Pathophysiology of the Systemic Right Ventricle in Hypoplastic Left Heart Syndrome

Bellsham-Revell, Hannah Rosemary

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Pathophysiology of the Systemic Right Ventricle in Hypoplastic Left Heart Syndrome

Dr Hannah Rosemary Bellsham-Revell

2013

Thesis submitted to King’s College London for the degree of Doctor of Medicine (MD res)

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Abstract

**Background:** Hypoplastic left heart syndrome (HLHS) describes a spectrum of underdevelopment of the left heart, rendering it incapable of supporting the systemic circulation. Improved results from Norwood palliation mean more children are surviving into later childhood. The assessment of right ventricular (RV) function is an important prognostic factor, but is complicated by wide heterogeneity and complex geometry. Novel MRI and echocardiographic techniques are non-invasive and may offer insight into the pathophysiology of the systemic RV.

**Methods:** Current methods for assessing the RV were reviewed. MRI and echocardiography were used and compared prospectively in HLHS patients to investigate RV performance and changes in ventricular volumetry across the palliative stages. The novel approach of pre-Fontan assessment using MRI and central venous pressure (CVP) measurement alone was compared to the current literature.

**Results:** Echocardiographic subjective assessment of RV function in HLHS had little concordance with MRI ejection fraction, showing the limitation of using this method alone. MRI demonstrated significant RV volume unloading after hemi-Fontan, with a shift of the Starling curve suggesting improved contractility. The novel pre-Fontan assessment showed no difference in outcomes from the published literature. Tissue Doppler time intervals were significantly different in HLHS patients compared to normal hearts. Differences were also seen in
tissue Doppler indices and speckle tracking derived strain between those with a significant residual left ventricle and those without.

**Conclusions:** Novel MRI and echocardiographic techniques give unique and reproducible insights into the morphologic and functional development of the systemic RV across the stages of surgical palliation. Important differences between the morphological subtypes were also noted. Based on this MD thesis, reliable, easy to use, reproducible and non-invasive screening tools have been established, validated and used for longitudinal follow-up. These techniques may also lead to improved follow-up: predicting, or possibly preventing systemic RV failure.
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I would also like to acknowledge all the families and children who have very kindly given permission for their child’s heart to be studied in the hope that we may learn more about this condition. It has been an honour to follow these children through the palliative stages and they have been a source of true inspiration, in particular the first HLHS patient I met, David, to whom this is dedicated.
Publications arising from thesis

CHAPTER 10
*both authors equally contributed to that publication

CHAPTER 11

CHAPTER 12
Statement of Conjoining Work

This thesis is the primary work of Dr Hannah Bellsham-Revell. Chapters 5, 7 and 8 include brief descriptions of work from other papers and Chapter 15 on future directions briefly describes work in the latter paper.

CHAPTER 5, CHAPTER 8

CHAPTER 7

CHAPTER 15
Chapter 1 - Introduction

In a normal heart the right ventricle (RV) pumps blood in the low-pressure pulmonary circulation. In some congenital heart diseases the RV is required to take over the role of the pump for the high-pressure systemic circulation. The fibre orientation, contraction pattern and geometry of the RV are not designed to operate at such high pressures for a sustained period of time. Although a degree of adaptation can occur (1), over time this ‘systemic right ventricle’ will begin to fail (2).

Better understanding of the anatomy and physiology of this systemic RV will enable earlier detection of failure and the ability to better design and tailor treatments. Assessment of the size and function of the RV has always been a challenge due to its complex geometry and therefore methods for assessment of function commonly performed on the left ventricle (LV) cannot simply be applied to the RV.

Hypoplastic left heart syndrome (HLHS) describes a spectrum of left heart hypoplasia rendering it unable to support the systemic circulation. There is no curative procedure, but a three stage palliative approach is used to create a single systemic RV to support the systemic arterial circulation. The systemic veins are anastomosed surgically to the pulmonary arteries to provide pulmonary arterial blood flow. This “Fontan” circulation thus has the systemic and pulmonary venous return in series with a functionally single systemic ventricle, in contrast to the normal circulation where there are both sub-pulmonary and sub-systemic ventricles.
HLHS was universally fatal until the Norwood procedure was developed in America in the 1980s, and implemented in the UK in the early 1990s. There is therefore a cohort of patients who are entering their teenage years, when the systemic RV has been observed to deteriorate in the context of other single ventricle palliations. Approximately 120 Norwood procedures are performed in the UK each year(3). With improved intensive care and surgical experience, more patients are surviving (4). RV function is known to be of prognostic significance (5) and it is therefore important to better understand the complex physiology and further develop assessment techniques to improve knowledge of why and when the systemic RV fails which may in turn, improve management.

The ideal assessment tool for such patients would be readily available, non-invasive, accurate and reproducible. After conductance catheterisation, the most accurate and reproducible non-invasive method of assessing RV systolic function is currently magnetic resonance imaging (MRI) which can compute ventricular volumes, ejection fraction and blood flow (6). However, this is not always readily available and requires general anaesthetic in most children younger than 10 years. Echocardiography is available and non-invasive and can additionally offer information on regional and diastolic function but data to validate the accuracy and repeatability of the technique to assess the RV is limited in the setting of paediatric congenital heart disease with a systemic RV.

The pathophysiology of the systemic RV in HLHS is investigated in this thesis using MRI and echocardiography. The current available techniques for the
assessment of the RV are reviewed and novel echocardiographic measures are investigated.
Chapter 2 - The Right Ventricle

INTRODUCTION
The components of the heart are named after their morphology rather than their position in the chest, as the morphology is more important physiologically than their anatomical position. The most reliable indicator of atrial morphology is considered to be the morphology of the atrial appendages. However, identification of appendage morphology may be difficult in clinical practice.

The ventricles have several differentiating features, some of which are easily visible on basic imaging modalities such as echocardiography, whereas other features can only be truly shown post-mortem (Table 1)

Table 1 Differences in ventricular morphology (7-9)

<table>
<thead>
<tr>
<th>Embryology</th>
<th>Right Ventricle (RV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Originates from the primary heart field</td>
<td>Originates from the secondary heart field</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Atrioventricular Valve Morphology</th>
<th>Left Ventricle (LV)</th>
<th>Right Ventricle (RV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usually two leaflets</td>
<td>Usually trileaflet (variations, can be two leaflets in children and 4 in older people)</td>
<td></td>
</tr>
<tr>
<td>No septal attachments, comparatively large papillary muscles</td>
<td>Septal attachments, relatively small papillary muscles</td>
<td></td>
</tr>
<tr>
<td>More basal position of AV valve</td>
<td>More apical position of AV valve</td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Geometry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bullet shaped – conforms more easily to mathematical models</td>
<td>Has inlet, apical trabecular and outlet components – highly heterogenic with variation in geometry making fitting to mathematical models challenging</td>
<td></td>
</tr>
<tr>
<td><strong>Trabeculations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fine trabeculations, oblique, smooth septal surface</td>
<td>Coarse trabeculations (often straight), moderator band</td>
<td></td>
</tr>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td></td>
</tr>
<tr>
<td><strong>Outlet</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic mitral continuity</td>
<td>Leaflets of pulmonary valve supported by muscular infundibulum</td>
<td></td>
</tr>
<tr>
<td><strong>Coronary Supply</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generally supplied by two coronary arteries, the anterior descending and circumflex</td>
<td>Generally from one coronary artery, the right coronary artery</td>
<td></td>
</tr>
</tbody>
</table>
**Conduction System**

| Left bundle has superior (to the superior papillary muscle group - anterolateral), middle and inferior (to the inferior papillary muscle group – posteriomedial) radiations | Right bundle branch has superior radiation (runs via septal and moderator bands to anterolateral papillary muscle group of RV) |

**FIBRE ORIENTATION**

There have been many attempts over the years to describe the complex myoarchitecture of the heart, from dissection to diffusion tensor magnetic resonance imaging. Current thinking (10,11) describes three layers of muscle fibres in the normal heart - subepicardial, middle and subendocardial (the middle layer is only seen in the LV). Effective contraction is dependent on the inter-relation of these layers.

**Subepicardial layer:** Fibres running obliquely across the interventricular groove present across both ventricles

**Middle layer:** Circular muscle fibres, not found in the RV

**Subendocardial layer:** Longitudinal fibres passing through vortices inserting in three places: atrioventricular and arterial orifices, membranous interventricular septum and the papillary muscles

Figure 1 shows the normal myoarchitecture of the human RV and LV in a post-mortem specimen as well as the average geometry of a canine heart (created from an atlas of canine hearts using MRI diffusion tensor imaging). The latter is
currently used for input into computational models of the human heart as in-vivo diffusion tensor imaging is not yet ready for clinical use. The normal pattern of RV contraction is predominantly longitudinal compared to the normal circumferential pattern of the LV, which is reflected in the normal fibre direction with the middle layer of circular fibres only found in the normal LV.

Figure 1 Normal myoarchitecture in the human heart and average geometry from diffusion tensor ex-vivo canine hearts

The myoarchitecture is not fixed, as can be seen with patients after the Mustard/Senning operation for transposition of the great arteries (TGA) or patients with tetralogy of Fallot (TOF) (12). After atrial switch surgery in patients with TGA, a change was seen in the contraction pattern from predominantly longitudinal (normal RV pattern) to predominantly circumferential (normal LV pattern) (1). When post-mortem specimens of patients with TOF were studied, changes were seen in the myoarchitecture: the subepicardial layer was more oblique in patients with TOF and in these hearts a middle layer was present in
both the LV and RV, compared to only being present in the LV of normal hearts. Figure 2 (12) shows the changes in the myoarchitecture from the normal heart.

**Figure 2** Changes in the myoarchitecture from the normal heart (A – front and B – back) to a heart with TOF (C – front, D – back) and a heart with TOF with pulmonary atresia (E – front, F - back) (12).

**RIGHT VENTRICULAR ADAPTATION**

**General Considerations**

The LV is designed structurally and physiologically to support the high-pressure systemic circulation (average adult systemic blood pressure is 120mmHg systolic). The RV has a different morphology and physiology, which is better suited to supporting the lower pressure pulmonary circulation (normal RV pressure is approximately 20mmHg). During fetal life the RV supports the systemic circulation and after birth it initially faces systemic pressures until the
pulmonary vascular resistance falls. It is thought that the different embryological origins of the LV and RV affect the potential for adaptation to changes in pressure and volume load (13).

**Contraction Pattern**

LV contraction consists of circumferential and longitudinal shortening, as well as torsion caused by the anti-clockwise movement of the apex against the clockwise movement of the base (14). In the RV, the inlet and trabeculated myocardium contract first, followed by the infundibulum (15). This creates an almost ‘peristaltic’ movement of blood (16). There is no middle layer and so relies more on the longitudinal contraction.

**Pressure-Volume Relationship (Figure 3)**

The pressure-volume relationship of the RV also significantly differs from that of the LV and is far more load dependent. Isovolumic times are less well defined in the RV than the LV leading to a more trapezoid shape pressure-volume relationship. This relationship is efficient when coupled with a low-pressure circuit, but becomes less so when afterload is persistently elevated. In the biventricular setting, if the increase is gradual and adaptation is possible, then the relationship changes to become more like the LV (17).

Henning et al. (18) illustrated the afterload dependency of the RV. The fall in cardiac output with positive pressure ventilation was initially thought to be solely due to decreased venous return, although even with volume the cardiac output remained reduced. This was due to an increase in the pulmonary vascular resistance.
Figure 3 Pressure volume loops in the LV and RV (14) after Shaver et al. (19)

Adaptation

The normal RV has thinner walls reflecting the lower pulmonary pressures, meaning it can adapt quicker to changes in preload (13). Adaptation seen in increased afterload (such as pulmonary arterial hypertension) is related to Laplace’s Law. To maintain a constant wall stress, as pressure increases and the ventricle becomes more round, the wall thickness must increase (Figure 4) (13).
Figure 4 Right ventricular adaptation to pulmonary hypertension (13)

In the normal RV the α-isotype of the myosin heavy chain (MHC) protein is around 23-34% with the remainder being the β-isotype. In pulmonary hypertension-associated RV failure there is a decrease in α-MHC to around 5%. This fall means a relative increase in the levels of β-MHC which has lower adenosine triphosphatase activity and this change is therefore associated with a decrease in systolic function (13). The normal sub-pulmonary RV has a lower mass with lower resting coronary blood flow as it has lower oxygen demands than the LV at rest and stress. When placed in a higher-pressure situation an increase in hypertrophy and mass occurs, meaning the RV becomes more susceptible to ischaemia, which in turn contributes to impaired systolic function.

Ventricular Interaction

Fibres within the interventricular septum can be considered to ‘belong’ to both ventricles. Ventricular function cannot be considered in isolation as there is an important ventricular interaction. In an electrically isolated heart, Damiano et al. (20) demonstrated this interaction. When the RV alone was stimulated,
pressure in the LV did not significantly increase whereas when the LV alone was stimulated, there was a significant increase in pressure in the RV. This study suggested that this LV contribution could account for 30% of the energy of the RV. A further study (21) went on to show that RV dilatation affects LV contractility. This interaction is likely to be significant in HLHS and the impact of the size of the residual LV is likely to cause some variability (22).

