wide contemporary definition [4] of FGR comprises a spectrum from rather mild to severe cases. Within that spectrum, our FGR participants were on the mild side.

The same neonatologist did all the postnatal ultrasound examinations and all off-line analyses, eliminating inter-rater variability.

We had insufficient inclusions of premature non-FGR participants to carry out comparison with the early-FGR cohort and we had few early-FGR participants. The comparison between early- and late-FGR had restricted statistical power to detect but clear differences. Study results hence primarily represent differences between our late-FGR and non-FGR cohorts.

Although the circulation in dichorionic, diamniotic twin pregnancies is not completely independent, we accepted these pregnancies in our study because they have separate placentas and could act as each other's controls, and because twin pregnancies are an important part of the FGR-population.

Adjusting for repeated measurements, GA and BW is usually a relevant refinement, but concerns may be raised when the compared cohorts in the statistical model differ substantially in these characteristics. Although our statistical model allowed adjusting for gestational age, the wide range for gestational age might be a concern. For indices exhibiting significant changes between days, it would be critically important to acquire images at the same day-after-birth when assessing differences between groups.

5. Conclusion

FGR significantly impacted neonatal heart function the first three days after birth. Adaptations in late-FGR included increased septal contraction and reduced left diastolic function compared with non-FGR. Late-FGR had no impact on dynamic changes between the first three days after birth, and the changes in heart function during transition were most evident for excursions and diastolic indices in lateral walls. Heart rate impacted systolic and diastolic heart function indices. Early-FGR exhibited similar heart function as late-FGR.

A particular focus on left heart function may be important when

Table 4
Heart function indices in late-FGR and early-FGR without adjustments (left columns) and adjusted for sex, twin/singleton, gestational age, and birth weight (right columns). Estimated Marginal Means (standard error of the mean) by use of gestational age 35 weeks and birth weight 1.9 kg. Excursions and velocities were normalised for heart size by dividing by the length of the left ventricular septum.

	Unadjusted			Adjusted		
	Late-FGR	Early-FGR	p	Late-FGR	Early-FGR	p
Excursion of atrioventricular plane normalised for septum length (%)						
Left	15.6 (0.8)	18.1 (1.4)	0.126	16.3 (1.1)	15.7 (2.2)	0.820
Septal	15.1 (0.6)	14.7 (1.0)	0.704	15.5 (0.6)	13.8 (1.2)	0.259
Right	26.0 (1.1)	29.3 (1.8)	0.125	25.8 (1.3)	30.9 (2.7)	0.144
Peak systolic tissue velocity normalised for septum length (/s)						
Left	1.21 (0.06)	1.48 (0.10)	0.034	1.26 (0.08)	1.22 (0.16)	0.761
Septal	1.26 (0.04)	1.39 (0.07)	0.118	1.34 (0.05)	1.19 (0.10)	0.211
Right	2.10 (0.10)	2.51 (0.18)	0.055	2.22 (0.14)	2.34 (0.28)	0.746
Peak early diastolic tissue velocity normalised for septum length (/s)						
Left	1.33 (0.09)	1.66 (0.15)	0.084	1.45 (0.12)	1.44 (0.25)	0.974
Septal	1.41 (0.06)	1.61 (0.10)	0.096	1.54 (0.07)	1.51 (0.14)	0.860
Right	2.17 (0.11)	2.42 (0.18)	0.256	2.39 (0.11)	2.24 (0.23)	0.598
Peak diastolic tissue velocity during atrial systole normalised for septum length (/s)						
Left	1.46 (0.10)	1.71 (0.17)	0.205	1.62 (0.12)	1.19 (0.25)	0.176
Septal	1.69 (0.08)	1.92 (0.13)	0.120	1.85 (0.09)	1.57 (0.18)	0.226
Right	2.82 (0.14)	3.07 (0.24)	0.375	3.07 (0.18)	2.59 (0.37)	0.305
E/e′						
Left	17.5 (1.7)	14.2 (2.8)	0.336	15.6 (2.2)	17.7 (4.6)	0.709
Right	7.2 (0.4)	8.4 (0.7)	0.151	6.9 (0.5)	7.0 (1.0)	0.949
Other indices						
Heart rate (/min)	128 (3)	148 (5)	0.001	134 (3)	126 (5)	0.253
FS (%)	31 (1)	30 (2)	0.401	31 (1)	32 (3)	0.722
FAC (%)	28 (2)	28 (4)	0.969	29 (3)	26 (6)	0.777

