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BMJ Open Assessment of Diastolic Function during the transitional period and infancy using Serial Echocardiography in a tertiary neonatal unit (DiFuSE): a longitudinal prospective observational study protocol

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ABSTRACT

Introduction There are structural and functional modifications that occur to the neonatal heart immediately after birth. While a number of studies recently have assessed cardiac function in the newborn, there is a dearth of data on diastolic function in the neonatal period during transition and into infancy. The objective of this study is to assess diastolic function in a large cohort of infants to provide normative reference values and to assess the influence of predefined maternal and infant characteristics.

Methods and analysis This is a single-centre observational study of babies born at 35 weeks of gestation and above, involving echocardiography in the first 2 DOL and longitudinal follow-up of these infants up to 18 months of age. The echocardiographic measurements to assess diastolic function used in this study include conventional echo measures, novel echo measures using tissue Doppler imaging and deformation measures using 2D speckle tracking echocardiography.

Ethics and dissemination The protocol was approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals. The findings from this study will be disseminated in peer-reviewed journals and during scientific conferences.

Trial registration number NCT06200519.

INTRODUCTION

Cardiac functional assessment during the transitional period (first 48 to 72 hours of life) is an increasing area of interest in neonatal care. There are established reference values for measures of systolic function in day of life (DOL) 1 and in the first year, including novel echocardiographic measures such as tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE) to evaluate deformation and rotational characteristics of the myocardium.¹ The parameters that reflect normal diastolic function

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ One of the strengths of Diastolic Function during the transitional period and infancy using Serial Echocardiography is that it will have a large sample size in each of the cohorts and has been powered to assess if there is an influence of different infant and maternal characteristics on diastolic function in this population.
- ⇒ The longitudinal aspect of the study means that any changes found can be followed to see when or if they normalise.
- ⇒ A limitation of this study includes the risk that participants may be lost to follow-up.

in the neonatal population have also been explored; however, this has focused more on the preterm neonates and with relatively small sample sizes (ranging from 20 to 110) in term neonates.²⁻⁶

There are structural and functional modifications that occur to the neonatal heart immediately after birth. Due to the sudden drop in pulmonary vascular resistance and increase in systemic vascular resistance, there is a progressive decrease in right ventricular (RV) wall thickness and growth in left ventricular (LV) mass after birth.³ Endomyxial collagen type I decreases with increasing gestation; however, the term neonate still has a relatively high total collagen content when compared with the paediatric and adult population.⁷ This has a significant impact on ventricular compliance, affects all three filling phases of diastole (early filling, diastasis and atrial filling) and is reflected as decreased myocardial velocity measured on TDI during the



transitional period.^{7 8} A study assessing diastolic function in a small cohort of preterm infants found that the peak flow velocity of early diastole (Evmax) at the mitral valve at 6 hours of life was similar to that of fetal values of the same gestational age and progressively increased over the next 48 hours.⁷ This intrinsic diastolic dysfunction (DD) during transition results in a limited ability to increase cardiac output (CO), which occurs predominantly by increasing heart rate. This may paradoxically decrease CO by reducing the end-diastolic ventricular filling time and preload.⁹ Therefore, understanding the mechanism of cardiac (dys)function is necessary to optimise management.

Up to 20% of preterm infants have some degree of DD on echo and LV DD in the first 12 hours after birth has been shown to be independently associated with the need for mechanical ventilation in DOL 1.^{6 10} Furthermore, LV DD was found to be a risk factor for the development of bronchopulmonary dysplasia, especially in infants under 28 weeks gestational age at birth.¹¹ It is a known negative prognostic indicator in infants and children with structural heart disease.¹² In term infants with neonatal encephalopathy (NE), early DD is also found to be present and is found to slowly resolve at around DOL 4.¹³

