



**TRINITY
COLLEGE
DUBLIN**

Functional Echocardiography in the Preterm infant

Adam James

A thesis submitted to Trinity College Dublin in fulfilment of
the requirements for the degree Medical Doctorate (M.D.)

September 2017

Rotunda Hospital

Supervisors: Prof Afif El-Khuffash

Dr David Corcoran

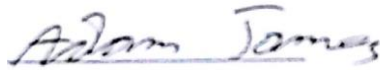
Dr Orla Franklin

Declaration

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work.

I agree to deposit this thesis in the University's open access institutional repository or allow the library to do so on my behalf, subject to Irish Copyright Legislation and Trinity College Library conditions of use and acknowledgement.

Signed



Student Number : 97538116

Date _____ 29th September 2016 _____

Table of Contents

Declaration	ii
Table of contents	iii
List of figures	ix
List of tables	xii
Abbreviations	xiv
Summary	xvi
Dedication	xvii
Acknowledgements	xviii
Research Output	xix
1. Chapter 1: General Introduction	1
1.1 Preamble	1
1.2 Cardiovascular physiology of preterm infants	3
1.3 Transitional Circulation	7
1.4 Clinical assessment of haemodynamics in preterm infants	10
1.5.1 Current techniques of assessing systolic and diastolic function	13
1.5.2 Assessment of Systolic function	13
1.5.3 Assessment of Diastolic function	14
1.6.1 New Methods of Assessment of Myocardial Performance	16
1.6.2 Tissue Doppler Velocities	17
1.6.3 Strain imaging	18
1.6.4 Tissue Doppler Derived deformation imaging	25
1.6.5 Speckle tracking imaging	26
1.7 Twist/torsion	30

1.8.1	Right Ventricular dysfunction and its role in prematurity	35
1.8.2	RV specific functional parameters	36
1.8.3	Fractional Area Change and Tricuspid annular plane systolic excursion	37
1.9	Use in Paediatrics	40
1.9.2	Role in neonates	41
1.10	Reference values	43
1.11	Knowledge gap	44
1.12	Pulmonary hypertension	44
1.13	Patent Ductus Arteriosus (PDA)	45
1.14	Bronchopulmonary Dysplasia	46
1.15	Desirable Qualities of the measurement	47
1.16	Conclusion	48
1.17	Aim	49
1.18	Study Objectives	49
1.19	Hypothesis to be examined	49
2	Chapter 2: Materials and Methods	50
2.1	Patient population and study setting	50
2.2	Clinical parameters	51
2.3	Antenatal History	54
2.4	Delivery details	55
2.5	Measurements at time of Echo	56
2.6	Echocardiography parameters	56
2.6.1	Conventional Echocardiographic parameters	59
2.6.2	RV functional assessment	79
2.6.3	Tissue Doppler Velocities	84

2.7	Tissue Doppler-derived Strain and Strain Rate	86
2.8	Rotational Mechanics	88
2.9	Statistics	92
3	Chapter 3: Feasibility and Reliability	93
3.1	Background	93
3.2	Methods	94
3.3	Results	96
3.3.1	Tissue Doppler derived Strain and Strain rate and RV Function Parameter	96
3.3.2	Feasibility and Reproducibility of Twist measurements	100
3.4	Discussion	103
3.4.1	Feasibility and reproducibility of Tissue Doppler derived Strain and strain rate, RV dimensions and function	103
3.4.2	Feasibility and Reproducibility of LV Rotational Mechanics in Preterm	104
3.5	Conclusion	105
4	Chapter 4: Longitudinal strain and strain rate in preterm infants	106
4.1	Introduction	106
4.2	Methods	107
4.2.1	Study population	107
4.2.2	Echocardiography Assessment	108
4.2.3	Statistical Analysis	110
4.3	Results	111
4.3.1	Image Quality and Measurement feasibility	114
4.3.2	Longitudinal Changes in Function and Dimensions	114
4.3.3	Influence of Gestation, Birthweight, Heart Rate and Systemic Vascular Resistance (SVR) on Day 1 Values	120
4.3.4	Relationship between a PDA on Day 5 - 7 and Functional Measurements	123