Fogel et al. (23) investigated strain (using MRI tagging) in the systemic RV in patients after atrial switch (for TGA) and patients with HLHS after Fontan completion. They found significant differences from a normal LV as well as significant differences between the two groups of patients. The differences observed between the two groups appeared to be related to the presence of an LV. However the atrial switch patients were significantly older than the Fontan patients, so some differences may be explained by systemic RV adaptation with increasing age.
Chapter 3 - Hypoplastic Left Heart Syndrome

INTRODUCTION

HLHS describes a spectrum of defects affecting the left side of the heart leaving it unable to support the systemic circulation (4). These include mitral valve, aortic valve and aortic arch abnormalities. Figure 5 shows the unoperated anatomy in classical HLHS.

![Unoperated hypoplastic left heart syndrome (illustration Dr AJ Bell)](image)

**Figure 5** Unoperated hypoplastic left heart syndrome (illustration Dr AJ Bell)

First described in 1851 (24), the term “hypoplastic left heart syndrome” has been used since 1958 (25). The incidence has been reported to be between 0.16-0.27/1000 (26,27) live births, although the true incidence is likely to be higher due to terminations of pregnancy and intrauterine deaths.

Data from the National Institute for Cardiovascular Outcomes Research (NICOR) from 2007-2008 showed 98 Norwood procedures were performed in the UK. Survival at 30 days in this period was 81.6% and 68.4% at 1 year.
Survival has increased with increased surgical experience (4) and so a growing cohort of patients with this condition are completing Fontan palliation and therefore being exposed to the longer term consequences of Fontan physiology.

**MORPHOLOGY**

Classical HLHS is usually described as aortic and mitral atresia, often with aortic arch hypoplasia; in these cases the LV is extremely hypoplastic and may only be detected at post-mortem. Other severe left heart lesions may also produce a hypoplastic LV unable to support the systemic circulation and these also form part of the HLHS spectrum.

The spectrum and classification of HLHS has been discussed previously (28). It can sometimes be difficult to assess patency of the mitral and aortic valves in-vivo, particularly if they are small and regurgitant. The three main subtypes described are shown in Table 2.
**Table 2 Different morphological subtypes in HLHS**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mitral Atresia with Aortic Atresia (MA/AA)</strong></td>
<td>Slit like or virtually undetectable LV</td>
</tr>
<tr>
<td><img src="image1.png" alt="Images" /> <img src="image2.png" alt="Images" /></td>
<td></td>
</tr>
<tr>
<td><strong>Mitral Stenosis with Aortic Atresia (MS/AA)</strong></td>
<td>Globular LV, often with endocardial fibroelastosis</td>
</tr>
<tr>
<td><img src="image3.png" alt="Images" /> <img src="image4.png" alt="Images" /></td>
<td></td>
</tr>
<tr>
<td><strong>Aortic Stenosis with Mitral Stenosis (MS/AS)</strong></td>
<td>Varying degrees of LV hypoplasia, usually a larger LV than the other groups</td>
</tr>
<tr>
<td><img src="image5.png" alt="Images" /> <img src="image6.png" alt="Images" /></td>
<td></td>
</tr>
</tbody>
</table>
The coronary systems are usually of normal size and anatomy (29) but there can be left coronary to LV fistulae. An autopsy study by O’Connor et al in 1982 (30) showed several different abnormalities in children with MS/AA. This was thought to have been due to increased LV pressures in utero. They found persistent microembryonic vasculature with multiple ventriculocoronary arterial connections. The coronary arteries in this study also appeared to have thicker walls and the LV myocardium was noted to be abnormal with endocardial fibroelastosis (EFE), scarring and calcification. Baffa et al also supported these findings, reporting coronary-cameral connections and tortuosity to be significantly associated with the MS/AA group, who also had more EFE. In 2004, Salih et al. (31) showed that there appeared to be less collagen per field in both the LV and RV. They suggested that the abnormalities associated with HLHS do not only impact on the LV but also on the RV, which will become the systemic ventricle.

**MANAGEMENT OPTIONS**

**General considerations**

HLHS is not compatible with life without intervention – untreated most children will die within 30 days (32) of birth. In the UK, most cases of HLHS are detected on obstetric anomaly scans (33) therefore most parents are able to consider all options with respect to the pregnancy. Data is available to confirm the benefit of prenatal diagnosis on early neonatal outcome (34). The options include delivery at a specialist centre to optimise postnatal outcome, with initial Norwood palliation. Extra-cardiac and chromosomal abnormalities, which may coexist in up to 10% may also be identified prior to birth. Given the guarded
prognosis of HLHS, parents may elect to terminate the pregnancy or else to deliver the baby but elect for comfort care only. Antenatal counselling provides the time and information for parents to make an informed choice. The detection rates in the south of England, where the Evelina Children’s Hospital is located, are among the highest in the UK.

**Immediate perinatal management**

There must be a patent interatrial communication and a patent arterial duct for the infant to survive in HLHS. Any child with HLHS or suspected HLHS is therefore commenced on a prostaglandin E infusion to keep the arterial duct open. A small subgroup of infants will have a severely restrictive atrial septal communication and may require either balloon septostomy or surgical septectomy as an emergency.

In America, transplantation may be offered as a primary procedure in infancy, however in the UK this is not typically a viable option due to the limited number of donor hearts and different criteria for brain stem death.

**STAGED SURGICAL PALLIATION IN HLHS**

**The Norwood Procedure**

The Norwood Procedure was first described in 1983 (35). This is the first of three steps towards a Fontan circulation using the RV as the systemic ventricle and is performed at a few days of age. The atrial septum is resected and the arterial duct ligated. The branch pulmonary arteries are disconnected from the
main pulmonary artery, which is then anastamosed to the aortic arch, which is reconstructed (forming the ‘neo-aorta’).

The native aorta is anastamosed onto the side of the neo-aorta (a connection called the Damus-Kaye-Stansel). This allows perfusion of the coronary arteries retrogradely from the neo-aorta. A shunt is placed between the innominate artery and the right pulmonary artery to supply blood to the pulmonary arteries.

The circulation is therefore thus: deoxygenated blood (from the superior and inferior caval veins) and oxygenated blood (from the pulmonary veins) flows to the atrial mass. This drains through the tricuspid valve to the RV. Blood is pumped via the neo-aorta around the body from the RV. Shortly after leaving the RV, some blood will flow retrogradely down the native aorta and supply the coronaries. Some of the blood will also flow down the shunt and into the pulmonary arteries.

**Sano Modification**

The Sano modification replaces the modified Blalock-Taussig shunt with an RV to pulmonary artery conduit. This was felt to confer an advantage in pulmonary artery growth in addition to continuing pulsatile blood flow to the lungs (36,37). It does, however, involve a right ventriculotomy.

Following the Norwood Procedure, there is obligatory mixing and patients remain desaturated. In this circulation both systemic and pulmonary venous return are to the functionally single RV, which is therefore markedly volume loaded. Depending on the size of the shunt, the pulmonary to systemic blood
flow ratio (Qp:Qs) can be over 1.5:1. Figure 6 shows the classical Norwood Procedure and the Sano modification.

**Figure 6** HLHS after the Norwood Procedure. Classical Norwood with modified Blalock-Taussig shunt (left) and Sano modified Norwood with a RV to pulmonary artery conduit (right) (illustration Dr AJ Bell)

**The Hybrid Procedure**

In more recent years a different approach has been described (38,39). The hybrid procedure involves stenting of the arterial duct and application of pulmonary artery bands. This allows maintenance of the patency of the arterial duct for blood supply to the systemic circulation, as well as protecting the pulmonary circulation from excessive flow. The hybrid procedure does not involve cardiac bypass and is therefore preferred where there has been a substantial hypoxic insult, for example in a collapsed neonate with a postnatal diagnosis. It can also be utilised for children less than 2.5kg for whom the Norwood Procedure would be high risk, or for those with borderline left heart structures (a situation where it is thought that there is a possibility that the left ventricle may be suitable to support the systemic circulation).
Reassessment occurs at around 3 months of age and the child will either proceed to a biventricular repair if the left heart structures are deemed suitable (40), or undergo a “comprehensive combined Stage 1 and 2” procedure – formation of a neo-aorta, septectomy and Damus connection with pulmonary blood supply from a superior cavopulmonary connection (see below) and progress down the Fontan pathway. Figure 7 shows HLHS after the hybrid procedure.

Figure 7 HLHS after the hybrid procedure (illustration Dr AJ Bell)

Superior cavopulmonary connection (Glenn or hemi-Fontan)

The second stage of palliation is performed around 6 months of age, following assessment for suitability. The pulmonary blood supply is from the superior caval vein (SVC), which is low pressure; if the pulmonary pressures are high, this is unlikely to be successful. The assessment was traditionally performed by cardiac catheterisation, although in recent years non-invasive MRI has been used to assess suitability for progression to the next stage (41).
The shunt is ligated and the SVC is anastomosed to the right pulmonary artery. If there is a left-sided SVC it is connected to the left pulmonary artery. The type of anastomosis depends on the type of Fontan completion (extracardiac or intracardiac).

- If an extracardiac Fontan is planned, then the anastomosis is of the SVC to the right pulmonary artery (Glenn)
- If an intracardiac Fontan is planned, then the anastomosis is of the SVC to the right pulmonary artery and to the roof of the right atrium. A baffle is then placed between the anastomosis and the right atrium (hemi-Fontan)

The pulmonary circulation is therefore more secure and supplied by the SVC. The child is still desaturated as the inferior caval vein (IVC) return is still to the common atrial mass, but saturations are often slightly higher. The ventricle is volume off-loaded at this operation with a Qp:Qs of approximately 0.5:1. Figure 8 shows HLHS after hemi-Fontan and Glenn anastomosis.
Total cavopulmonary connection (TCPC/Fontan completion)

The final stage is performed after assessment of suitability via a cardiac catheter or MRI scan with central venous pressure measurement (42). The final stage is performed around the ages of 2-5 years.

- Intracardiac Fontan – A tunnel is created in the right atrium and the baffle is removed. A small fenestration is left in this tunnel, which acts as a ‘blow off’ valve.
- Extracardiac Fontan – A tunnel is made outside the heart connecting the Glenn anastamosis to the IVC.

After this operation the two circulations are separated. The pulmonary blood supply is from the superior and inferior caval veins. Oxygenated blood then flows back to the atrial mass via the pulmonary veins. This then flows through the tricuspid valve to the RV and is pumped around the body via the neo-aorta. Following this operation, there is no longer obligatory mixing and so the child
will be predominantly pink. The fenestration is open initially, allowing some right to left flow as the lungs adjust to the new circulation physiology resulting in saturations in the high 80s. This often closes over time, at which point the saturations will increase to the normal range. There is little change in volume loading between the superior and total cavopulmonary connections. Figure 9 shows HLHS after TCPC using the lateral tunnel Fontan method and the extra-cardiac conduit method.

![Figure 9](image)

**Figure 9** HLHS after TCPC using the lateral tunnel Fontan method (left) and the extra-cardiac conduit method (right) (illustration Dr AJ Bell)

**FONTAN COMPLICATIONS**

The Fontan circulation is dependent on low pulmonary pressures to work. Additionally in HLHS the single systemic ventricle is an RV. Over time, the systemic ventricle and/or Fontan circulation will begin to fail. Reasons for earlier single RV failure have been discussed previously in this thesis. The mechanism behind Fontan complications is not clearly known, but likely to be due to a combination of factors.
1. **Protein losing enteropathy (PLE)** – proteins are lost through the bowel wall, leading to hypoalbuminaemia and oedema with their associated complications. This is thought to arise particularly in patients with high Fontan circuit pressures, especially in the lower circuit. It can be controlled with steroids, but is very difficult to treat and does not always resolve with cardiac transplantation.

2. **Plastic bronchitis** – thick, sticky casts are formed in the airways, which are then coughed up. As they can be very viscous, critical airway obstruction can occur. This is also difficult to manage with unpredictable results.

3. **Exercise tolerance** – Fontan patients have a lower exercise tolerance than the normal population. This can be more marked as the patient gets older and is likely due to a combination of systemic ventricular failure and chronic reduced preload (see Chapter 15).

4. **Arrhythmias** – arrhythmias can be seen after the Fontan procedure. They can either relate to surgery or structural disease, or be secondary to atrial dilatation. Some patients may require atrial reduction, ablation or pacemaker insertion.
INTRODUCTION

The most commonly used imaging modality in paediatric cardiology is echocardiography. Echocardiography was developed in the mid-20th century. It was first used in congenital heart disease in the late 1950s (43) and became more commonly practised in the late 1970s and early 1980s. Prior to this, the mainstay of diagnosis in congenital heart disease was auscultation and cardiac catheterization. Consistent improvements in technology have resulted in improved definition and the development of high frequency probes that can be used in the smallest of babies.

Cross-sectional echocardiography is now regularly used, but several techniques commonly used in adult practice (e.g. pulsed tissue Doppler, speckle tracking) are still being investigated in congenital heart disease. This chapter looks at these techniques in more detail, as well as the advantages and disadvantages of echocardiography.