There are many factors that can affect diastolic function in this early transitional period. There has been some evidence of mode of delivery impacting transitional cardiac mechanics. Delivery by caesarean section has been shown to affect diastolic function on DOL 2, although these changes were not shown to persist.⁴ Maternal diabetes affects cardiac function in the term neonate, irrespective of whether there was good glycaemic control during the pregnancy.^{14 15} Another factor shown to affect cardiac function during the early neonatal period is birth weight (BW), being small for gestational age (SGA) and being large for gestational age. A previous study looked at 24 term infants who had evidence of fetal growth restriction and SGA at birth and found that these infants had systolic and diastolic ventricular dysfunction during the transitional period.⁵ Infants born via the use of assisted reproductive technologies (ART) have a degree of cardiovascular remodelling that can persist into infancy¹⁶ and also a difference in functional parameters in the newborn period.¹⁷

The objective of this study is to assess diastolic function parameters in a consecutive sample of late-preterm and term neonates and to assess the influence of predefined antenatal, intrapartum, maternal and neonatal factors on cardiac function, both in the first few days of life (the transitional period) and longitudinally, over the first year of life in these infants.

Study objectives and outcomes

Infants enrolled in the study will be assigned to one of the following groups based on their presentation, antenatal history, clinical exam and/or diagnosis within the first 18 hours of life.

Study groups

1. Controls (infants who do not fit into any of the below groups).
2. Transient tachypnoea of newborn (TTN).
3. Maternal gestational diabetes mellitus (GDM) or pre-existing diabetes mellitus (DM).
4. SGA: defined as BW <10th centile post-natal.¹⁸
5. Mild NE.
6. Moderate and severe NE receiving therapeutic hypothermia.

The six groups are mutually exclusive, meaning that infants can only be assigned to one group. The control group includes only infants who do not meet the criteria for any of the other five groups (ie, no TTN, no maternal GDM/DM, no SGA and no NE). Infants in any of the condition-specific groups (groups 2 to 6 above) must not have any of the conditions that define the other groups.

Primary objective

To assess whether diastolic functional parameters on DOL 1 and 2 are lower in each of study groups two to six when compared individually to the control group. No comparisons will be made between groups two and 6.

Secondary objectives

1. To assess whether the following maternal characteristics are associated with diastolic functional parameters in the control group:
 1. Maternal pre-eclampsia.
 2. Pregnancy conceived by ART.
 3. Mode of delivery: vaginal delivery (VD), VD with instrumentation, emergency/elective caesarean section.
2. To assess whether the following infant characteristics are associated with diastolic functional parameters in the control group:
 1. Gestational age at birth: 35–36⁺⁶ gestation group.
3. To assess whether any differences in diastolic functional parameters found during DOL 1 and 2 persist into infancy (6–9 months of life, 12–18 months of life).
4. To assess if there are differences in clinical parameters (growth, hospital admissions) between the study groups in infancy (6–9 months of life, 12–18 months of life).

METHODS AND ANALYSIS

Study design

This is a single-centre longitudinal prospective observational cohort study, which will take place in the neonatal unit and post-natal wards of Cork University Maternity Hospital (CUMH), a tertiary neonatal centre in Ireland. Recruitment for this study will take place over an approximate 18 month period from February 2024 until July 2025. This timeframe ensures that a large number of participants will be captured, and it also allows time for the longitudinal follow-up of all the recruited participants. Follow-up will continue for approximately 12 to 18 months beyond the date that new recruitment has