4.3.5	Influence of CLD on LV and RV Function at 36 weeks PMA	124
4.4	Discussion	126
4.5	Conclusion	130
5	Chapter 5: Rotational Mechanics	131
5.1	Introduction	131
5.2	Methods	132
5.2.1	Terminology	133
5.2.2	Measurements of Twist, LV twist and untwist rates	135
5.2.3	Statistical Analysis	138
5.3	Results	139
5.3.1	Feasibility and Reproducibility of Twist measurements	141
5.3.2	Longitudinal Rotation, Twist, Torsion, Twist and Untwist values	141
5.3.3	Effect of Clinical Parameters and Correlation between Torsion and LVUTR	147
5.4	Discussion	149
5.4.1	Feasibility and Reproducibility of LV Rotational Mechanics in Preterms	149
5.4.2	Comparison of Rotational Mechanics between Preterm and older Population	150
5.4.3	Effect of Loading Conditions on LV Twist in Preterm Infants	154
5.4.4	Clinical Implications	156
5.5	Limitations	156
5.6	Conclusion	156
6	Chapter 6: RV Fractional Area Change and Systemic blood flow	158
6.1	Introduction	158
6.2	Methods	159
6.2.1	Clinical Demographics	160
6.2.2	Echocardiography	160

6.2.3	Statistical Analysis	163
6.3	Results	164
6.3.1	Relationship between RV FAC and prenatal characteristics	164
6.3.2	Relationship between RV FAC and P/IVH	167
6.3.3	Relationship between RV FAC and a persistent PDA	167
6.4	Discussion	171
6.5	Clinical Implications and Conclusion	174
7	Chapter 7: PDA Severity score	175
7.1	Introduction	175
7.2	Methods	177
7.2.1	Study Design, Setting and Patient Population	177
7.2.2	Clinical Data Collection	178
7.2.3	Echocardiography assessment	178
7.2.4	Statistical Analysis	180
7.2.5	Developing the PDA Severity Score	180
7.3	Results	184
7.3.1	Univariate Analysis of the Echocardiography Parameters	186
7.3.2	PDA Severity Score	188
7.4	Discussion	193
7.5	Limitations	198
7.6	Conclusion	198
8	Chapter 8: Magnesium Sulphate and its influence on haemodynamics during the transitioning period	200
8.1	Introduction	200
8.2	Methods	201
8.2.1	Clinical Demographics	202

8.2.2	Echocardiography Assessment	202
8.2.3	Statistical Analysis	204
8.3	Results	204
8.4	Discussion	210
8.5	Conclusion	212
9	Chapter 9: Conclusion	213
9.1	Introduction	213
9.2	Reliability	214
9.3	Longitudinal changes	214
9.4	Rotation	216
9.5	Patent Ductus Arteriosus	216
9.6	Magnesium Sulphate	217
9.7	Fractional area change and Systemic blood flow	218
9.8	Future Direction	219
9.9	Summary	219

List of Figures

1.1	Diagram of a myocyte in the term and preterm infants.	4
1.2	Graphic depiction of the relationship between ventricular function and afterload.	6
1.3	Foetal and Postnatal circulations	9
1.4	Doppler imaging of the Mitral valve showing the E and A waves	15
1.5	Tissue Doppler derived Strain of the intraventricular septum showing the peak systolic Strain (S)	21
1.6	Tissue Doppler derived strain rate of the septal wall	23
1.7	Speckle Tracking derived Strain of the Left Ventricle	29
1.8	Apical rotation of the Left Ventricle (LV) using Speckle tracking echocardiography	31
1.9	Basal rotation of the Left Ventricle (LV) using Speckle tracking echocardiography	32
1.10	Graphical representation of the net twist of the Left Ventricle (LV)	33
1.11	RV focussed 4 chamber view showing measurement of right ventricular fractional area change	38
1.12	M-mode imaging of the tricuspid valve to give the Tricuspid Annular Plane Systolic Excursion (TAPSE)	39
2.1	M mode imaging through the parasternal long axis of the heart giving Left Ventricle cavity dimensions from which the shortening fraction can be calculated	60
2.2	4-chamber view of the Left ventricle at end systole and end-diastole. 2 chamber view of the Left ventricle at end-systole and end-diastole	62
2.3	Pulsed wave Doppler of the Aortic Valve showing the Velocity Time Integral (VTI)	64
2.4	Pulmonary valve and the Right ventricular outflow tract (RVOT) with corresponding pulsed wave Doppler signal of the RVOT	66
2.5	Mitral Doppler flow pattern	68
2.6	Tricuspid Doppler flow pattern.	70