E/e′: Peak early diastolic blood velocity of the mitral (left) and tricuspid (right) valves, divided by the left and right lateral early peak diastolic tissue velocity.
FS: Fractional shortening, relative change in left ventricular diameter during systole.
FAC: Fractional area change, relative change in right ventricular area during systole.

treating early postnatal circulatory failure in FGR neonates.

Category of study

Clinical observational.

Declaration of competing interest

None.

Acknowledgements

We thank the parents and their neonates that participated in this study, and the hospital staff for facilitating the study. We acknowledge the assistance received from Dr. Nina Harsem, Dr. Henrik Husby and Dr. Tom Hartgill for patient recruitment and prenatal data acquisition and valuable advice in the planning of the study. This study is part of a Ph.D. project funded by the University of Oslo and did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] D.J. Barker, C.N. Hales, C.H. Fall, C. Osmond, K. Phipps, P.M. Clark, Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth, Diabetologia. 36 (1993) 62–67, https://doi.org/10.1007/bf00399095.
[2] S. Harris, L. Perston, K. More, P. Graham, N. Ellis, C. Frampton, et al., Cardiac structure and function in very preterm-born adolescents compared to term-born controls: a longitudinal cohort study, Early Hum. Dev. 163 (2021), 105505, https://doi.org/10.1016/j.earlhumdev.2021.105505.
[3] A. Wacker-Gussmann, J. Engelhard, R. Oberhoffer-Fritz, J. Schopen, P. Ewert, J. U. Ortiz, et al., Cardiovascular outcome of former late-onset small-for-gestational-age children at 1 year of age: CURIOSA study, Arch. Gynecol. Obstet. 306 (2022) 1455–1461, https://doi.org/10.1007/s00404-022-06404-8.
[4] S.J. Gordijn, I.M. Beune, B. Thilaganathan, A. Papageorghiou, A.A. Baschat, P. N. Baker, et al., Consensus definition of fetal growth restriction: a Delphi procedure, Ultrasound Obstet. Gynecol. 48 (2016) 333–339, https://doi.org/10.1002/uog.15884.
[5] E. Demicheva, F. Crispi, Long-term follow-up of intrauterine growth restriction: cardiovascular disorders, Fetal Diagn. Ther. 36 (2014) 143–153, https://doi.org/10.1159/000353633.
[6] P. Johnson, D.J. Maxwell, M.J. Tynan, L.D. Allan, Intracardiac pressures in the human fetus, Heart. 84 (2000) 59–63, https://doi.org/10.1136/heart.84.1.59.
[7] T. Kiserud, C. Ebbing, J. Kessler, S. Rasmussen, Fetal cardiac output, distribution to the placenta and impact of placental compromise, Ultrasound Obstet. Gynecol. 28 (2006) 126–136, https://doi.org/10.1002/uog.2832.
[8] K. Mäkikallio, P. Jouppila, J. Räsänen, Retrograde aortic isthmus net blood flow and human fetal cardiac function in placental insufficiency, Ultrasound Obstet. Gynecol. 22 (2003) 351–357, https://doi.org/10.1002/uog.232.