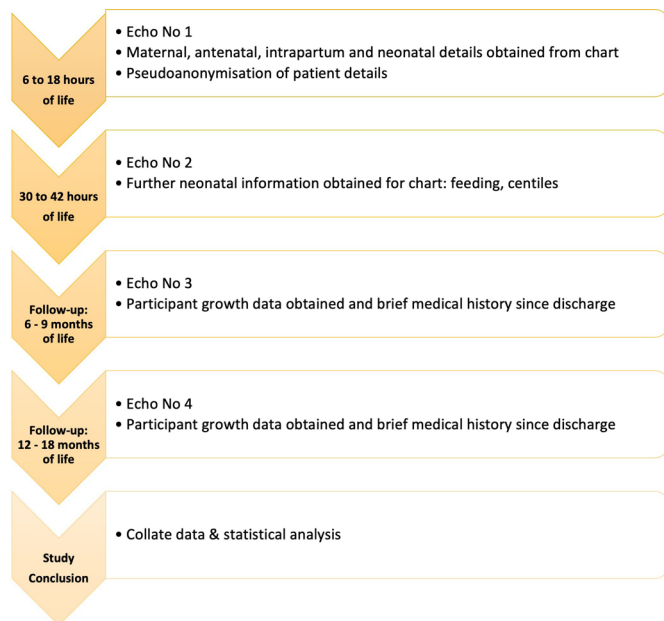


Figure 1 Study timeline.

ceased. The longitudinal follow-up scans will take place in the outpatients' department of CUMH and in the Irish Centre for Maternal and Child Health Research (INFANT) centre in Cork University Hospital. We expect to enrol approximately 250 neonates during the 18 month recruitment period based on annual deliveries at CUMH. The study timeline and timing of the echos are outlined in [figure 1](#).

Participant selection

All neonates meeting the inclusion criteria and who do not meet any of the exclusion criteria ([table 1](#)) will be recruited consecutively during the study period. Informed consent will be obtained from the parent prior to inclusion.

Recruitment

When a potentially eligible neonate is identified, his/her parent(s) or legal guardian(s) will be approached by study personnel, either antenatally or within the first 18 hours after birth if possible. A parent information leaflet will

Table 1 Inclusion and exclusion criteria for the Diastolic Function during the transitional period and infancy using Serial Echocardiography study

Inclusion criteria	Exclusion criteria
Birth at 35 weeks gestation or above	Any apparent congenital anomalies
Informed consent obtained	Any known chromosomal abnormalities
	Any known congenital structural heart disease (excluding PDA, ASD/PFO or VSD)
ASD, atrial septal defect; PDA, patent ductus arteriosus; PFO, patent foramen ovale; VSD, ventricular septal defect.	

be given, and the study will be explained to them in full. Ample opportunity will be given to discuss any queries/questions regarding the study. Once the parent(s)/guardian(s) indicate their willingness for their infant to participate, written informed consent will be obtained, and the neonate will be enrolled in the study.

Compensation

There will be no direct compensation provided to the participants or their parents for participating in this study. On returning for the 6–9 months and 12–18 months echoes, parents are provided with a parking voucher for free parking in the hospital car park. There will be no cost implications to the health service executive or to the participants.

Withdrawal of participants from the study

Participation is voluntary, and parents may withdraw their infant from the study at any time and for any reason. All withdrawals will be documented, and the reasons recorded where possible. Parents will be informed that their decision not to continue participation at any stage will not restrict their own/baby's access to healthcare services normally available to them.

Data collection

Echo 1: 6 to 18 hours of life; echo 2: 30 to 42 hours of life

The initial echo will be completed within the first 6 to 18 hours of life approximately (DOL 1 scan) to assess diastolic function. At approximately 30 to 42 hours of life (DOL 2 scan), the echo will be repeated to reassess diastolic function. Both scans will also involve a comprehensive structural assessment to confirm normal anatomy. The scans will be reviewed within a reasonable time period by a consultant paediatric cardiologist, in compliance with the recommendations of the American Society of Echocardiography (ASE), the European Association of Echocardiography (EAE) and the Association for European Paediatric Cardiologists (AEPC).^{19 20}

Echocardiographic scans will be completed using the Vivid E95 ultrasound machine using a 6-MHz or 12-MHz transducers (GE Vingmed Ultrasound AS, Horten, Norway). Post-procedure analysis will be completed using EchoPACs software.

Maternal and neonatal data

Pseudonymised maternal and neonatal data will be extracted from the electronic healthcare records. Data collected will include:

1. Birth details: date and time of birth, gestation, mode of delivery, septic risk factors, BW and centile.
2. Maternal details: antenatal complications, antenatal scans, maternal co-morbidities including medications.
3. Neonatal details: feeding method, clinical exam details and diagnosis, respiratory support details and results of investigations.