2.7	Pulmonary venous drainage to the Left Atrium.	71
2.8	Four chamber view of the heart.	72
2.9	Direction of flow across the Patent Ductus Arteriosus (PDA).	74
2.10	Left atrial to aortic ratio (LA:Ao) as measured from the parasternal long axis view	76
2.11	Colour Doppler through the tricuspid valve with tricuspid regurgitation.	78
2.12	Tricuspid annular plane systolic excursion (TAPSE).	80
2.13	Right Ventricular Three-chamber view and Right Ventricular dimension measurement in the four chamber view.	82
2.14	Tissue Doppler velocities of the Left Ventricle, Right ventricle and interventricular septum	85
2.15	Tissue Doppler-derived measurement of strain and strain Rate.	87
2.16	Apical and Basal rotation of the Left Ventricle	90
2.17	Graphic representation of the Twist of the Left Ventricle.	91
3.1	Intra- and Inter-observer variability of Left Ventricle, Septal and Right Ventricle Strain	98
3.2	Bland-Altman graphs for LV torsion twist and untwist.	101
4.1	Longitudinal strain of the Left ventricle (LV), septum and Right ventricle (RV)	118
4.2	Comparison of RV Longitudinal Strain (RV BLS) and RV late diastolic strain rate (RV SRa) in infants with and without Chronic Lung Disease (CLD)	125
5.1	Graphical display of apical rotation, basal rotation and the resultant net torsion of the left ventricle.	134
5.2	Left ventricle (LV) twist and untwist rate	137
5.3	Bland-Altman graphs for LV torsion twist and untwist.	144
5.4	Apical and Basal rotation and LV torsion over the three time points.	145
5.5	LV twist and untwist rate over the three time points.	146
5.6	Relationship between Systolic torsion and diastolic untwist rate across the three timepoints.	148

6.1	Measurement of right ventricular fractional area change.	162
6.2	Correlation between RV FAC and LVO and RV FAC and SVR during the first day of age.	166
6.3	RV FAC in infants with and without P/IVH and infants with and without a PDA on Day 5 – 7.	170
7.1	Echocardiography parameters measured across the three time points between the two groups.	187
7.2	Difference in the PDA severity score between infants with and without CLD/Death (A) and the relationship between the score and the predicted probability of CLD/Death in the entire cohort (B).	190
7.3	Receiver operating characteristics curve of the ability of PDA_{sc} to predict CLD/death.	192

List of Tables

Table 3.1	Reliability of parameters of left, septal and Right Ventricular function and dimensions	99
Table 3.2	Intra- and inter-observer reliability data for the parameters	102
Table 4.1	Clinical parameters at the time of the echocardiogram over the first week of life	112
Table 4.2	Conventional Echocardiography parameters and Markers of pulmonary vascular resistance	113
Table 4.3	LV and Septal Function values over the four time points	115
Table 4.4	RV Function values over the four time points	116
Table 4.5	Longitudinal Changes in Deformation parameters	117
Table 4.6	Longitudinal Changes in Dimension parameters	119
Table 4.7	Correlation between Systemic Vascular Resistance and functional parameters on day 1 of life	121
Table 5.1	Cardiorespiratory characteristics of the infants across the three time points.	140
Table 5.2	Intra- and inter-observer reliability data for the parameters.	142
Table 5.3	Rotation, torsion, twist and untwist rate over the three time points.	143
Table 5.4	Comparison of Rotational Mechanics across different age groups.	152
Table 6.1	Infants Perinatal Characteristics and Outcomes divided by the presence or absence of peri- intraventricular haemorrhage.	169
Table 7.1	Demographics and antenatal details in the two groups.	183
Table 7.2	Distribution of other outcomes between the two groups.	185
Table 7.3	Results of the regression model used to devise the PDA severity score.	189
Table 8.1	Infant Characteristics and Clinical Outcomes.	206
Table 8.2	Difference in cardiorespiratory characteristics and echocardiography parameters between infants with and without MgSO₄ on days 1 and 2.	208

Table 8.3 **Independent effect of MgSO₄ and antenatal steroids on outcome parameters using logistic and linear regression.**

209

Abbreviations

PDA: Patent Ductus Arteriosus

CLD: Chronic Lung Disease

NEC: Necrotising Enterocolitis

ROP: Retinopathy of Prematurity

RDS: Respiratory Distress Syndrome

PVL: Periventricular Leukomalacia

PFO: Patent Foramen Ovale

VLBW: Very Low Birth Weight

PPHN: Persistent Pulmonary Hypertension of the Newborn

IVH: Intraventricular Haemorrhage

PMA: Post Menstrual Age

BP: Blood Pressure

MAP: Mean Airway Pressure

EF: Ejection Fraction

SF: Shortening Fraction

VCfc: Velocity of Circumferential Fibre Shortening

PAAT: Pulmonary artery acceleration time

RVET: Right ventricular ejection time

LVEDD: LV end diastolic diameter

LVESD: LV end systolic diameter

LVPWD: LV posterior wall diameter in diastole

VTI: Velocity Time Integral

LVO: Left Ventricular Output

RVO: Right Ventricular Output

TDI: Tissue Doppler Imaging

STE: Speckle Tracking Echocardiography

SR: Strain rate

BLS: Basal Longitudinal Strain

TAPSE: tricuspid annular plane systolic excursion

FAC: Fractional Area Change

LVTR: LV twisting rate

LVUTR: LV untwisting rate

MRI: Magnetic Resonance Imaging
NICU: Neonatal Intensive Care Unit
LV: Left Ventricle
RV: Right Ventricle
MV: Mitral valve
TV: Tricuspid Valve
PA: Pulmonary Artery
IVS: Interventricular Septum
PVR: Pulmonary Vascular Resistance
SVR: Systemic Vascular Resistance
RVSp: RV systolic pressure
TR: Tricuspid Regurgitation
FPS: Frames per Second
FR/HR: Frame rate: Heart Rate ratio
SD: Standard Deviation
IQR: Interquartile Range
ROI: Region of Interest
MgSO₄: Magnesium Sulphate