MYOCARDIAL AND DEFORMATION ECHOCARDIOGRAPHIC IMAGING

Strain

Strain describes the deformation of an object normalized to its original shape. In a pure one dimensional (1D) structure, the only strain is shortening or lengthening. This can be described by the following equation ($\varepsilon$ – Strain, $L$ – Length after deformation, $L_0$ – Original length):
Strain is unit-less and is usually presented as a percentage. Convention dictates that lengthening is a positive strain and shortening is a negative strain. There are two types of strain: Lagrangian strain and natural strain. Lagrangian strain is instantaneous strain, relative to the initial length. Natural strain describes where the reference value is not constant over time, but changes due to deformation (44). At small strains (5-10%), Lagrangian and natural strains are equal. Lagrangian strains are currently used in clinical practice although it has been suggested that natural strain may be more appropriate for cardiac use (44).

For two dimensional (2D) and three dimensional (3D) structures, strain occurs in more than one plane. 2D structures have four strain patterns: two referred to as ‘normal’ strain and two ‘shear’ strain. Normal strains occur along the given x or y-axis, whereas shear strains refer to the relative displacement along the right/left or upper/lower borders. 3D structures have three normal strains (along each given x, y or z axis) and therefore six shear strains. The axis for these strains is often different to the axis assigned to the heart and so tensor diagonalisation is performed to determine the strain tensor.
The heart's co-ordinate system is generally defined as a local system, rather than using one co-ordinate system for the heart as a whole. In the local system, the three axes are:

- **Longitudinal** – from base to apex (points to base from apex)
- **Circumferential** – around the heart (perpendicular to radial and longitudinal, so the axis is right handed)
- **Radial** – from epicardium to endocardium (points away from the cavity)

**Figure 10** The local system of axes in the heart (44,45)

The normal strains in the heart are therefore radial, circumferential and longitudinal. The six shear strains are derived from combinations of the above.

**Strain Rate**

Strain rate is derived from strain and is defined as the rate at which strain occurs. It is represented by $\varepsilon'$ and has the units $s^{-1}$. The strain rate is equal to the strain divided by the time taken to achieve that strain. This is a simple equation in a 1D object, but a 3D object has potentially nine potential strain
components, all at specific rates. There may also be interactions of these strain components.

Strain has been measured in various ways over time, from invasive measurements using implanted tags or crystals to more recent MRI tagging. The earlier methods were invasive and the very act of placing the crystals and tags may have altered the strain pattern. MRI tagging is performed by non-invasively ‘tagging’ the myocardium in diastole, then imaging in many planes and time points. This is non-invasive, but the post-processing is time consuming.

**PULSED TISSUE DOPPLER**

Pulsed tissue Doppler describes the technique of using pulsed wave Doppler to analyse myocardial tissue velocities rather than blood velocities. Again, it is very angle dependent and subject to movement caused by whole heart translocation. The sample is placed on the area of tissue in question and a pulsed Doppler is acquired, displaying tissue velocities against time. The maximum velocities acquired on pulsed Doppler can then be used to set the Nyquist scale for further colour myocardial Doppler imaging.

The first positive deflection seen in systole represents the isovolumic contraction. This is followed by another positive wave, the s’ wave representing ejection. There then follows an early diastolic wave (negative) representing isovolumic relaxation. Another two negative waves follow, the e’ wave and the a’ wave. The e’ wave representing passive filling and the a’ wave atrial contraction. Figure 11 shows the pattern described for the left ventricle.
Figure 11 The pulsed wave tissue Doppler trace for the left ventricle. IVC = isovolumic contraction, IVR = isovolumic relaxation

SPECKLE TRACKING (46-48)
Speckle tracking relies on the tracking of speckles caused by ultrasonic scatterers. These speckle patterns are unique and can therefore be followed through subsequent images using pattern matching. Each speckle region of interest is called a kernel. Spatial velocity resolution is determined by the size of the kernel and the velocity range is determined by the size of the region being searched (Table 3).
Table 3 Analogy for Kernel and region size in speckle tracking

<table>
<thead>
<tr>
<th>Two balls bouncing, the blue one is the ball of interest</th>
<th>Too large a kernel (blue) and we have poor spatial resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two balls bouncing, the blue one is the ball of interest</td>
<td>Too large a kernel (blue) and we have poor spatial resolution</td>
</tr>
<tr>
<td>Too small a search area (red) and the ball has already moved out of the area, we cannot track the ball</td>
<td></td>
</tr>
</tbody>
</table>

The pattern-matching algorithm then finds the best match, and the vector for that kernel is therefore defined. The time for this move is known, and so the velocity can be calculated. This can be performed in 1D, 2D or 3D and in 2D or 3D is not angle dependent.

Speckle tracking requires standard basic cross-sectional views. It is not angle dependent and is quick and easy to acquire and analyse. The main limitation is that generally the frame rate is in the range of 60-90/second and the accuracy of the speckle tracking is based on how well it tracks the speckles. This means that in a poor quality image, the speckles may not be accurately tracked.
If a cord is drawn between two points and their movement over time recorded, then the change in length of the cord over time can be measured. The change in length of the cord (strain) and rate of change (strain rate) can then be calculated. Displacement of parts of the heart over a time period can also be measured using speckle tracking (see tricuspid annular descent in Chapter 8). Endocardial and epicardial borders can be tracked, allowing information on torsion to be collected.

ADVANTAGES OF ECHOCARDIOGRAPHY

Most modern echocardiography machines are very mobile and some are very portable, including laptop-sized machines and the recently released hand held machines. This allows the test to be taken to the bedside and for the presence of multiple machines, or machines in smaller hospitals. Echocardiography is non-invasive and painless, making it a very attractive and useful tool, particularly in paediatrics. It is also therefore useful for regular, routine follow-up. Echocardiography is widely available and performed regularly and is therefore easier to teach than MRI.

Most scans do not need any form of sedation, although occasionally sedation is required. General anaesthetic is generally used for trans-oesophageal echocardiography, which is more invasive, and only used when transthoracic pictures are sub-optimal or a particular area needs to be imaged (e.g. atrial septal defect for assessment for closure).
Echocardiography can also be performed under the same anaesthetic as other imaging, for example magnetic resonance imaging. This multi-modality imaging can be very useful in surgical decision-making, particularly in complex congenital heart disease. The scan itself is generally relatively quick depending on what data is needed.

**DISADVANTAGES OF ECHOCARDIOGRAPHY**

Data quality is dependent on the operator's experience and skills as well as the patient's compliance. Experience and skill are important, although as it is used regularly, most cardiology trainees will rapidly be able to acquire adequate images in relatively compliant patients. Patient compliance varies, and is dependent on the patient's age and state of health. Some children are very compliant, whereas in others scanning may be near impossible. A child who behaves when well may be upset and difficult to scan when feeling unwell or in pain.

There can also be significant interuser variability in the analysis both online and offline. For example, in the right ventricle where no standard function analysis techniques (e.g. M Mode) exist, assessment of the function is usually visual. It was shown that this varies greatly with experience (49).

The patient's acoustic windows also affect data. These can be affected by the patient's size and body habitus, age and condition. For example, newborn babies often have good acoustic windows whereas older adults often have much poorer windows. Acoustic windows decrease with increased subcutaneous tissue. Ultrasound is also affected by air and so patients with a
lot of air in their chest, either from emphysema, pneumothorax or post-operatively, are harder to scan. Certain thoracic structures can also be challenging to image. The right ventricle and pulmonary artery are generally quite anterior structures. Higher structures such as the aortic arch and upper caval veins can also be challenging to image.
Chapter 5 - Magnetic Resonance Imaging Assessment of the Right Ventricle

INTRODUCTION

Magnetic resonance imaging (MRI) was developed in the mid-20th century and has been in use in congenital heart disease since the 1980s. Accessibility, however, remains relatively centre-specific. Different sequences allow the review of structures in different ways as well as providing excellent extracardiac imaging. Commonly used sequences in paediatric cardiology are described below, along with the advantages and disadvantages of MRI.

COMMONLY USED SEQUENCES

*Balanced-steady-state-free precession (SSFP) cine imaging*

Cine images are used to capture moving images of the heart. These are particularly good at looking at heart function and the competency of the atrioventricular and ventriculoarterial valves. Standard views taken may include:

- Four chamber view
- Left ventricular outflow tract
- Left ventricular three chamber view
- Right ventricular outflow tract
- Right ventricular three chamber view
- Aortic arch
• Short axis of the ventricles (also used to assess function quantitatively)

In very complex heart disease, it can be useful to take a series of cine images in each plane. Cine images can be planned in any plane as MRI is not limited by acoustic windows. As MRI is a relatively slow image data acquisition technique, cardiac and respiratory motion needs to be addressed. To compensate for cardiac motion, cine images are either retrospectively (now the preferred technology) or prospectively ECG gated. The most commonly used technique for addressing chest movement from respiratory motion is a breath hold. Short axis (or transverse) cine images can be used to calculate ventricular end systolic and end diastolic volumes, and therefore stroke volume, ejection fraction and cardiac output. End diastole and end systole are identified and the endocardial contour is traced on each slice from the apex to the plane of the atroventricular valve (50,51). The volumes are then calculated using the modified disc summation method (Figure 12). Ventricular mass can also be calculated from the short axis cine images by tracing the epicardial contour. This is the current gold standard in assessing systemic RV volumes.
Figure 12 Figure showing the position of each short axis cine stack slice on the four chamber view in a patient with HLHS. The endocardial contours have been traced excluding trabeculations.

‘Black Blood’ Imaging (Figure 13)

Two inversion pulses are used, each at 180° and one immediately after the other. The first pulse inverts the whole imaging volume and the second pulse inverts only the slice of interest. In this way, all the spins outside the slice are inverted, whereas the spins within the slice have been inverted then re-inverted and so appear unchanged. It is calculated so that the blood that flows into the slice of interest will be nulled and appear black, whereas the surrounding tissues are not nulled, hence ‘black blood’. This works for moving blood, but very slowly moving blood (i.e. not moving out of the slice) will not be nulled. The presence of MRI contrast agents will also affect the ability of blood (or tissue where the contrast agent enhances) to be nulled.

This technology has been clinically used for cardiac MRI from the very early days and proved to be a very good method to image vascular structures. Due
to the inversion pulse flow, artefacts due to stenoses (for example in the branch pulmonary arteries or the aortic arch in coarctation) are rare. This technique is usually ECG gated. Breath holds are commonly used to compensate for respiratory motion, although these sequences can be run using a higher noise signal average (52) free breathing or with a respiratory navigator (53). Free breathing techniques can be invaluable in a cardiovascularly unstable child.

In patients with HLHS, these images were usually acquired as a multiple slice transverse stack. Orthogonal views of structures of interest (for example, the pulmonary arteries, aortic arch or shunt) are then acquired, often needing fewer slices.

![Image of aortic arch and branch pulmonary arteries](image)

**Figure 13** Black blood images of the aortic arch and the branch pulmonary arteries (with hemi-Fontan also seen)

**Balanced Three Dimensional SSFP**

This sequence is respiratory navigator gated and also acquires only in set (defined by the user) cardiac rest periods (systole and diastole) (50,54,55). The systolic and diastolic rest periods are calculated from a four-chamber cine. In
this way cardiac gating is achieved, allowing crisp pictures. It is often run straight after the Gadolinium enhanced angiography to maximise the signal from the blood pool due to contrast agent injection.

In a patient who is awake, no breath holds are required as data is only acquired within a preset gating window. To increase the acquisition time in patients under general anaesthetic, breath holds can be used to set the respiratory gating window to a certain position (56). Subsequent breath holds in exactly the same position are then used throughout the scan to increase the time that the diaphragm is within the gating window.

This sequence acquires a 3D block of data with isotropic image resolution which allows this data to be manipulated and viewed in any plane. As this isotropic dataset is acquired with respiratory gating and is ECG triggered, the great arteries and the intracardiac anatomy can be viewed in great detail (54,55). Four examples of 3D datasets reformats are shown below in Figure 14.
The sequence is run as either single phase (systole or diastole) or dual phase (systole and diastole). The dual phase allows analysis of structures in systole and diastole. This can be very useful for ventricular septal defects (Figure 15) and stenoses. Some structures are better seen in systole whereas others are better seen in diastole (e.g. coronary arteries), so the dual phase allows optimal imaging of structures in systole and diastole (54).
Figure 15 Dual phase looking at the ventricular cavity in a patient with HLHS (i-ii) and in a patient with multiple ventricular septal defects (iii-iv)

3D Gadolinium Contrast Enhanced MRI

MRI contrast agents are usually Gadolinium based. Gadolinium reduces T1 and so enhances areas where it is present. In congenital cardiac MRI the main use of gadolinium is for MR angiography. The use of these contrast agents in children is regarded as being very safe as long as dose restrictions and contraindications such as sufficient kidney function are respected. Nevertheless there are reports of allergic reactions. Some patients may feel nauseous after administration. Gadolinium is renally excreted and so can build up in renal impairment, which is considered the main contraindication for its use. If Gadolinium builds up in tissues, then patients may get nephrogenic
systemic fibrosis (NSF), a severe condition causing severe fibrosis of the patient’s tissue, which can be fatal (57),

**Angiography**

As Gadolinium based contrast agents provide plenty of contrast due to T1 shortening complete 3D datasets can be acquired within a very short time. The abundance of contrast can be used for time reduction and increased spatial resolution (58,59). Therefore complete 3D datasets can be acquired at different time points after the injection. In patients with HLHS different vascular anatomy is highlighted (arterial versus venous phase). The data is acquired with a breath hold to suppress respiratory motion. Due to time constraints to acquire the data within a breath-hold no ECG gating is used. This limits this technology to image extracardiac vessels accepting slightly blurry vessel borders. Due to the absence of ECG gating, intracardiac structures are not adequately imaged. This technique is very well suited for 3D post-processing techniques to demonstrate complex 3D vascular structures present at different stages of HLHS palliation.