Long-term follow-up

All participants will be invited to return for follow-up targeted echocardiography assessments to evaluate function at approximately 6–9 months and 12–18 months of life. At each of these visits, the following infant details will also be collected from the parents and the medical notes:

1. Current weight and height.
2. Details of any interim hospital admissions, serious illnesses or medical issues.
3. Current medications.

Data storage

Both hardcopy and electronic data will be stored for this study, which will be coordinated by INFANT and UCC at CUMH. Pseudonymised data will be stored for data analysis in password-protected excel spreadsheets on a secure web-based database on UCC/INFANT servers. Computers used to collate the data will have limited access measures by encryption codes, username and passwords.

Outcome measures: measurements for the assessment of diastolic function

When assessing diastolic function, the main factors involved are impaired LV relaxation, reduced restoring forces and increased diastolic stiffness.²¹ Hence, the rationale behind the measurements used to assess diastolic function includes direct or indirect evaluation of these factors. Diastolic function has traditionally been assessed and graded using patterns of mitral filling.^{22 23} In neonatology, recent studies have assessed DD in small cohorts using TDI to calculate the velocity of the movement of the myocardial wall or STE to evaluate ventricular deformation.^{4 8 24–26}

The echocardiographic measurements to assess diastolic function to be used in this study are:

Conventional echo measures of diastolic function

1. Mitral and tricuspid E/A ratios and deceleration times.
2. Pulmonary venous systolic/diastolic ratios.

Novel echo measures of diastolic function

1. TDI: peak velocity of myocardial wall movement in diastole (e' and a') for the RV and LV free walls and the interventricular septum (IVS).
2. Mitral and tricuspid E/e' ratios.
3. Deformation measures using 2D STE, including:
 1. Early and late diastolic strain rates (SRe and SRa, respectively) for the RV and LV free walls and the IVS
 2. Peak atrial longitudinal strain (PALS) measures.
 3. Circumferential and radial LV deformation measures
 4. Measures to assess the myocardial twist of the LV.

Other echo factors to be recorded are measurements of the sizes of the ventricles and vessels and relevant z-scores, measures to assess systolic function, pulmonary hypertension assessment, patent ductus arteriosus (PDA) evaluation and degree of shunting through either PDA or patent foramen ovale, as all of these can influence diastolic functional assessment.

Primary outcome measure

The primary outcome for this study is the peak velocity of myocardial wall movement in diastole e' for the LV free walls (LV TDI e').

Secondary outcome measures

The secondary measures are all other echocardiographic measurements to assess diastolic function (described below). They will also include other infant details such as growth measures and details of any hospital admissions or illnesses obtained at the follow-up visits (6–9 months and 12–18 months).

E/A ratio

Indirect assessment of diastolic performance can be assessed by obtaining Doppler traces of the biphasic blood flow pattern across the mitral and tricuspid valves in the four-chamber apical view.^{27 28} The peak velocity (Vmax) of the early wave (E-wave) and peak velocity of the second phase of atrial contraction (A-wave) can be calculated and used to assess the E/A ratio. If there is mild DD, the majority of the filling will occur during the A-wave, resulting in a higher A-wave peak velocity (AVmax) or an E/A ratio less than one.^{27 28} If the DD worsens, the E-wave peak velocity (EVmax) will become the dominant waveform again and severe DD will result in an E/A ratio >2 and >2.1, for mitral and tricuspid flow, respectively.²³

Myocardial muscle velocity using TDI

TDI can be used on apical four-chamber view to assess the systolic and diastolic myocardial velocities across the IVS, RV free wall and LV free wall, moving from the base to the apex.^{8 27} Assessment of myocardial muscle velocity using pulsed-wave TDI (pwTDI) has allowed for a non-invasive measure of diastolic function, by using the principles of Doppler to measure the peak velocity of myocardial wall movement in systole (s') and diastole (e' and a').^{8 27 28} The e' wave is a measure of the ventricular relaxation and has been shown to be a good early marker of DD in adults and found to correlate well with invasive measurements.^{25 29 30} It has been shown to more accurately detect LV DD than conventional pulsed-wave Doppler in term infants with perinatal asphyxia.²⁹ It also allows calculation of the isovolumic relaxation time (IVRT)—a component in the myocardial relaxation process—and the isovolumic contraction time (IVCT).⁷ Pulsed-wave TDI will be used to obtain peak myocardial wall velocities and obtain s', e' and a' measurements for the RV and LV free walls and the IVS.