[9] M. Rodríguez-López, M. Cruz-Lemini, B. Valenzuela-Alcaraz, L. Garcia-Otero, M. Sitges, B. Bijnens, et al., Descriptive analysis of different phenotypes of cardiac remodeling in fetal growth restriction, Ultrasound Obstet. Gynecol. 50 (2017) 207–214, https://doi.org/10.1002/uog.17365.
[10] F. Crispi, J. Miranda, E. Gratacós, Long-term cardiovascular consequences of fetal growth restriction: biology, clinical implications, and opportunities for prevention of adult disease, Am. J. Obstet. Gynecol. 218 (2018) S869–s79, https://doi.org/10.1016/j.ajog.2017.12.012.
[11] F. Crispi, B. Bijnens, E. Sepulveda-Swatson, M. Cruz-Lemini, J. Rojas-Benavente, A. Gonzalez-Tendero, et al., Postsystolic shortening by myocardial deformation imaging as a sign of cardiac adaptation to pressure overload in fetal growth restriction, Circ. Cardiovasc. Imaging 7 (2014) 781–787, https://doi.org/10.1161/circimaging.113.001490.
[12] D. Sharma, S. Shastri, P. Sharma, Intrauterine growth restriction: antenatal and postnatal aspects, Clin. Med. Insights Pediatr. 10 (2016) 67–83, https://doi.org/10.4137/CMPed.S40070.
[13] S. Turan, O.M. Turan, M. Salim, C. Berg, U. Gembruch, C.R. Harman, et al., Cardiovascular transition to extrauterine life in growth-restricted neonates: relationship with prenatal Doppler findings, Fetal Diagn. Ther. 33 (2013) 103–109, https://doi.org/10.1159/000345092.
[14] L. Bjarkø, D. Fugelseth, N. Harsem, T. Kiserud, G. Haugen, E. Nestaas, Cardiac morphology in neonates with fetal growth restriction, J. Perinatol. 43 (2022) 187–195, https://doi.org/10.1038/s41372-022-01538-8.
[15] A.C. Staff, A. Kvie, E. Langsesæter, T.M. Michelsen, K. Moe, K.M. Strand, et al., Hypertensive svangerskapskomplikasjoner og eklampsi. https://www.legeforeningen.no/foreningsledd/fagmed/norsk-gynekologisk-forening/veiledere/veileder-i-fodselshjelp/hypertensive-svangerskapskomplikasjoner-og-eklampsi/, 2020. (Accessed 10 November 2022).
[16] S.L. Johnsen, T. Wilsgaard, S. Rasmussen, R. Sollien, T. Kiserud, Longitudinal reference charts for growth of the fetal head, abdomen and femur, Eur. J. Obstet. Gynecol. Reprod. Biol. 127 (2006) 172–185, https://doi.org/10.1016/j.ejogrb.2005.10.004.
[17] G. Acharya, T. Wilsgaard, G.K. Berntsen, J.M. Maltau, T. Kiserud, Reference ranges for serial measurements of umbilical artery Doppler indices in the second half of pregnancy, Am. J. Obstet. Gynecol. 192 (2005) 937–944, https://doi.org/10.1016/j.ajog.2004.09.019.
[18] C. Ebbing, S. Rasmussen, T. Kiserud, Middle cerebral artery blood flow velocities and pulsatility index and the cerebroplacental pulsatility ratio: longitudinal reference ranges and terms for serial measurements, Ultrasound Obstet. Gynecol. 30 (2007) 287–296, https://doi.org/10.1002/uog.4088.