**Phase Contrast Flow Imaging**

Phase contrast flow imaging is an integral part of evaluation of patients with congenital heart disease (50). Directional phase shift is proportional to the velocity in that particular direction. Each pixel can be assessed for its velocity. The flow detection is also subject to peak velocity levels, which must be set prior to the sequence. After acquisition, the images are post-processed to calculate flow. Each image (representing the vessel at different points in the cardiac cycle) is reviewed. A contour is drawn around the colour coded pixels
in the vessel of interest. In each slice, it is possible to detect the velocities and also the mean phase shift (converted to a velocity). This can then be multiplied by the area, giving the flow in that slice. Flow:time curves are then plotted, the area under the curve being the stroke volume of that vessel. Through plane flows are used to calculate flow, maximum velocity and regurgitant fraction in a vessel. Flows can also be used to measure ventricular inflow if acquired as a through plane of the atrioventricular valve. They can be planned in any plane and used on virtually any vessel, however there are limitations regarding vessel size and flow patterns (60). This technique can be used to calculate the differential pulmonary blood flow, atrio-ventricular valve regurgitation, Qp:Qs and, in conjunction with pressure measurements, pulmonary vascular resistance (61).

**Dobutamine Stress MRI**

Dobutamine has been used for several years as a stress agent for the assessment of patients with coronary artery disease (62,63) in conjunction with MRI and echocardiography. In our institution it is used to ‘stress’ patients undergoing MRI, or MRI catheter to allow assessment of haemodynamics at stress as well as rest (64). The standard protocol is to start at 10mcg/kg/min. An effect is generally seen after around 10 minutes, when repeat measurements are taken. The measurements taken are dependent on the indication for the scan, but usually include volumetry and flow measurements to calculate the cardiac output. If the patient is stable, then the dobutamine can be increased to 20mcg/kg/min, again with relevant measurements repeated after a response is seen. The response to dobutamine can vary from person to person (65).
ADVANTAGES OF MRI

MRI uses no radiation, and even in MRI catheter, the radiation dose is less than with a standard catheter (66), and may even be eliminated if the entire procedure is guided by MRI alone. For a standard MRI only a cannula is required if a contrast agent is to be administered.

MRI acquisition is not limited by acoustic windows and there is no structure within the thorax that is inaccessible with MRI. Often structures are viewed with more than one type of sequence allowing cross-checking and not all sequences are susceptible to such significant artefact from stents.

![Image](image.png)

**Figure 16** Coarctation of the aorta after endovascular stenting (left to right) reformat from 3D SSFP, black blood imaging and 3D reconstruction from gadolinium-enhanced angiography

The assessment of flow in different vessels allows calculations such as the pulmonary to systemic flow ratio (Qp:Qs) as seen in Figure 17. It is also therefore possible to non-invasively determine the differential blood flow in the pulmonary arteries. This can indicate pulmonary artery pathology (e.g. a pulmonary stenosis) or potentially a pulmonary hypertensive lung (as blood will
preferentially flow to the lower pressure lung). All MRI image datasets can be combined as they have been acquired during the same imaging session without the patient changing position.

**Figure 17 Calculation of the shunt flow in a patient with complex congenital heart disease**

During an MRI catheter, flow and volume measurements can be combined with invasive pressure measurements at rest and with stress (e.g. dobutamine), nitric oxide and/or high flow oxygen to assess pulmonary vascular resistance (61) and for assessment of the pressure/volume relationship.

Myocardial assessment using perfusion and late enhancement imaging has also been applied to patients with HLHS and borderline left heart structures (51,67,68), although high heart rates and relatively thinner myocardium impose some quite technical challenges for these MRI techniques.
DISADVANTAGES OF MRI

Currently, paediatric cardiac MRI is not as widely available as echocardiography or cardiac catheterisation. Even though most hospitals will have an MRI scanner, specific training is necessary to perform a paediatric cardiac MRI. In order to answer the relevant questions, a profound knowledge of MRI technology and the anatomy and physiology in patients with congenital heart disease is required. Another current limitation is the incomplete literature for normal ranges for ventricular volumes and vessel diameters in neonates, infants and children.

As MRI is a relatively long examination, general anaesthetic or deep sedation in younger patients may be necessary. Careful planning of MRI exams in awake patients keeps the scanning time to a minimum. Communication with the patient throughout the exam can significantly improve the results of the MRI exam in congenital paediatric patients. Cardiac and respiratory motion is a particularly important challenge in paediatric patients. Major achievements have been accomplished (54,56) but novel image reconstruction techniques are very promising to improve paediatric cardiac MRI even further (58,69,70).

As described previously, artefact from stents and devices can impact on image quality significantly, making a diagnostic MRI exam impossible. Patients with pacemakers and implantable defibrillators currently have limited access to cardiac MRI due to safety issues.
Even though 3D volume rendering is well suited for demonstration of complex 3D structures, vascular dimensions and anatomical details always need to be checked on the original source images. For example, 3D volume rendering often exaggerates a stenosis according to the thresholds used (Figure 18).

**Figure 18** The left pulmonary artery in a child after Norwood Stage 1 (left to right) 3D reconstruction from gadolinium enhanced angiography, reformat of gadolinium enhanced angiography, reformat of 3D SSFP and black blood imaging

Compared to echocardiography, temporal and spatial resolution is limited, and therefore currently available MRI tagging and speckle tracking software is at this time restricted to larger ventricles.
Chapter 6 - Current Assessment of Hypoplastic Left Heart Syndrome

ECHOCARDIOGRAPHY

Antenatal diagnosis

Antenatal diagnosis has been shown to improve outcomes in many congenital heart defects (71) including HLHS (72). In the UK, ultrasonic assessment routinely takes place at around 12 and 20 weeks. If significant abnormalities are noted on the 12 week or 20 week scan, then the patient may be referred at that stage for further assessment. HLHS is generally recognised as being an evolving condition and so may not present until scans later in the pregnancy.

Findings on antenatal echocardiography can vary from no visible left heart structures (usually presenting earlier) to borderline left heart structures. In the case of borderline left heart structures, it is not always possible to ascertain antenatally whether the left heart will be sufficient to support the systemic circulation.

A small LV with small or atretic mitral and aortic valves (and ascending aorta) may be seen. If these valves are patent, there may be marked regurgitation. Associated with these abnormalities may be LV wall motion abnormalities (73). There may be coarctation of the aorta and the presence of retrograde flow in the aortic arch may suggest that the left heart will be unable to support the circulation (73). The presence of a dilated, poorly function LV has also been described in HLHS and critical aortic stenosis (74).
It is also important to know antenatally whether there are any abnormalities of pulmonary venous return, restriction of the atrial septum or tricuspid regurgitation. All of these have been shown to impact on the survival of patients with HLHS (75).

**After birth**

The majority of cases of HLHS are now detected antenatally (33). Postnatal echocardiogram is still important in these patients to confirm and further define the anatomy.

Postnatal echocardiography is particularly important in those where the left heart structures were not clearly inadequate for supporting the systemic circulation and is instrumental in deciding the management of these patients. Although initial echocardiography can be used to assist in the surgical strategy for these patients, it has been recently shown that in some cases left heart structures can grow and even permit a biventricular repair (76). A full echocardiogram is performed postnatally with particular attention to:

- Direction of flow in the arterial duct (to help assess likelihood of duct dependency)
- Branch pulmonary artery size (small branch pulmonary arteries may be sub-optimal for the Fontan circulation (77))
- Pulmonary venous drainage (anomalous pulmonary venous drainage is associated with HLHS (78))
- Size and restrictiveness of atrial septum (restrictive atrial septum will need urgent surgery (79))
• Ventricular function (impaired function may affect prognosis (5))
• Tricuspid valve morphology and degree of regurgitation (this is the systemic valve, competency may affect prognosis (80))
• Pulmonary valve (this will be the systemic valve, competency and stenosis may affect prognosis)
• Aortic arch (for presence and degree of coarctation, to plan arch repair)
• Size of left heart structures (81) (if biventricular repair is a possibility (76))

**Borderline left hearts**

In children where there is the potential for the left heart structures to be able to support the systemic circulation, several extra measurements are required to help ascertain this. Mitral and aortic valve sizes as well as arch dimensions (ascending aorta, transverse arch and descending aorta) are required. The LV length and heart length are also measured.

There is literature describing z-scores (81,82) which can be useful in assessing whether a biventricular repair is possible. However, many of these discriminant scores are based on specific lesions, e.g. critical aortic stenosis, and are not therefore designed for those with multiple levels of obstruction. It should also be borne in mind that some structures may have the potential to grow (40) and may be volume and load dependent.

**After staged procedures**

Any assessment after the staged procedures requires a full echocardiogram as described above, but in addition the following should have particular attention:
After the Norwood Procedure

- Blalock-Taussig shunt (size, narrowings at either end, flow velocities)
- Branch pulmonary arteries (any narrowings due to the shunt)
- Aortic arch (any evidence of recoarctation)
- Damus connection
- Ventricular and valvar function (worsening due to volume loading or ischaemia)

After Superior Cavopulmonary Connection (HF)

- Hemi-Fontan connection and branch pulmonary arteries
- Aortic arch (any evidence of recoarctation)
- Damus connection
- Ventricular and valvar function (worsening due to ischaemia)

After Total Cavopulmonary Connection (TCPC)

- Lateral tunnel and branch pulmonary arteries
- Aortic arch (any evidence of recoarctation)
- Damus connection
- Ventricular and valvar function (worsening due to ischaemia)

MAGNETIC RESONANCE IMAGING

**Introduction and Background**

MRI has proven to be a suitable replacement of cardiac catheterisation in assessment prior to superior cavopulmonary connection (41). For the last eight years in our institution, children have also been assessed prior to TCPC with
MRI and central venous pressure (CVP) measurement (from the internal jugular vein) rather than cardiac catheter.

Due to the length of the scan, noise and breath holds, scans in our institution are performed under general anaesthetic in children under approximately 10 years of age (the decision in older children can be made in conjunction with the family and play specialists).

In 1977, selection criteria (known as the ‘Choussat Criteria’) (77) were drawn up based on factors that appeared to affect the outcome after the Fontan operation. As the Fontan operation has developed, these criteria have been adapted and are several are less strictly adhered to. Some, however, remain very important.

- Age above 4 years
  ⇒ Most institutions would consider performing the Fontan operation from a younger age, particularly in symptomatic children.

- No distortion of lung arteries from prior shunt surgery
  ⇒ Many children undergoing Fontan completion will have distorted pulmonary artery anatomy. If there are significant stenoses, these may be dilated interventionally prior to surgery, or the child may undergo augmentation at the time of surgery.

- Normal venous drainage
  ⇒ Total anomalous pulmonary venous drainage (TAPVD) can be associated with HLHS and so some children may have had this repaired at the time of the Norwood Procedure. Significant
pulmonary vein stenosis or lymphangiectasia (potential complications of TAPVD) associated with elevated pulmonary pressures may be a contra-indication for TCPC

- Normal ventricular function
  ⇒ In some situations Fontan completion is undertaken even in ventricular function is not normal. The definition of 'normal function' in these patients is also challenging

- Adequate pulmonary artery size
  ⇒ Following the Norwood Procedure a mildly hypoplastic left pulmonary artery (LPA) is frequently observed. This does not necessarily prevent children progressing to completion but any significant stenosis may need to be addressed either prior to completion or during surgery

- No atrioventricular valve leak
  ⇒ Many children have a degree of atrioventricular valve regurgitation and several with moderate to severe regurgitation have undergone a valve repair either before or during the completion surgery. In these situations careful imaging of the atrioventricular valve is essential

- Low pulmonary artery pressure (below 15 mmHg)
  ⇒ This remains one of the most important factors that is still seriously considered. In our institution, if the pressures are high then children may then undergo an MRI catheter or standard cardiac catheter to assess these further and may require intervention before being suitable for TCPC
• Low lung blood vessel resistance
  ⇒ As above

• Normal heart rhythm
  ⇒ Most children prior to TCPC would be in sinus rhythm. This would be assessed on a case by case basis

• Normal right atrial size
  ⇒ The right atrium is not usually significantly dilated prior to TCPC unless there is significant atrioventricular valve regurgitation (which would be addressed as above)

The current protocol in our institution is shown in Figure 19. MRI prior to HF is usually performed around 3 months of age and MRI prior to TCPC around 2 years of age. If there have been significant abnormal findings on the MRI scan, then the child may go on to have further interventions (for example pulmonary artery or arch balloon dilatation) before undergoing the next stage. Some children may also undergo additional procedures at their next stage, e.g. arch augmentation or tricuspid valve repair.