Similar to the peak velocities, pwTDI can be used to measure systolic and diastolic time parameters and thus calculate the myocardial performance index (MPI) or Tei index—a quantitative measure of global ventricular function that is independent of heart rate and blood pressure.^{4 5 27}

$$\text{MPI} = (\text{IVRT} + \text{IVCT}) / \text{ejection time}$$

E/e' ratio

The E/e' ratio can be calculated at the LV and RV by dividing the mitral and tricuspid E velocity by the mitral and tricuspid annular e' velocity.^{21 31} The mitral and tricuspid E/e' ratio can be used to predict LV and RV filling pressures, respectively.²¹ The mitral E/e' ratio may be elevated due to slowed LV relaxation or increased mitral inflow (secondary to increased pulmonary pressures).¹¹

Deformation imaging

Deformation imaging has come into practice in neonatology in the last decade and refers to a change in shape of the myocardium in multiple planes from its baseline shape at end-diastole to its deformed shape at end-systole.⁸ The two measures calculated are myocardial strain (ϵ) and strain rate (SR). The strain is expressed as a percentage change from the baseline. SR is defined as the speed at which deformation occurs and is thought to be a more accurate representation of intrinsic myocardial contractility.³² SR can be used as a measure of diastolic function by measuring the rate at which the deformed myocardium returns to the baseline.²⁷ Two-dimensional (2D) STE will be used to calculate strain and SR in the Diastolic Function during the transitional period and infancy using Serial Echocardiography (DiFuSE) study.

STE

Deformation imaging using 2D STE involves tracking the movement of fixed tissue markers called speckles within the myocardial wall.³² Specialised programmes can calculate strain and SR values for different regions of the myocardial wall, and this method is not dependent on the angle of insonation, as the speckles can be tracked in any direction.³²

Atrial strain measures as a marker of atrial function, specifically PALS, have gained traction in adult studies focusing on heart failure and mitral valve dysfunction in the last few years.^{33 34} Studies in premature infants have identified PALS as a feasible measure of left atrial function.³⁵ It has been used as an indicator of diastolic function and has been used to differentiate between intrinsic DD and DD secondary to pulmonary venous hypertension when assessing cardiac findings during early respiratory disease of the preterm infant.¹⁰

There is a unique pattern of rotation to the LV. This is due to the arrangement of the circumferential and longitudinal fibres of the LV myocardium in the mid-wall layer and the endocardial and epicardial layers, respectively.³⁶ The LV base rotates in a clockwise motion, and the apex rotates in an anticlockwise direction, which effectively results in a myocardial twisting motion.^{36 37} The mitral e-wave component of diastole was previously thought to have been a 'passive' filling of the LV; however, it is more likely due to the negative pressure gradient created by the recoil of the LV from the twisting motion during systole.^{36 37} Therefore, measurements of the twist, LV twist rate and the LV untwist rate will be included.³⁸

Pulmonary venous systolic/diastolic ratio (S/D ratio)

Unlike most venous flow in the body, pulmonary venous flow has a pulsatile nature. This biphasic flow pattern has been attributed to a combination of the changes in left atrial pressure that occur during diastole and systole, the suction force created by LV relaxation and the transmission of the RV pressure pulse through the pulmonary vessels.^{22 39} The resultant biphasic waveform has three components: the early systolic flow wave (S1) caused by the drop in atrial pressure, the mid-late systolic flow (S2) and the diastolic component (D).²² The ratio between the peak systolic and diastolic velocities (S/D ratio) can be used as one marker to assess diastolic function.²²