[19] J. Kessler, S. Rasmussen, M. Hanson, T. Kiserud, Longitudinal reference ranges for ductus venosus flow velocities and waveform indices, Ultrasound Obstet. Gynecol. 28 (2006) 890–898, https://doi.org/10.1002/uog.3857.
[20] O. Gómez, F. Figueras, S. Fernández, M. Bennasar, J.M. Martínez, B. Puerto, et al., Reference ranges for uterine artery mean pulsatility index at 11-41 weeks of gestation, Ultrasound Obstet. Gynecol. 32 (2008) 128–132, https://doi.org/10.1002/uog.5315.
[21] S.L. Johnsen, S. Rasmussen, R. Sollien, T. Kiserud, Fetal age assessment based on femur length at 10-25 weeks of gestation, and reference ranges for femur length to head circumference ratios, Acta Obstet. Gynecol. Scand. 84 (2005) 725–733, https://doi.org/10.1111/j.0001-6349.2005.00691.x.
[22] S.L. Johnsen, S. Rasmussen, R. Sollien, T. Kiserud, Fetal age assessment based on ultrasound head biometry and the effect of maternal and fetal factors, Acta Obstet. Gynecol. Scand. 83 (2004) 716–723, https://doi.org/10.1111/j.0001-6349.2004.00485.x.
[23] R.M. Lang, L.P. Badano, V. Mor-Avi, J. Afilalo, A. Armstrong, L. Ernande, et al., Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, Eur. Heart J. Cardiovasc. Imaging 16 (2015) 233–270, https://doi.org/10.1093/ehjci/jev014.
[24] E. Nestaas, U. Schubert, W.P. de Boode, A. El-Khuffash, European Special Interest Group 'Neonatologist Performed E, Tissue Doppler velocity imaging and event timings in neonates: a guide to image acquisition, measurement, interpretation, and reference values, Pediatr. Res. 84 (2018) 18–29, https://doi.org/10.1038/s41390-018-0079-8.
[25] L. Lopez, S.D. Colan, P.C. Frommelt, G.J. Ensing, K. Kendall, A.K. Younoszai, et al., Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council, J. Am. Soc. Echocardiogr. 23 (2010) 465–495, https://doi.org/10.1016/j.echo.2010.03.019 (quiz 576-7).
[26] B.H. Eriksen, E. Nestaas, T. Hole, K. Liestol, A. Stoylen, D. Fugelseth, Myocardial function in premature infants: a longitudinal observational study, BMJ Open 3 (2013), https://doi.org/10.1136/bmjopen-2012-002441.
[27] T. Terada, K. Mori, M. Inoue, H. Yasunobu, Mitral annular plane systolic excursion/left ventricular length (MAPSE/L) as a simple index for assessing left ventricular longitudinal function in children, Echocardiography. 33 (2016) 1703–1709, https://doi.org/10.1111/echo.13325.
[28] A. Støylen, H.E. Mølmen, H. Dalen, Relation between mitral annular plane systolic excursion and global longitudinal strain in normal subjects: the HUNT study, Echocardiography. 35 (2018) 603–610, https://doi.org/10.1111/echo.13825.
[29] B.H. Eriksen, E. Nestaas, T. Hole, K. Liestol, A. Stoylen, D. Fugelseth, Longitudinal assessment of atrioventricular annulus excursion by grey-scale m-mode and colour tissue Doppler imaging in premature infants, Early Hum. Dev. 89 (2013) 977–982, https://doi.org/10.1016/j.earlhumdev.2013.09.006.
[30] B.H. Eriksen, E. Nestaas, T. Hole, K. Liestol, A. Stoylen, D. Fugelseth, Myocardial function in term and preterm infants. Influence of heart size, gestational age and postnatal maturation, Early Hum. Dev. 90 (2014) 359–364, https://doi.org/10.1016/j.earlhumdev.2014.04.010.
[31] E. Nestaas, A. Stoylen, D. Fugelseth, Myocardial performance assessment in neonates by one-segment strain and strain rate analysis by tissue Doppler - a quality improvement cohort study, BMJ Open 2 (2012), https://doi.org/10.1136/bmjopen-2012-001636.
[32] L. Rodriguez-Guerineau, M. Perez-Cruz, M.D. Gomez Roig, F.J. Cambra, J. Carretero, F. Prada, et al., Cardiovascular adaptation to extrauterine life after intrauterine growth restriction, Cardiol. Young 28 (2018) 284–291, https://doi.org/10.1017/s1047951117001949.
[33] M. Cruz-Lemini, F. Crispi, B. Valenzuela-Alcaraz, F. Figueras, M. Sitges, B. Bijnens, et al., Fetal cardiovascular remodeling persists at 6 months in infants with intrauterine growth restriction, Ultrasound Obstet. Gynecol. 48 (2016) 349–356, https://doi.org/10.1002/uog.15767.