Summary

From our research we have shown that myocardial function assessment using tissue Doppler derived strain, strain rate, torsion and fractional area change is both feasible and reliable. We applied these novel echocardiographic markers to assess certain disease states such as assessment of a patent ductus arteriosus, chronic lung disease, treatment with antenatal magnesium sulphate as well as longitudinal follow up over the early neonatal period and found that they may be a useful tool as part of a comprehensive functional myocardial assessment in the preterm population. With the advancement in echocardiography and the continued widespread use for the assessment of the preterm infant these tools may pave the way forward for its clinical use in aiding the diagnosis and management of pathological conditions of preterm infants to improve both morbidity and mortality.

Dedication

I would like to dedicate this thesis to my wife Karen and my three kids Conor, Lily and Ciara

Acknowledgement

I would like to thank my Supervisors, Prof Afif El-Khuffash, Dr David Corcoran and Dr Orla Franklin for their support during my thesis in particular Afif who was a great mentor, friend and support through the whole process and helped me achieve more than I could have ever expected at the start of this journey.

I would like to thank all the premature infants and their parents who always amaze me in their resilience and willingness to help.

My family who remain supportive and caring.

And most importantly to my wife who is the light of my life and is the best support and companion anyone could wish for. To my kids who are always smiling and loving and put everything into perspective. Without all of them this thesis would have been a struggle, but with them it is a blessing.

Research Output from Thesis

- 2016; **Novel Echocardiography Methods in the Functional Assessment of the Newborn Heart.**
Breatnach CR, Levy PT, **James AT**, Franklin O, El-Khuffash A.
Neonatology. 2016 Jun 10;110(4):248-260.
- 2016; **Longitudinal Assessment of Left and Right Myocardial Function in Preterm Infants Using Strain and Strain Rate Imaging**
James AT, Corcoran JD, Breatnach CR, Franklin O, Mertens L, El-Khuffash A.
Neonatology. 2016 Jan;109(1):69-75
- 2016; **Clinical utility of right ventricular fractional area change in preterm infants.**
James AT, Corcoran JD, Franklin O, El-Khuffash AF.
Early Hum Dev. 2016 Jan;92:19-23
- 2015; **A Patent Ductus Arteriosus Severity Score Predicts Chronic Lung Disease or Death before Discharge.**
El-Khuffash A, **James AT**, Corcoran JD, Dicker P, Franklin O, Elsayed YN, Ting JY, Sehgal A, Malikiwi A, Harabor A, Soraisham AS, McNamara PJ.
J Pediatr. 2015 Dec;167(6):1354-1361
- 2015; **The effect of antenatal magnesium sulfate on left ventricular afterload and myocardial function measured using deformation and rotational mechanics imaging.**
James AT, Corcoran JD, Hayes B, Franklin O, El-Khuffash A.
J Perinatol. 2015 Nov;35(11):913-8.
- 2014; **Treatment of Premature Infants with Pulmonary Hypertension and Right Ventricular Dysfunction with Milrinone: A Case Series.**
James AT, Bee C, Corcoran JD, McNamara P, Franklin O, El-Khuffash A.
J Perinatol. 2015 April 35(4): 268-73
- 2014; **Left Ventricular Rotational mechanics in Preterm Infants Less than 29 Weeks Gestation over the First week after birth.**
James AT, Corcoran JD, Franklin O, Mertens L, El-Khuffash A.
J Am Soc Echocardiogr. 2015 Jul;28(7):808-17.
- 2014; **The Effect of Milrinone on Right and Left Ventricular Function when used as a Rescue Therapy for Term Infants with Pulmonary Hypertension.**
James AT, Corcoran D, McNamara P, Franklin O, EL-Khuffash A.
Cardiology in the Young 2016 Jan;26(1):90-9

2014;

Assessment of myocardial performance in preterm infants less than 29 weeks gestation during the transitional period.

James AT, Corcoran D, Jain A, McNamara PJ, Mertens L, Franklin O, EL-Khuffash A.

Early Hum Dev 2014 Oct 29; 90(12):829-835