The MRI scan prior to TCPC is carried out under general anaesthetic and the central venous pressure is measured under general anaesthetic using an internal jugular line. If there have been concerns that the child may have raised pulmonary pressures, for example if they have severe tricuspid regurgitation, multiple aortopulmonary collateral arteries (MAPCAS) or SVC syndrome symptoms then they may instead undergo an MRI cardiac catheter. This involves invasive assessment of pulmonary artery pressures which when combined with MRI derived flows can be used to calculate the pulmonary
vascular resistance (61). Dobutamine may be used to assess how the heart could cope under stress. This may also be performed in children where there is the possibility that the left heart could cope with the systemic circulation.

**Figure 19** MRI assessment protocol currently in use at Evelina Children’s Hospital (CVP – central venous pressure measurement)

**MRI in HLHS**

All patients with HLHS undergo a scan tailored to their clinical situation, but a minimum dataset is as follows:

- Four chamber view
- ‘Black bloods’: axial stack, left and right pulmonary arteries and shunt
- Gadolinium angiography and 3D SSFP
- Cine imaging of the right ventricular outflow tract from two views and cine imaging of the aortic arch
- Short axis cine stack of the ventricles
• Phase contrast flow:
  o Pre-HF: neo-aortic flow (native aortic flow if biventricular repair is considered)
  o Pre-TCPC: neo-aortic flow, branch pulmonary artery flows, superior caval vein flow
  o Although not in the time period of data collection for this thesis, our current protocol includes superior caval vein and descending aorta flow to calculate the pulmonary to systemic blood flow ratio prior to HF, and pulmonary vein flow and descending aorta flow to evaluate aortopulmonary collateral flow prior to TCPC

• If there are concerns about regional abnormalities, then late-gadolinium enhancement images can be acquired, although these are difficult in smaller children

Figure 20, Figure 21 and Figure 22 show examples of the sequences used and pictures obtained when assessing patients with HLHS using MRI.

Figure 20 From right to left: SSFP cine 4 chamber view showing a volume loaded right ventricle; black blood images showing proximal LPA stenosis; coronal and sagittal black blood images looking in more detail at the branch pulmonary arteries and shunt
Figure 21 Top row: SSFP cine short axis stack and SSFP cine of the right ventricular outflow tract and aortic arch. Bottom row, left to right: Reformats of the branch pulmonary arteries, arterial shunt, Damus connection, HF connection and coronary arteries.

Figure 22 From left to right: Gadolinium enhanced angiography of the arterial shunt, HF connection, whole heart and Fontan circuit.
Areas of Assessment

Ventricular Function – from ventricular volumetry and flow data (can be performed on both ventricles if there is a question that the LV may still be adequate)

Tricuspid regurgitation – assessed visually from usually at least two views as well as an estimation based on ventricular volumetry and flows

Branch pulmonary arteries and shunt/HF – assessed from black blood imaging, MRI angiography and 3D SSFP

Damus connection and aortic arch – assessed from black blood imaging, MRI angiography and 3D SSFP

Coronary arteries – assessed from the 3D SSFP (not always possible in the very small babies with high heart rates)

MRI scan after TCPC

Currently there is no routine schedule for MRI scans after completion of Fontan in children with HLHS. Children are usually referred for MRI or MRI catheter assessment after TCPC due to concerns over the Fontan circuit or function. These are predominantly in five groups:

1. In the immediate post-operative period due to complications such as prolonged chest drainage
2. Following development of syndromes associated with a failing Fontan, e.g. plastic bronchitis and protein losing enteropathy
3. Decreased exercise tolerance with no identifiable cause obvious on echocardiography
4. To reassess tricuspid regurgitation or possible collaterals
5. Routine assessment prior to adolescence

*Combined MRI Catheterisation*

MRI catheter describes a procedure where MRI and invasive pressure data are collected. This generally requires less radiation than a standard catheter (66) and may not use any radiation if the procedure is entirely MRI guided. The patient is usually on a table that can move between the MRI scanner and the catheter suite. In some situations these are in two adjacent rooms but in our institution they are in the same room. During an MRI catheter, standard catheterisation techniques can be used, as well as combining the invasive pressure data with MRI measurements.

Pulmonary vascular resistance (PVR) studies can be performed measuring pulmonary pressures (catheter) and pulmonary artery flows (MRI) – including differential flow and hence differential PVR – at baseline and then with oxygen and nitric oxide. Dobutamine stress studies can be performed with simultaneous measurements of ventricular pressure (catheter) and volumetry/cardiac output (MRI) at different levels of stress, typically Dobutamine 10mcg/kg/min and Dobutamine 20mcg/kg/min.
Chapter 7 - Assessment of Cardiac Function in Hypoplastic Left Heart Syndrome

INTRODUCTION

Although survival has been increasing, there are still relatively small numbers of patients with HLHS. Studies have therefore usually been hampered by this, or by the combining of ‘single ventricle’ patients, making it hard to tease out the HLHS group. Additionally, there is wide heterogeneity within the group and many studies include patients with other HLHS variants, such as double outlet right ventricle or unbalanced atrioventricular septal defects (AVSD). Many also group together all HLHS, although more recent studies have shown important differences between the subtypes (22,83).

Another important limitation is that several studies compare their functional parameters to either subjective functional assessment or other echocardiographic functional assessment parameters, which are themselves prone to error. Correlation with the current gold standard, MRI is used in several studies. However MRI ejection fraction (the most frequently used parameter) only assesses systolic function and interpretation may be complicated if there is significant tricuspid regurgitation (TR). The majority of studies investigate systolic function, but it has been described previously that diastolic dysfunction is important also in the Fontan circulation (84). The use of indices requiring the presence of TR (for example change in pressure by time, time intervals) are therefore confounded in patients with HLHS where the presence of TR is in itself a prognostic indicator (80).
Studies using speckle tracking and strain analysis have usually used the left ventricular model and extrapolated to the RV. Assessment of the RV has been further hampered by the lack of post-processing software designed to assess the RV and the lack of a widely accepted method of RV segmentation. Furthermore, there is marked heterogeneity of the RV shape in patients with HLHS.

**ECHOCARDIOGRAPHY**

*Two Dimensional parameters*

Trowitzsh et al. (85) described in 1985 a good correlation between echocardiographically derived ejection fraction and angiographically derived ejection fraction in patients with HLHS and transposition of the great arteries. Despite this good correlation, the fractional area change (FAC) from echocardiography correlated less well, the best correlation being seen when measuring short axis area change. A lower FAC was seen in 11 HLHS patients compared to 18 control patients along with lower peak emptying and filling – Kimball et al. (86) concluded that the atrial contribution was more significant in those with HLHS.

Michelfelder et al. (87) investigated simultaneous Doppler and catheter measurement of change in pressure/change in time (dP/dT) in 13 patients with HLHS. They showed poor reproducibility between 0 and 2m/s, but this was improved by measuring between 1 and 3m/s. Petko et al. (88) found reduced tricuspid annular plane systolic excursion (TAPSE) in a group of patients with a single systemic RV compared to those with normal sub-pulmonary RV.
**Pulsed wave tissue Doppler**

Christensen (89) investigated tissue Doppler velocities in 12 patients with HLHS <24 hours after admission, <24 hours before the Norwood procedure and at discharge or 10 days after Norwood. Overall there was no significant change in tricuspid annulus s’ and e’ velocities, although there was an increase from admission to pre-Norwood and then a decrease to post-Norwood surgery. Tricuspid annulus e’ significantly decreased from admission to post-Norwood, although this was not seen in the septal e’ velocity.

Myocardial performance index (MPI) was investigated by Zhang et al. (90) who demonstrated that this was significantly higher than both the normal left and right ventricles in patients with HLHS. This was also determined by Wisler (91) who moreover noted that there was an apparent increase in MPI with increasing age and operative stage. This increased MPI was also found by Williams et al. (92) in a mixed group of single ventricle patients compared to a control population. They also demonstrated a shorter ejection time (ET) and longer combined isovolumic contraction times (IVCT) and isovolumic relaxation times (IVRT). Mahle again demonstrated an increased MPI in the single RV compared to controls, along with, contrastingly, a longer ET and no difference in IVCT plus IVRT (93). They also noted lower FAC and more reliance on atrial contraction in those with a single RV.

Friedberg et al. (94) reported on the systolic to diastolic time ratio (from a tricuspid regurgitation trace) in patients with HLHS compared to controls. They demonstrated that the systolic to diastolic time ratio (S:D) was higher in patients with HLHS (who had a higher systolic fraction) and it was higher still in patients...
with poor cardiac function assessed by echocardiography. They also demonstrated a higher MPI in patients with HLHS.

**Strain, strain rate and dyssynchrony**

In 2007 Friedberg (95) described dyssynchrony in 16 patients with HLHS compared to normal left and right ventricles, and also demonstrated that this was not related to the QRS duration or RV FAC. Petko et al. (83,96) also investigated dyssynchrony and strain in the RV of patients with HLHS. They found that there was no change in global strain, strain rate, segmental strain rate or dyssynchrony when comparing patients before and after HF, but there was a decrease in the mid-lateral and basal lateral segment velocities, which they hypothesised was related to decreased preload after HF. Additionally, lower strain was noted in the septum, leading onto a further study (83) which showed no differences in RV function, global strain or strain rate in patients with MA/AA compared to other subtypes. However, a higher strain was noted in the basal septal and mid-septal and a higher strain rate in the mid-septal segment in those with MA/AA, as well as a shorter wall-to-wall delay.

Khoo et al. (97) showed reduced isovolumic acceleration and strain rate with increased post-systolic strain pre-HF compared to pre-Norwood. They hypothesised that this increase in post-systolic strain was related to ongoing ischaemia. They also notably found decreased TAPSE and peak s’ after Norwood and an increased sphericity index. There was some limited correlation with MRI, with MRI derived ejection fraction correlating linearly with strain, strain rate and dyssynchrony index. Using this, they also proposed that
those who did not develop a more ‘LV-like’ contraction pattern had reduced ventricular contractile function.

**Three Dimensional Echocardiography**

Three dimensional echocardiographic volumes have been used to assess RV systolic function by creation of end diastolic and end systolic volumes by a semi-automated method. This has been shown to have good correlation in adults and children with normal hearts (98-101), but in a recent study Bell et al. showed that although reproducible, 3D echocardiographic assessment were consistently lower than MRI derived volumes in patients with HLHS, and that this was more marked in smaller patients (102). 3D assessment could therefore be considered for serial measurements in these patients, but can not be used interchangeably with MRI. The development of new, more automated techniques which use inbuilt models of the RV based on multiple patients (103) will hopefully improve the usefulness of 3D techniques in these complex patients.

**MAGNETIC RESONANCE IMAGING**

The ability of MRI to assess single RV systolic function coupled with its ability to demonstrate great vessel and branch pulmonary artery anatomy has lead to it being used to assess patients before HF and TCPC. Groups have previously described the safety and use prior to HF (41,104) and this has now been extended to pre-TCPC assessment (42,105,106).

MRI tagging was used by Fogel et al. (107) to investigate the differences between seven HLHS Fontan patients and eleven systemic RV in patients after
the Senning/Mustard procedure. Patients with HLHS had less strain in the anterior wall and a greater heterogeneity of strain at the atrioventricular valve plane. This pattern, along with lower apical strain, was described as being more like a ‘normal LV’. There were differences in twist at the atrioventricular valve level as well as radial motion, but similarities in twist at apical level. It is not clear whether these changes reflect ‘adaptation’ or ‘maladaptation’ of the RV to the systemic position.

Delayed gadolinium enhancement has also been studied in HLHS. Harris et al. (68) showed delayed enhancement in areas where there had been previous surgery, although it was noted that delayed enhancement was also seen in the atrioventricular valves of normal patients. It is of no surprise that there is late enhancement in the region of previous surgery, however in the case of patients after a Sano (RV to pulmonary artery) shunt at Norwood, this scar may well impact on RV function. Dobutamine stress MRI has also been used to assess HLHS patients: Robbers-Visser et al. (108) showed an abnormal drop in indexed end diastolic volume meaning that the patients could only increase their cardiac output by increasing their heart rate. This dependence on heart rate may well explain a degree of the exercise tolerance experienced by patients in this group. The exact aetiology of the drop in end diastolic volume is not clearly understood but may reflect reduced filling due to the absence of a sub-pulmonary ventricle impacting on ventricular preload.

TRICUSPID REGURGITATION

In the setting of single ventricle physiology, competence of the atrioventricular valve of the systemic ventricle assumes great prognostic importance. Barber
et al. (80) reviewed the echocardiograms of 100 children (71 HLHS, 21 DORV and 8 AVSD) prior to Norwood. The majority had none or mild TR, with 16 having moderate or severe TR. They found no difference in the degree of TR in the pre-, early post- or late post-operative setting. However, a significant difference in the 2-year survival was seen. Of the 84 children who had no or mild TR 20 had TCPC, compared to only 2/16 from the moderate to severe group. The value of these results is limited slightly by the surgical era, and also because the group included children with AVSD. TR has been used in risk analysis for the Norwood operation (79).

