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Serial measures of cardiac performance using tissue Doppler imaging velocity in preterm infants <29 weeks gestations

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ABSTRACT

Introduction: Tissue Doppler imaging (TDI) is a useful marker of myocardial performance in preterm infants. We aimed to demonstrate serial changes in TDI velocity in preterm infants <29 weeks gestation, to assess the impact of inotropes and a haemodynamically significant patent ductus arteriosus (hsPDA).
Methods: This was a prospective observational study of preterm infants <29 weeks gestation. Echocardiography was performed at days 1, 2, 5–7 and at 36 weeks, or before hospital discharge. Infants with hsPDA's on day 5–7 and those who received inotropes in the first week of life were not included in the Reference Cohort. Systolic (s`) and diastolic (e` and a`) velocity waves were assessed at the mitral and tricuspid annulus and basal septum.
Results: One hundred and thirty nine infants with a mean (SD) gestation and birthweight of 26.7 (1.5) weeks and 946 (247) grams were enrolled. The 66 infants (47%) in the Reference Cohort demonstrated an increase in functional parameters with increasing age [LV s`, Septal s`, and RV s`, Day 1–36 weeks: 2.8 (0.6) to 4.7 (1.0), 2.4 (0.6) to 4.6 (0.8), 3.6 (0.6) to 6.9 (1.0) cm/s respectively; all $p < 0.05$). The 24 infants who received inotropes had lower LV e` [2.9 vs. 3.6 cm/s], Septal e` [2.3 vs. 2.8 cm/s] and a` [3.2 vs. 3.9 cm/s], and lower RV a` [3.3 vs. 3.9 cm/s] on Day 1 (all $p < 0.05$). Fifty five infants had a hsPDA on Day 5–7, demonstrating higher LV [4.7 vs. 4.0 cm/s] and Septal e` [3.9 vs. 3.3 cm/s], and a higher LV E/e` [13 vs. 10] (all $p < 0.05$).
Conclusion: Extremely preterm infants display a gradual increase in tissue Doppler velocities from birth until 36 weeks corrected age. The presence of a hsPDA increases diastolic TDI velocities. Infants requiring inotropes have lower diastolic myocardial velocities on Day 1.

1. Introduction

Tissue Doppler velocity imaging (TDI) is an echocardiography modality which measures the velocity of muscle movement by direct Doppler of the myocardium. The high velocity signal generated by the movement of blood is filtered out, facilitating the measurement of the lower velocity Doppler signals of the muscle walls [1]. TDI can measure systolic and diastolic function of the basal area of the left and right ventricles, in addition to the septum [2–4]. Recent studies have demonstrated that TDI is a feasible and reliable technique in the assessment of heart function in premature infants [2,5], and can more accurately characterise myocardial performance when compared with shortening fraction (SF) and ejection fraction (EF) [6–9].

However, despite the existence of some normative reference values for TDI measurements, particularly over the transitional period [2,10], there is a lack of studies presenting serial data up to 36 weeks post menstrual age (PMA) in extremely premature infants. In addition, the relationship between myocardial function measured using TDI and loading conditions during the transitional period is not fully understood. The impact of important conditions such as hypotension requiring inotropes is lacking evidence. The effect of a haemodynamically significant patent ductus arteriosus (hsPDA) on TDI velocities also warrants further investigation.

We aimed to present TDI velocities and event timings of the left (LV) and right (RV) ventricle in addition to the septum in a Reference Cohort of preterm infants <29 weeks gestation, and assess the impact of certain disease states and loading conditions on those measurements in an additional cohort of infants with certain conditions: requirement for inotropes and a hsPDA. We hypothesised that hypotension requiring inotropes and the presence of a hsPDA would have a significant impact on TDI velocities.

2. Methods

This was a prospective observational study of infants <29 weeks gestation born in the Rotunda Hospital, Dublin, Ireland; a tertiary maternity

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centre catering for up to 9000 births per year. Infants were recruited between July 2014 and June 2016. Preterm infants underwent serial echocardiography assessments on Day 1, Day 2, Day 5–7 and at 36 weeks PMA. Patients were excluded if: they had a suspected or definite chromosomal abnormality or congenital heart disease other than a patent ductus arteriosus (PDA) and a patent foramen ovale (PFO); parents refused consent; or if the infant died within the first week of life.

2.1. Patient cohort

The preterm Reference Cohort consisted of infants born <29 weeks gestation without the need for inotropic support or inhaled nitric oxide (iNO) in the first week of life and without the presence of a hsPDA on echocardiography scan at day 5–7. Infants in the Inotrope Group were defined as any infant in receipt of inotropes over the first week of age for hypotension defined as a systolic, mean and diastolic blood pressure less than the 3rd centile for any given gestation, or at the discretion of the attending neonatologists. Infants in the hsPDA Group were defined as those with a PDA identified on echocardiogram on Day 5–7 with the following features: presence of a PDA diameter > 1.5 mm measured in 2D at the pulmonary end, flow reversal in the descending aorta and a non-restrictive flow pattern in the ductus according to Smith et al. [11]. Of note, treatment of PDA is not attempted in our institution over the first week of age. This is usually carried out beyond the first week of age in infants with ventilator dependence and the presence of a hsPDA as outlined above. In Table 1, the Disease Group refers to infants in the Inotrope Group and those in the hsPDA Group combined.