Statistical methods

Sample size justification

The primary outcome for this study is the LV TDI e' and the primary objective is to construct 95% reference intervals for this outcome for each of the groups. As the outcome is normally distributed, reference intervals using the normal distribution method will be calculated. To construct a 95% reference interval for each group, a sample size of 53 infants per group is required. This is based on the assumption that the width of the 90% CI for the reference interval limits is no more than 0.2 times the width of the reference interval.⁴⁰ This sample size would also give a power of 98% to detect a large effect size (Cohen's $d=0.8$) in an independent samples t-test comparing the mean of the primary outcome in one of the groups with that in the control group.⁴¹

Statistical analysis

At each timepoint separately, 95% reference intervals will be constructed for the primary outcome and the secondary outcomes assessing diastolic function using the normal distribution method. Unadjusted and adjusted linear regression models will be used to compare the primary outcome (and continuous secondary outcomes) between the study groups. Binary secondary outcomes will be compared between the study groups using unadjusted and adjusted logistic regression models. Regression models will also be used to investigate the effect of maternal and infant characteristics on outcomes in the control group. Linear and logistic mixed models will be used to investigate if there are changes in the primary and secondary outcomes over time and if those changes depend on the study group or maternal/infant characteristics. All tests will be two-sided and a p value ≤ 0.05 will be considered to be statistically significant. Statistical analysis will be performed using the latest versions of IBM SPSS Statistics and Stata.

DISCUSSION

This study will be one of the first to assess diastolic function using conventional and novel echocardiographic methods on such a large scale in this population. This knowledge could help establish what is considered to be



normal in different settings in the neonatal population and thus what is abnormal. The longitudinal aspect of this study will help to add to the whole clinical picture of these infants by establishing whether these changes in the neonatal period persist over time.

Status of study

Recruitment for the study has been ongoing since 12 February 2024; however, no data has been analysed. Prospective recruitment is anticipated to continue for another 18 months (until end of June 2025). The end of the study will be after completion of Echo No four for the last participant; approximately 12–18 months after their recruitment.

Ethics and dissemination

The study is conducted following the version Fortaleza, Brazil, October 2013 of the Declaration of Helsinki 1964. The Protocol, Patient Information Leaflet and the Informed Consent Form have been approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals (CREC) before commencement (approval letter ECM 4 (o) 24/10/2023 & ECM 5 (2) 07/11/2023 & ECM 3 (ff) 05/12/2023). On 8 November 2023, protocol version one was approved by the CREC (approval letter ECM 4 (o) 24/10/2023 & ECM 5 (2) 07/11/2023), and on 29 November 2023, an amendment to the Patient Information Leaflet was approved by the CREC (ECM 4 (o) 24/10/2023 & ECM 5 (2) 07/11/2023 & ECM 3 (ff) 05/12/2023).

The scans will be reviewed within a reasonable time period by a consultant paediatric cardiologist, in compliance with the recommendations of the ASE, EAE and AEPC. The trial is sponsored by University College Cork (College Road, Cork T12 K8AF, Ireland, +353 (0)21 490 3000). The sponsor is not involved in study design; collection, management, analysis and interpretation of data; writing of the report; and the decision to submit for publication. The findings from this study will be disseminated in peer-reviewed journals and during scientific conferences.

Contributors IS wrote the manuscript. IS, ED, NB and DF were involved in the study conception, design and developing the research protocol. VL wrote the statistical analysis description and sample size justification during the design phase of this study. All the authors were involved in the acquisition of ethical approval and in the review of this manuscript. IS will be responsible for recruitment and implementation of the study, acquisition of echocardiography, post-echo processing of images and other data collection. ED is responsible for the overall content as guarantor. The final manuscript has been reviewed by all the authors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Clinical Research Ethics Committee of the Cork Teaching Hospitals (CREC). CREC Review Reference Number: ECM 4 (o) 24/10/2023 & ECM 5 (2) 07/11/2023 & ECM

3 (kkk) 10/12/2024. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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