Stamm et al. (109) reviewed 82 post mortem specimens of children with HLHS. They found differences in the tricuspid valve (TV) compared to normal hearts, and also within the different subsets of HLHS (the abnormal valves were seen more often in those with a patent mitral valve):

- 12% had a bileaflet right atrioventricular valve
- 33% had a moderately dysplastic valve
- 2% had a severely dysplastic valve

In the group of patients with mitral atresia, the majority had a concave septal surface compared to the normal convex septal surface (probably reflecting the much smaller left ventricle than the groups with a patent mitral valve). The septal attachments were also different in this group; instead of normal direct tendinous attachments, freestanding papillary muscles were observed. When the mitral valve was patent, the number of direct attachments was higher.
Nii et al. (110,111) reported on three-dimensional annular function in normal hearts based on 3D echocardiography. They then extended this work to look at patients with HLHS, divided into those with no or mild TR and those with moderate or severe TR. They looked at the annular area change, the bending angle of the TV, the diameter of the valve in different places throughout the cardiac cycle and the lateral angle of the anterior papillary muscle.

In a normal heart, the mitral valve plays a significant role in TV shape change. The normal tricuspid valve annular area changes are:

- **Early to midsystole**: TV area decreases due to ventricular contraction
- **From later systole**: TV area increases due to atrial filling until TV opening
- **Early to middiastole**: TV area increases
- **Late diastole**: TV area decreases due to atrial contraction

They found that both HLHS groups had a similar pattern to the normal TV, but with no decrease in diastole. This was most marked in those with moderate or severe TR (Figure 23 and Figure 24). The other differences between the normal group and the HLHS patients are summarised in Table 4.
Figure 23 from Nii et al., JASE 2006. Top: TV annular area change as % of the cardiac cycle in those with severe TR (top line), mild TR (middle line) and the normal heart (bottom line). The changes in the normal TV are shown in the bottom chart. Diastolic filling (DF), ventricular ejection period (EP), isovolumic contraction period (ICP), isovolumic relaxation period (IRP).

Figure 24 from Nii et al., JASE 2006. The different contraction forces on the TV in the normal heart and HLHS with different degrees of TR.
Table 4 Differences in the TV between the normal heart and HLHS

<table>
<thead>
<tr>
<th>Normal Heart</th>
<th>HLHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bending angle becomes acute from midsystole, maximal angle in early diastole</td>
<td>Bending angle does not change in systole</td>
</tr>
<tr>
<td>Septal-lateral diameter of TV annulus reduced from lateral forces from LV: maintains ellipse shape and therefore good coaptation between leaflets (Figure 24)</td>
<td>Mild TR group: more homogenous with similar forces of contraction around whole annulus (Figure 24)</td>
</tr>
<tr>
<td>Annulus and anterior papillary muscle maintained angle of 90° in systole</td>
<td>Severe TR group: more heterogenous, reduced forces in septal-lateral (opposite to normal)</td>
</tr>
<tr>
<td>Mild TR group: angle 100° – suggests tethering anterior leaflet and posterior to allow better coaptation</td>
<td></td>
</tr>
<tr>
<td>Severe TR group: angle similar to normals with sub-optimal coaptation</td>
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</tbody>
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Chapter 8 - General Methods

ETHICAL APPROVAL

Ethical approvals were sought and obtained through the Integrated Research Application System (IRAS) in accordance with national policy. Details of each ethical application are given in Appendix 1.

INCLUSION CRITERIA

All patients included in studies in this thesis have HLHS as defined below and have undergone/are undergoing surgical palliation with the Norwood procedure followed by HF (with left Glenn anastamosis for those with bilateral superior caval veins) and then fenestrated lateral tunnel TCPC.

Hypoplastic left heart syndrome was defined as atrioventricular and ventriculoarterial concordance with mitral stenosis/atresia and aortic stenosis/atresia with a hypoplastic LV rendering the left heart incapable of supporting the systemic circulation. Patients with unbalanced AVSD and those with large ventricular septal defects were excluded.

Patients were included in three different settings:

1. Patients undergoing routine MRI or MRI catheter assessment with or without general anaesthesia

2. Patients being reviewed in outpatient clinic

3. Patients being reviewed on the paediatric cardiology ward or paediatric intensive care unit, pre- and post-cardiac surgery or investigation
EXCLUSION CRITERIA

Patients were not included if they did not have cardiac anatomy as described previously or if parental consent was not obtained. Additionally, patients were not included if haemodynamic instability or time constraint meant that the additional echocardiogram could not be performed.

ECHOCARDIOGRAPHY

Rationale for techniques used

Ethical approval was for a limited period of echocardiography up to 15 minutes under the same anaesthetic as the MRI scan, and so studies were kept as short as possible. Novel speckle tracking techniques as described below were used rather than the built-in models. (These assume a uniform LV geometry, which cannot be applied to the RV in HLHS). An additional advantage was that they could also be applied to standard views acquired as part of the normal study and therefore required no extra acquisition time.

Tissue Doppler imaging was chosen as there are published normal paediatric ranges. It also allows calculation of composite indices in one acquisition and does not require the presence of tricuspid regurgitation.

Although 3D echocardiography is described in HLHS, a previous study by our group had shown that, although there is correlation with MRI ejection fraction, it is less reliable in smaller patients\(^{112}\) (which form a large section of our group). Isovolumic acceleration time was not chosen in this study because of poor repeatability (as it measures a slope of a very short time interval).
**Acquisition**

All echocardiograms were acquired using the Philips IE33 ultrasound system (Philips Inc, Andover, Mass, USA). Ultrasound probes were those that are commercially available for this platform, including S5-1, S8-3, S12-4, X7-2, X3-1, as appropriate for the size and age of the child. The X3-1 and X7-2 probes are 3D matrix probes used for all 3D echocardiographic acquisitions.

Routine echocardiograms (clinic or ward/intensive care setting) were performed following departmental protocol. Sedation was not used, though some children scanned prior to the Norwood procedure may have been ventilated and sedated.

**Departmental protocol for HLHS**

Subcostal views (2D loops with and without colour and 3D loop)

- Short axis – situs view
- Abdominal aorta
- Inferior caval vein and bicaval view
- Atrial septum
- Right ventricle: subcostal long axis and tilted
- Pulsed wave Doppler of neo-aortic outflow
- Continuous wave Doppler of neo-aortic regurgitation

Apical 4 chamber (2D loops with and without colour and 3D loop)

- Pulsed Doppler of tricuspid inflow
- Continuous wave Doppler of TR
- Tissue Doppler imaging with pulse wave Doppler of RV free wall and septum
Parasternal long axis (2D loops with and without colour and 3D loop)

Parasternal short axis (2D loops with and without colour)

- At the level of the valve
- At the mid-portion
- At the apex
- Native aortic valve and coronary arteries
- Branch pulmonary arteries
- High parasternal short axis: arterial duct, pulmonary venous drainage, pulsed wave Doppler of the pulmonary veins

Suprasternal

- Aortic arch: branching, sidedness, coarctation
- Number of superior caval veins

Analysis

Echocardiograms were analysed using Qlab v7 software on a Philips Excelera workstation (Philips Inc, Andover, Mass, USA). The commercially released version of Qlab v7 can only perform speckle tracking analysis on images obtained using a “pure wave” crystal probe (probes X7-2, S5-1). A pure wave probe was used for acquisition wherever possible, but where this was inappropriate (e.g. in a small baby) an appropriate sized probe was used (S12-4, S8-3, X3-1). A research version of Q lab 7 was made available to our department, which permitted speckle-tracking analysis on all ultrasound probes.

All scans were analysed by two observers, the author and Dr. J Simpson. Demographics of the patients (including age, stage, height, weight and body
surface area) were recorded as well as the following measurements (the RR interval was also measured for each set of measurements):

*Morphology of the LV*

LV morphology was described visually and classified into three categories (Figure 25):

(i) No discernible or slit like LV (usually representing patients with mitral and aortic atresia)

(ii) Globular LV (usually representing patients with mitral atresia and aortic stenosis)

(iii) Borderline LV (usually representing patients with mitral and aortic stenosis)

*Figure 25* Left to right - slit or no visible LV; globular LV; ‘borderline’ LV
Measurements

Figure 26 Pulmonary/neo-aortic valve annulus (2D subcostal)

Figure 27 Tricuspid valve annulus (2D apical 4 chamber)

Ventricular height and width, in systole and diastole (2D apical 4 chamber). Measured just below the tricuspid valve (width) and from the tricuspid valve plane to the apex (length). The ratio of these dimensions was then calculated (Figure 28)

Figure 28 Left – dimensions in systole, right – dimensions in diastole
Pulmonary/neo-aorta (Figure 29):

(i) maximum outflow velocity (2D subcostal, pulsed wave (PW) Doppler)

(ii) pulmonary/neo-aortic acceleration slope (2D subcostal, PW Doppler)

(iii) right ventricular pre-ejection period (from the onset of QRS complex wave to onset of flow, 2D subcostal, PW Doppler)

Figure 29 Pulsed wave Doppler pulmonary/neo-aortic outflow trace

Tricuspid Valve

Tricuspid inflow Doppler (apical 4 chamber, PW Doppler) (Figure 30)

- E and A velocities, E:A ratio
Figure 30 Pulsed wave Doppler tricuspid inflow trace

Tricuspid regurgitation (apical 4 chamber, continuous wave (CW) Doppler) (Figure 31)

(i) Maximum velocity of TR jet
(ii) \(\frac{dP}{dT}\) (the slope between 1m/s and 3m/s)
(iii) Subjective assessment (none, trivial, mild, moderate, severe)

Figure 31 Continuous Wave Doppler tricuspid regurgitation trace

Tissue Doppler

Pulsed wave tissue Doppler (interventricular septum and right ventricular free wall at the tricuspid annulus, apical 4 chamber) (Figure 32)
(i) e’, a’ and s’ velocities, E:E’ ratio
(ii) Time to peak s’ (from the R wave to peak s)
(iii) Isovolumic contraction time (time from end of the a’ wave to the beginning of the s’ wave)
(iv) Ejection (duration of the s’ wave)
(v) Isovolumic relaxation time (time from the end of the s’ wave to the beginning of the e’ wave)
(vi) MPI was calculated from (IVRT+IVCT)/ET

Figure 32 Pulsed tissue Doppler right ventricular free wall at the tricuspid annulus trace

Speckle-tracking (see individual chapter for definition)
Tricuspid annular descent from apical 4-chamber (% displacement, mid-point, free wall and septal displacement) (Figure 33 and videos 1 and 2)
Figure 33 Tricuspid annular descent (TAD) schematic and in vivo

Four cord strain (including time to peak strain, apical 4 chamber) and 4 cord speed strain (speed of the points placed at the annulus either side) (Figure 34 and video 3 and 4)

Figure 34 4 cord strain schematic and in vivo – strain (left) and speed (right)
Inferior cord strain (subcostal) (Figure 35 and video 5)

**Figure 35** Inferior cord strain schematic and in vivo

3D Echocardiography

3D volume acquisition: subcostal, apical 4 chamber, parasternal long axis

(Figure 36)

**Figure 36** Three dimensional acquisitions
MAGNETIC RESONANCE IMAGING

Acquisition

In our institution all patients with HLHS undergo pre-operative assessment for HF with echocardiography and cardiac MRI (under general anaesthetic) alone. This is usually performed around 3 months of age. Cardiac catheterisation would only be performed in those who require an intervention prior to HF. Prior to TCPC, patients are assessed with echocardiography and cardiac MRI under general anaesthetic with measurement of the central venous pressure via a cannula in the internal jugular vein. If there are concerns about possible elevated pulmonary vascular resistance (severe TR, poor RV function, significant aortopulmonary collaterals, airway pathology), then patients may then undergo MRI cardiac catheterisation combining MRI measurement of pulmonary arterial flows with invasive pressure measurements to calculate the pulmonary vascular resistance.

All MRI scans were performed on a Philips 1.5 Tesla Achieva Scanner (Philips Healthcare, Best, Netherlands) using an age and size appropriate coil (Flex-S, Flex-M or Cardiac Coil). Following a survey and SENSE (sensitivity encoding) reference scan, a real-time, interactive SSFP sequence was used to identify the imaging planes that would be used in subsequent scans. MRI scans were performed dependent on the patient’s surgical stage. As part of this study, a minimum dataset for HLHS at each surgical stage was developed (see Chapter 5).
Measurement of central venous pressure

During the anaesthetic for the pre-TCPC MRI scan, the CVP is measured from the internal jugular vein using a cannula as a surrogate for pulmonary venous pressure.

Analysis

MRI scans were analysed on the Viewforum EWS Version 2.0 (Philips Healthcare, Best, The Netherlands) workstation by the author and additionally for inter-user variation, by Dr. A Bell. Demographics of the patients (including age, stage, height, weight and body surface area) were recorded as well as the following measurements:

RV volumetry (short axis cine SSFP) (Figure 37)

End diastolic volume (EDV) and end systolic volume (ESV) measured by endocardial contour tracing, including tracing around the trabeculations. Stroke volume (SV) was calculated (EDV-ESV) as was cardiac output (CO) and ejection fraction (EDV-ESV/EDV).