We recruited a cohort of healthy term infants to act as a comparator group to the preterm cohort at 36 weeks PMA. These infants were defined as birth ≥37 weeks gestation, appropriately grown and born to mothers without significant maternal illness including diabetes, pre-eclampsia, pregnancy induced hypertension, absent/reversed end diastolic flow in the umbilical arteries, and chorioamnionitis. Ethical approval was granted from the hospital research ethics board and informed consent from parents was obtained. We have previously published early tissue Doppler imaging values, RV specific functional measurements and serial deformation measurements on some of infants included in this cohort [2,12,13].

Table 1
Patient demographics and outcomes in the Reference and Diseased Groups.

	Reference Cohort n = 66	Disease Group n = 73	p
Gestation (weeks)	27.2 (1.3)	26.2 (1.9)	<0.001
23 weeks	1 (2)	5 (7)	0.003
24 weeks	3 (4)	14 (19)	
25 weeks	7 (11)	11 (15)	
26 weeks	13 (20)	18 (25)	
27 weeks	16 (24)	15 (20)	
28 weeks	26 (39)	10 (14)	
Birthweight (g)	1023 (243)	875 (230)	<0.001
Multiple pregnancy	22 (33)	32 (44)	0.23
Male gender	40 (61)	39 (53)	0.49
Caesarean section	49 (72)	50 (69)	0.57
5 Minute Apgar score	9 [8–9]	9 [7–9]	0.34
Lowest cord pH	7.32 (0.08)	7.32 (0.09)	0.94
Antenatal steroids			
None	5 (7)	3 (4)	0.54
Incomplete course	11 (17)	16 (22)	
Complete course	50 (76)	54 (74)	
Magnesium sulphate	57 (86)	57 (78)	0.27
Pre-eclampsia	6 (8)	4 (6)	0.74
Surfactant at birth	53 (80)	67 (92)	0.08
Pulmonary haemorrhage	0	8 (11)	0.007
Invasive ventilation days	2 [0 − 10]	9 [2–24]	<0.001
Days on CPAP	28 [19–39]	34 [25–40]	0.021
Postnatal steroids	4 (6)	14 (19)	0.02
Severe IVH (grade 3/4)	9 (14)	14 (19)	0.49
Death before discharge	5 (8)	12 (16)	0.13
Chronic lung disease (in survivors)	22 (36)	41 (66)	0.001

Values are presented as means (SD), medians [IQR] or absolute count (%) unless otherwise indicated.

2.2. Clinical parameters

Antenatal details including: intrauterine growth restriction (IUGR); maternal pre-eclampsia (PET); administration of antenatal steroids and magnesium sulphate were recorded. We collected data on birth and neonatal characteristics including: gestational age; birth weight; resuscitation, Apgar scores at 1 and 5 min of age, and the need for surfactant therapy. Cardio-respiratory characteristics at the time of echocardiography assessments were collected. These included: systolic, diastolic and mean arterial blood pressure, heart rate, mean airway pressure, mode of ventilation, oxygen requirements, oxygen saturation, volume of fluid intake and pH on blood gas analysis. Important outcomes such as pulmonary haemorrhage, days on ventilation, use of postnatal steroids, death before discharge and chronic lung disease (CLD) were collected. CLD was defined as the need for oxygen at 36 weeks PMA.

2.3. Echocardiography

Echocardiography was performed using the Vivid S6 echocardiography system using 7 MHz or 12 MHz multi-frequency probe (GE Medical, Milwaukee, USA) at the following time points: 6–12 h of age; 36–48 h of age; day 5–7 of age and at 36 weeks PMA (or before hospital discharge). The healthy term infants had a single scan performed within the first 48 h of life. All studies were conducted using a standardised functional protocol adapted from recently published guidelines [14]. The scans were stored as raw data in an archiving system (EchoPac, General Electric, version 112, revision 1.3) for later offline analysis. We recorded the presence or absence of a PDA, PDA size, maximum PDA flow velocity, mitral and tricuspid valves E and A wave velocities obtained using pulsed wave Doppler, left ventricular output (LVO), LA:Ao ratio and pulse wave Doppler flow in the descending aorta. Systemic vascular resistance (SVR) was derived using this formula: SVR = mean blood pressure (MBP) / LVO as previously described by Noori et al. [15]. Blood pressure readings were obtained either invasively or non-invasively via cuff. Left ventricular end diastolic diameter (LVEDD) from the parasternal long axis view was also measured.

Tissue Doppler velocities were obtained from the basal segment of the left ventricular (LV) lateral wall, the septum and the right ventricular (RV) free wall using the apical 4 chamber view. The image sector width was narrowed and the depth reduced to focus on the wall of interest to maximise the frame rates [16]. The angle of insonation between the measurement cursor and the direction of myocardial motion was minimised to <20° and no angle corrected was used. The velocities recorded included the peak systolic velocity of the myocardial muscle (s` wave) the peak early diastolic velocity (e` wave) and the peak late diastolic (a` wave) [3,17]. When e` and a` wave fusion occurred, we recorded the result as a single a` wave. From the septal base, we measured the isovolumic contraction (IVCT) and relaxation times (IVRT) as well as the ventricular systolic and diastolic times. We calculated the e`/a` ratio as an additional marker of diastolic performance. Myocardial performance index (MPI, also known as Tei index) was calculated from the LV septal wall using the following formula: (IVRT + IVCT) ÷ Systolic time. We also assessed the E/e` ratio which is the relationship between the atrioventricular E wave on pulsed wave Doppler and the e` wave for the corresponding ventricular wall velocity.

Our group has recently demonstrated the feasibility and reproducibility of TDI-derived measurements in both premature and term infants. Intra- and inter-observer measurements obtained in the preterm population demonstrate minimal bias with intraclass correlation coefficients (ICC) > 0.85 for intra-, and >0.75 for inter-observer values. Similarly, term infant measurements demonstrate excellent