[34] S. Fouzas, A.A. Karatza, P.A. Davlouros, D. Chrysis, D. Alexopoulos, S. Mantagos, et al., Neonatal cardiac dysfunction in intrauterine growth restriction, Pediatr. Res. 75 (2014) 651–657, https://doi.org/10.1038/pr.2014.22.
[35] A. Jain, A.F. El-Khuffash, B.C. Kuipers, A. Mohamed, K.A. Connelly, P. J. McNamara, et al., Left ventricular function in healthy term neonates during the transitional period, J. Pediatr. 182 (2017) 197–203.e2, https://doi.org/10.1016/j.jpeds.2016.11.003.
[36] A. Jain, A. Mohamed, A. El-Khuffash, K.A. Connelly, F. Dallaire, R.P. Jankov, et al., A comprehensive echocardiographic protocol for assessing neonatal right ventricular dimensions and function in the transitional period: normative data and z scores, J. Am. Soc. Echocardiogr. 27 (2014) 1293–1304, https://doi.org/10.1016/j.echo.2014.08.018.
[37] A. Sehgal, R. Bhatia, C.T. Roberts, Cardiovascular response and sequelae after minimally invasive surfactant therapy in growth-restricted preterm infants, J Perinatol: official journal of the California Perinatal Association 40 (2020) 1178–1184, https://doi.org/10.1038/s41372-020-0682-5.
[38] M.M. Cheung, J.F. Smallhorn, M. Vogel, G. Van Arsdell, A.N. Redington, Disruption of the ventricular myocardial force-frequency relationship after cardiac surgery in children: noninvasive assessment by means of tissue Doppler imaging, J. Thorac. Cardiovasc. Surg. 131 (2006) 625–631, https://doi.org/10.1016/j.jtcvs.2005.09.056.
[39] C.M. Yu, J.W. Fung, Q. Zhang, L.C. Kum, H. Lin, G.W. Yip, et al., Tissue Doppler echocardiographic evidence of atrial mechanical dysfunction in coronary artery disease, Int. J. Cardiol. 105 (2005) 178–185, https://doi.org/10.1016/j.ijcard.2004.12.077.
[40] A.C. Boyd, N.B. Schiller, D.L. Ross, L. Thomas, Segmental atrial contraction in patients restored to sinus rhythm after cardioversion for chronic atrial fibrillation: a colour Doppler tissue imaging study, Eur. J. Echocardiogr. 9 (2008) 12–17, https://doi.org/10.1016/j.euje.2006.11.004.
[41] M. Wang, G.W. Yip, A.Y. Wang, Y. Zhang, P.Y. Ho, M.K. Tse, et al., Peak early diastolic mitral annulus velocity by tissue Doppler imaging adds independent and incremental prognostic value, J. Am. Coll. Cardiol. 41 (2003) 820–826, https://doi.org/10.1016/s0735-1097(02)02921-2.
[42] D. Shrivastava, A. Master, Fetal growth restriction, J. Obstet. Gynaecol. India 70 (2020) 103–110, https://doi.org/10.1007/s13224-019-01278-4.
[43] S.J. Gordijn, I.M. Beune, W. Ganzevoort, Building consensus and standards in fetal growth restriction studies, Best Pract. Res. Clin. Obstet. Gynaecol. 49 (2018) 117–126, https://doi.org/10.1016/j.bpobgyn.2018.02.002.
[44] J.A. Leipälä, K.O. Raivio, A. Sarnesto, A. Panteleon, V. Fellman, Intrauterine growth restriction and postnatal steroid treatment effects on insulin sensitivity in preterm neonates, J. Pediatr. 141 (2002) 472–476, https://doi.org/10.1067/mpd.2002.126725.
[45] A. Sehgal, S.M. Gwini, S. Menahem, B.J. Allison, S.L. Miller, G.R. Polglase, Preterm growth restriction and bronchopulmonary dysplasia: the vascular hypothesis and related physiology, J. Physiol. 597 (2019) 1209–1220, https://doi.org/10.1113/jp276040.
[46] S.R. Easter, L.O. Eckert, N. Boghossian, R. Spencer, E. Oteng-Ntim, C. Ioannou, et al., Fetal growth restriction: case definition & guidelines for data collection, analysis, and presentation of immunization safety data, Vaccine. 35 (2017) 6546–6554, https://doi.org/10.1016/j.vaccine.2017.01.042.
[47] A. Sehgal, B.J. Allison, S.M. Gwini, S.L. Miller, G.R. Polglase, Cardiac morphology and function in preterm growth restricted infants: relevance for clinical sequelae, J. Pediatr. 188 (2017) 128–134.e2, https://doi.org/10.1016/j.jpeds.2017.05.076.