Figure 37 SSFP cine short axis stack during analysis
Vessel flows (phase contrast flow)

Neo-aortic flow, aortic flow where applicable (both stages); SVC, right and left pulmonary artery flow (pre-TCPC) (Figure 38) measuring stroke volume, forward flow, backward flow, regurgitant volume, cardiac output

Figure 38 Phase contrast flow of the neo (red circle) and native (green circle) aorta during analysis

Morphology and measurements

Cardiac morphology including

(i) situs and apex direction

(ii) number of superior caval veins (review of all scan pictures and sequences including 3D SSFP, gadolinium enhanced angiography and cine images)
Measurements (from 3D SSFP or gadolinium enhanced angiography)

(i) Native aorta diameter (smallest), neo-aortic sinuses, ascending aorta (at the level of the pulmonary arteries), transverse arch (after the innominate), upper descending aorta, descending aorta at the diaphragm (Figure 39 and Figure 40)

Figure 39 Neo and native aortic measurements (i) native aorta (ii) neo-aortic sinuses (iii) ascending aorta (iv) transverse arch
Figure 40 Descending aortic measurements (i) upper descending aorta (ii) descending aorta at the diaphragm

(ii) Branch pulmonary arteries: distal RPA, proximal LPA and narrowest LPA
(Figure 41)

Figure 41 Measurement of the branch pulmonary arteries after Norwood Procedure (i) distal RPA (ii) proximal LPA (iii) narrowest LPA and after hemi-Fontan (i) proximal RPA (ii) proximal LPA and (iii) narrowest LPA
INTRA AND INTERUSER VARIABILITY

Echocardiography
All echocardiograms were analysed by the author. All parameters on twenty echocardiograms (representing all the surgical stages and ventricular morphologies) were reanalysed by the author and another observer (Dr. J Simpson) more than two weeks after the original analysis. Intra and inter-user variability was assessed using an intra-class coefficient two-way random model with absolute agreement.

Magnetic resonance imaging
All MRI scans were analysed by the author. Volumetry on twenty-seven MRI scans was also analysed by another observer (Dr. A Bell) more than two weeks after the original analysis. Intra and inter-user variability was assessed using an intra-class coefficient two-way random model with absolute agreement.
Chapter 9 - Outcomes in Patients with Hypoplastic Left Heart Syndrome Assessed by Cardiac MRI with Central Venous Pressure Measurement Prior to Total Cavopulmonary Connection Without Cardiac Catheterisation

AIM
To assess medium term outcomes in patients with HLHS who were assessed prior to TCPC with MRI and central venous pressure measurement alone (or MRI cardiac catheterisation in select high risk cases) rather than standard cardiac catheterisation.

HYPOTHESIS
Medium term outcomes in this patient group would be similar to patients evaluated using more established techniques, such as cardiac catheterisation.

INTRODUCTION
Standard investigative management prior to HF and TCPC has included cardiac catheterization for invasive measurement of pressure and to visualize pulmonary artery anatomy (113) although more recently MRI has been proposed either alone or in conjunction with cardiac catheterization (42,104). MRI alone in patients following the Norwood procedure to select candidates to proceed to HF has been investigated (41) and a randomized trial did not show any difference between the two approaches (114). MRI can accurately measure ventricular volumes, ejection fraction and aortic flow.
The proposed MRI approach with CVP measurement in the internal jugular vein to estimated the pulmonary artery pressures, has the advantage of avoiding cardiac catheterization in most cases and, therefore, avoiding ionizing radiation and the not insignificant morbidities associated with vascular access in these small patients (115,116). The outcomes of these patients who have undergone TCPC using the MRI based approach were compared to the published literature (42,105,117-123).
METHODS

Study population and design

Patients with HLHS who had undergone the Norwood procedure, HF and TCPC from February 2003 to July 2010 and had pre-operative evaluation for TCPC with cardiac MRI were included. Patients were identified using the departmental database (Heartsuite XP 3.9.14, Systeria, Glasgow UK). Patient demographics, surgical findings, inter-stage procedures and intermediate-term outcome data were collected from the patient case notes and the departmental database and compared to the published literature (42,105,117-123).

In our institution, children with HLHS are routinely referred prior to TCPC for cardiac MRI with CVP measurement. If CVP is elevated or if there are suspicions of elevated pulmonary pressures (severe tricuspid regurgitation, severe right ventricular dysfunction or significant airway pathology) then patients are referred for MRI and cardiac catheterization in a hybrid MRI catheter suite allowing calculation of pulmonary vascular resistance (61).

Image acquisition and analysis

All MRI scans were performed under general anaesthetic. Volumetric and flow data was collected as described in Chapter 8.

Central venous pressure measurement

CVP was measured using a water manometer connected to a cannula in the internal jugular vein. The measurements were converted from cm of water to mm of Hg. Patients who underwent MRI cardiac catheterization had direct
pressure measurements of the branch pulmonary arteries with wedge pressures to calculate the trans-pulmonary gradient and, combined with MRI phase contrast flow, pulmonary vascular resistance (61). Interventions under MRI guidance were not performed in this study group.

**Statistics**

Statistical tests were performed on SPSS 20.

**RESULTS**

Between February 2003 and July 2010, 75 patients with HLHS underwent the Norwood procedure, HF and TCPC at our institution (Figure 42). Seventy-one patients underwent assessment with cardiac MRI prior to TCPC. This group was used to compare outcomes after TCPC with the current literature. All patients in this study were suitable for TCPC.
Figure 42 Patients undergoing total cavopulmonary connection between February 2003 and July 2010 at Evelina Children’s Hospital. Five patients had assessment of pulmonary vascular resistance in a combined MRI – cardiac catheterization procedure.

Demographics and cardiovascular morphology for the patients are described in Table 5 and Table 6. Interstage procedures are recorded in Table 7. All patients had undergone the classical Norwood procedure with insertion of a 3.0mm, 3.5 or 4.0mm modified Blalock-Taussig shunt between the innominate artery and right pulmonary artery. After that a HF and fenestrated lateral tunnel TCPC was performed. Volumetric data is given in Table 8 and vessel size in Table 9.
**Table 5** Demographics and morphological details

<table>
<thead>
<tr>
<th>Pre-TCPC MRI Cohort</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>50 (70.4%)</td>
</tr>
<tr>
<td>Antenatal diagnosis</td>
<td>63 (90.0%)</td>
</tr>
<tr>
<td>Gestation &gt;37/40</td>
<td>67 (97.1%)</td>
</tr>
<tr>
<td>Normal atrial situs</td>
<td>71 (100%)</td>
</tr>
<tr>
<td>Apex to the left</td>
<td>71 (100%)</td>
</tr>
<tr>
<td>Left ventricular morphology</td>
<td></td>
</tr>
<tr>
<td>No visible/slit like LV</td>
<td>31 (43.7%)</td>
</tr>
<tr>
<td>Globular LV</td>
<td>31 (43.7%)</td>
</tr>
<tr>
<td>Borderline LV</td>
<td>9 (12.7%)</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>6 (8.5%)</td>
</tr>
<tr>
<td>Bilateral SVC</td>
<td>6 (8.5%)</td>
</tr>
<tr>
<td>Norwood Procedure Shunt</td>
<td></td>
</tr>
<tr>
<td>3.0mm</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>3.5mm</td>
<td>59 (84.3%)</td>
</tr>
<tr>
<td>4.0mm</td>
<td>10 (14.3%)</td>
</tr>
<tr>
<td>TCPC</td>
<td></td>
</tr>
<tr>
<td>Tricuspid valve repair</td>
<td>13 (18.3%)</td>
</tr>
<tr>
<td>Bypass time</td>
<td>51.2 mins (16.8)</td>
</tr>
<tr>
<td>Cross clamp time</td>
<td>32.1 mins (14.4)</td>
</tr>
<tr>
<td>Birth weight Mean (SD)</td>
<td>3.08 (0.42)</td>
</tr>
</tbody>
</table>
**Table 6 Age, weight and saturations: mean (standard deviation)**

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Weight, kg</th>
<th>Saturations, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norwood Procedure</td>
<td>0.01 (0.02)</td>
<td>3.07 (0.42)</td>
</tr>
<tr>
<td>Pre-HF MRI</td>
<td>0.44 (0.18)</td>
<td>5.80 (1.27)</td>
</tr>
<tr>
<td>HF</td>
<td>0.58 (0.20)</td>
<td>6.52 (1.29)</td>
</tr>
<tr>
<td>Pre TCPC MRI</td>
<td>2.91 (0.81)</td>
<td>13.01 (2.11)</td>
</tr>
<tr>
<td>TCPC</td>
<td>3.45 (0.89)</td>
<td>14.02 (2.13)</td>
</tr>
</tbody>
</table>

**Table 7 Interstage Procedures**

<table>
<thead>
<tr>
<th>Pre-HF</th>
<th>At HF</th>
<th>Pre-TCPC</th>
<th>At TCPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic arch*</td>
<td>4 (6.9%)</td>
<td>11 (19.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Pulmonary arteries</td>
<td>2 (3.4%)</td>
<td>4 (6.9%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

Tricuspid valve

<table>
<thead>
<tr>
<th>Collateral</th>
<th>Pre-HF</th>
<th>At HF</th>
<th>Pre-TCPC</th>
<th>At TCPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collateral occlusion§</td>
<td>0 (0.0%)</td>
<td>3 (5.1%)</td>
<td>0 (0.0%)</td>
<td>11 (19.0%)</td>
</tr>
<tr>
<td>Other^</td>
<td>0 (0.0%)</td>
<td>2 (3.4%)</td>
<td>3 (5.2%)</td>
<td>1 (1.7%)</td>
</tr>
</tbody>
</table>

*the 4 patients who had aortic arch balloons pre-HF are included in the 11 who had an arch repair at HF;

§ one patient had veno-venous collaterals occluded at HF and then veno-venous collaterals and aorto-pulmonary collaterals occluded prior to TCPC;

^ pre-HF: shunt stent; atrial septal stent. At HF: re-implantation of the innominate artery. Pre TCPC: surgical relief of pulmonary vein stenosis and ligation of collateral; plication of eventration of the right diaphragm
Table 8 Volumetric and flow data

<table>
<thead>
<tr>
<th></th>
<th>Pre-TCPC MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>89.9 (16.2)</td>
</tr>
<tr>
<td>iEDV, mls/m²</td>
<td>87.2 (22.0)</td>
</tr>
<tr>
<td>iESV, mls/m²</td>
<td>36.5 (12.6)</td>
</tr>
<tr>
<td>iSV, mls/m²</td>
<td>50.5 (12.7)</td>
</tr>
<tr>
<td>Cardiac index, l/min/m²</td>
<td>4.5 (1.4)</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>58.7 (8.0)</td>
</tr>
<tr>
<td>iNeo-aortic flow, mls/beat/m²</td>
<td>44.7 (9.1)</td>
</tr>
<tr>
<td>RSVC iSV, mls/beat/m² (n=61)</td>
<td>20.3 (6.9)</td>
</tr>
<tr>
<td>LSVC iSV, mls/beat/m² (n=4)</td>
<td>5.5 (4.8)</td>
</tr>
<tr>
<td>RPA iSV, mls/beat/m² (n=48)</td>
<td>12.5 (4.7)</td>
</tr>
<tr>
<td>LPA iSV, mls/beat/m² (n=40)</td>
<td>7.7 (3.4)</td>
</tr>
<tr>
<td>RPA flow, % (n=56)</td>
<td>61.7 (11.9)</td>
</tr>
<tr>
<td>LPA flow, % (n=56)</td>
<td>38.3 (11.9)</td>
</tr>
<tr>
<td>CVP, mmHg (n= 59)</td>
<td>12.1 (2.2)</td>
</tr>
</tbody>
</table>
### Table 9 Pulmonary artery and aortic sizes

<table>
<thead>
<tr>
<th></th>
<th>Pre-TCPC MRI</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Range</td>
</tr>
<tr>
<td>Distal RPA, mm²/m²</td>
<td>151.2 (51.8)</td>
<td>69.9-299.5</td>
</tr>
<tr>
<td>Proximal LPA, mm²/m²</td>
<td>101.7 (53.0)</td>
<td>26.3-283.5</td>
</tr>
<tr>
<td>Narrowest LPA, mm²/m²</td>
<td>51.2 (24.4)</td>
<td>8.2-128.1</td>
</tr>
<tr>
<td>Narrowest LPA: Proximal LPA, %</td>
<td>55.2 (21.4)</td>
<td>16.7-111.4</td>
</tr>
<tr>
<td>Native Ao, mm²/m²</td>
<td>59.0 (60.7)</td>
<td>11.2-341.0</td>
</tr>
<tr>
<td>Neo-Ao sinuses, mm²/m²</td>
<td>687.4 (179.6)</td>
<td>375.9-1505.3</td>
</tr>
<tr>
<td>Ascending Ao, mm²/m²</td>
<td>516.3 (150.4)</td>
<td>263.3-964.1</td>
</tr>
<tr>
<td>Transverse arch, mm²/m²</td>
<td>436.1 (159.9)</td>
<td>226.2-1252.3</td>
</tr>
<tr>
<td>Upper DAo, mm²/m²</td>
<td>172.9 (52.8)</td>
<td>89.6-318.1</td>
</tr>
<tr>
<td>Lower DAo, mm²/m²</td>
<td>112.3 (31.5)</td>
<td>35.3-212.9</td>
</tr>
<tr>
<td>Upper:lower DAo, %</td>
<td>158.5 (46.1)</td>
<td>83.3-350.0</td>
</tr>
</tbody>
</table>

**MRI assessment prior to TCPC**

Of the 71 patients assessed with MRI pre-TCPC, 66 patients were assessed with MRI and CVP measurement alone with CVP data documented in 58 patients (mean 12, SD 2.2, range from 6-16mmHg). Seventeen had a CVP above the group 75th centile (13.5mmHg). The length of stay and duration of chest drains in these 17 patients was not significantly different to the whole patient population (Table 10). Five patients underwent MRI combined with cardiac catheterization due to clinical concerns over raised PVR (Table 11). Based on CVP and PVR measurements all patients were suitable for TCPC.
Table 10  **Total cavo-pulmonary connection outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Total group (n = 71)</th>
<th>CVP ≤ 13.5mmHg (n = 41)</th>
<th>CVP &gt; 13.5mmHg (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (25-75\textsuperscript{th} centile)</td>
<td>Median (25-75\textsuperscript{th} centile)</td>
<td>Median (25-75\textsuperscript{th} centile)</td>
</tr>
<tr>
<td>*ITU stay, days</td>
<td>3 (2-3)</td>
<td>2 (2-3)</td>
<td>3 (2-5)</td>
</tr>
<tr>
<td>Number of inotropes</td>
<td>1 (1-2)</td>
<td>1 (1-1)</td>
<td>1 (1-2)</td>
</tr>
<tr>
<td>Ventilation, minutes</td>
<td>365.0 (243.8-600.0)</td>
<td>360.0 (232.5-580.0)</td>
<td>370.0 (250.0-652.5)</td>
</tr>
<tr>
<td>Total inpatient</td>
<td>9.0 (7.5-13.5)</td>
<td>9.0 (8.0-15.8)</td>
<td>9.0 (5.5-12.0)</td>
</tr>
<tr>
<td>duration of CD</td>
<td>13.0 (10.0-19.0)</td>
<td>13.5 (10.0-19.8)</td>
<td>13.0 (7.5-18.0)</td>
</tr>
<tr>
<td>Hospital stay</td>
<td>91.0 (89.4-93.0)</td>
<td>91.0 (89.5-93.8)</td>
<td>90.0 (88.8-92.0)</td>
</tr>
<tr>
<td>Discharge saturations</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CVP data documented in 58 of 66 patients; 5 patients underwent MRI combined with cardiac catheterization (see table 8); Chest drains (CD), intensive therapy unit (ITU); *p<0.05 on Mann-Whitney test (the patient who died in the immediate post-operative period from an intractable arrhythmia is excluded from this analysis as he died <24 hours post-operatively).
### Table 11 MRI Catheter Patients

<table>
<thead>
<tr>
<th></th>
<th>1(^{st}) MRI catheter CVP/PVR</th>
<th>2(^{nd}) MRI catheter CVP/PVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>24 mmHg/2.8 Woods units.m(^2)</td>
<td>N/A</td>
</tr>
<tr>
<td>Patient 2</td>
<td>18 mmHg/2.6 Woods units.m(^2)</td>
<td>N/A</td>
</tr>
<tr>
<td>Patient 3(^*)</td>
<td>18-20mmHg/2.4 Woods units.m(^2)</td>
<td>8mmHg/2.4 Woods units.m(^2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.7 Woods units.m(^2) with 100% O(_2))</td>
</tr>
<tr>
<td>Patient 4</td>
<td>5mmHg/1.9 Woods units.m(^2)</td>
<td>N/A</td>
</tr>
<tr>
<td>Patient 5(^**)</td>
<td>13mmHg/2.0 Woods units.m(^2)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

\(^*\)Tricuspid valve procedure between first and second MRI catheter,

\(^**\)occlusion of aorto-pulmonary collaterals after MRI catheter before TCPC

Twenty-five patients had significant stenosis of the LPA (more than 50%) as it passed behind the reconstructed neo-aorta. Although the LPA in patients with significant narrowing was inspected at the time of surgery, none of the patients had further reconstruction of the LPA at TCPC. No patients required any aorta or arch interventions at the time of TCPC or afterwards and no surgical interventions were performed on the neo-aortic valve. There was no significant difference between those with and without a >50% stenosis of the LPA (LPA narrowest: LPA proximal ratio) in duration of ventilation, ITU stay, hospital stay or discharge saturations. However, duration of chest drainage was significantly longer in patients with >50% LPA stenosis (mean of 15.3 versus 10.5 days).

### Intermediate-term Outcomes in the Group Assessed by MRI Prior to TCPC

Median follow-up was 766 days (interquartile range 231 to 1319 days). Current life status was checked by referring to their National Health Service (NHS)
number. One patient died from an intractable arrhythmia within 24 hours. No patient required takedown of the TCPC, extra-corporeal membrane oxygenation or transplantation. These outcomes are comparable to the published literature (42,105,117-123) (table 12). Three patients have PLE and two of these patients have required LPA stenting (228 and 320 days after TCPC) to optimize haemodynamics. One patient had a permanent pacemaker implanted for symptomatic bradycardia related to nodal rhythm and another required cardioversion for one episode of atrial flutter.
Table 12 TCPC outcomes compared to the published literature

<table>
<thead>
<tr>
<th>Group</th>
<th>Number (GALTIS)</th>
<th>Mortality</th>
<th>Transplant</th>
<th>Takeover</th>
<th>ECMO</th>
<th>PICU stay, days</th>
<th>Hospital stay, days</th>
<th>Chest drain days</th>
<th>Ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphonse, 2005</td>
<td>121 (16%)</td>
<td>3 (3%)</td>
<td>0 (0%)</td>
<td>2 (3%)</td>
<td>7 (3%)</td>
<td>6 (4-8)</td>
<td>18 (5-71)</td>
<td>11 (1-42)</td>
<td>6 (4-10)</td>
</tr>
<tr>
<td>Bexar, 2001</td>
<td>121 (16%)</td>
<td>3 (3%)</td>
<td>0 (0%)</td>
<td>2 (3%)</td>
<td>7 (3%)</td>
<td>6 (4-8)</td>
<td>18 (5-71)</td>
<td>11 (1-42)</td>
<td>6 (4-10)</td>
</tr>
<tr>
<td>Curny, 2004</td>
<td>10 (13%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>D'Alton, 2001</td>
<td>100 (13%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fabbri, 2001</td>
<td>98 (13%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fotherby, 2001</td>
<td>25 (36%)</td>
<td>3 (3%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lamers, 2001</td>
<td>101 (13%)</td>
<td>3 (3%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lima, 2004</td>
<td>121 (16%)</td>
<td>3 (3%)</td>
<td>0 (0%)</td>
<td>2 (3%)</td>
<td>7 (3%)</td>
<td>6 (4-8)</td>
<td>18 (5-71)</td>
<td>11 (1-42)</td>
<td>6 (4-10)</td>
</tr>
<tr>
<td>Salmin, 2007</td>
<td>100 (13%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sauled, 2008</td>
<td>135 (19%)</td>
<td>2 (2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Prabhu, 2009</td>
<td>24 (4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Prabhu, 2011</td>
<td>71 (10%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

ECMO = extracorporeal membrane oxygenation, PICU = pediatric intensive care unit, GALTIS = group of adult lung transplant intensive care unit survival.
DISCUSSION

Assessment of these patients using MRI with CVP measurement pre-TCPC only, with invasive pulmonary vascular resistance assessment reserved for a small subset of high-risk patients produces outcomes comparable to routine invasive cardiac catheterization assessment as described in the published literature (table 12) (42,105,117-123).

LIMITATIONS

As there was a complete change in clinical practice from catheterization to MRI with CVP assessment, a control population was not available for comparison. The current median follow-up time is just over 2 years and so information on longer-term complications is limited at this stage.

CONCLUSION

Assessment using MRI with CVP measurement pre-TCPC only, with invasive pulmonary vascular resistance assessment reserved for a small subset of high-risk patients, produces outcomes comparable to routine invasive cardiac catheterization assessment as described in the published literature (42,105,117-123).
SUMMARY

Background: Suitability for TCPC in HLHS is traditionally assessed using cardiac catheterisation. Studies have shown that cardiac MRI is equivalent to cardiac catheterisation for selection for HF; we propose that MRI with CVP measurement avoids routine cardiac catheterization prior to TCPC and produces outcomes equivalent to the published literature.

Methods: MRI with CVP measurement was performed pre-TCPC. Post-operative and intermediate-term TCPC outcomes (n=71) were compared to the published literature.

Results: All patients were suitable for TCPC (mean pre-TCPC CVP 12mmHg; range 6-16 mmHg) with comparable results to patients assessed with cardiac catheterization.

Conclusions: MRI coupled with CVP measurement pre-TCPC has produced comparable results to patients assessed with cardiac catheterization.
Chapter 10 - Serial Magnetic Resonance Imaging in Hypoplastic Left Heart Syndrome Gives Valuable Insight Into Ventricular And Vascular Adaptation

J Am Coll Cardiol. 2013 Feb 5;61(5):561-70

AIM
To review changes in ventricular and vascular parameters before and after the hemi-Fontan in patients undergoing staged palliation for HLHS and assess the factors that influence these changes.

HYPOTHESIS
There will be a reduction in RV volumes following the unloading from the change from the arterial shunt to HF circulation and that this reduction may be influenced by tricuspid regurgitation.

INTRODUCTION
The use of cardiac MRI prior to HF and subsequently prior to TCPC provides the opportunity to examine the changes in the RV, neo-aorta and pulmonary artery size after the volume reduction following the removal of the systemic to pulmonary artery shunt. MRI can accurately measure ventricular volumes, ejection fraction and aortic flow. This can be coupled with measurement of the pressure in the internal jugular vein under the same general anaesthetic as the MRI scan prior to TCPC, providing an indication of pulmonary arterial pressure. In this study we investigate, with serial MRI in children with HLHS the vascular and ventricular changes that occur after the HF.
METHODS

Study population and design

Patients with HLHS who had undergone the Norwood procedure, HF and TCPC from February 2003 to July 2010 and had pre-operative evaluation with cardiac MRI were included. Patients were identified using the departmental database (Heartsuite XP 3.9.14, Systeria, Glasgow UK). Patient demographics, surgical findings and inter-stage procedures were collected from the patient case notes and the departmental database.

CVP measurement was taken in patients pre-TCPC under the same general anaesthetic as the MRI. If the central venous pressure was >16mmHg, MRI and cardiac catheterization in a hybrid MRI catheter suite was performed allowing calculation of pulmonary vascular resistance (61). Additionally, some children were referred primarily for MRI cardiac catheterization by the child’s principal cardiologist for vascular and PVR assessment (e.g. severe tricuspid regurgitation, severe RV dysfunction on echocardiography, previous total anomalous pulmonary venous drainage or significant airway pathology).

Image acquisition and analysis

Following a survey and sensitivity encoded (SENSE) reference scan, a real-time, interactive, SSFP sequence was used to identify the imaging planes that would be used in subsequent scans. Cine SSFP four, two and three chamber views were performed to delineate ventricular morphology and the subjective degree of TR. As the effect on the RV was more likely to be due to the residual morphology of the LV than the presence/absence of forward flow, LV morphology was described as: no LV visible or slit-like LV, globular LV or
Borderline LV. Borderline LV was defined as a more mildly hypoplastic LV that could be considered potentially able to support the systemic circulation (4). In general, the no visible or slit like LV corresponded to the mitral atresia and aortic atresia subgroup, the globular LV corresponded to the mitral stenosis and aortic atresia subgroup and the ‘borderline’ LV to the mitral stenosis and aortic stenosis subgroup.

Tricuspid regurgitation was qualitatively classified as none/trivial/mild or moderate/severe from the 2D SSFP cine images. If quantitative data were available, TR fraction was calculated from ventricular stroke volume (from short axis stack) less neo-aortic forward flow (from phase contrast flow) and expressed as a percentage of the ventricular stroke volume. Patients with large ventricular septal defects were excluded from the quantitative assessment of TR due to the unquantified shunt across the ventricular septal defect.

RV EDV and ESV, SV and EF were calculated from a stack of short-axis 2D SSFP cine images using the disc summation method as described in Chapter 8. Phase contrast flow measurements were analyzed to calculate neo-aortic, SVC and, in those pre-TCPC, branch pulmonary artery flow. SVC flow was obtained below the innominate and measured bilaterally if the patient had bilateral SVCs. Neo-aortic flow was measured below the level of the Damus-Kaye-Stansel anastamosis. Differential pulmonary blood flow was calculated from independent branch flows or in some patients with only SVC and one branch pulmonary artery flow from RPA = SVC minus LPA or LPA = SVC minus RPA. All volumes and flows were indexed to body surface area (BSA) (124). Differential branch pulmonary flows were not performed prior to HF as turbulent
and fast flow patterns from an aorto-pulmonary shunt in small pulmonary vessels make it very difficult to obtain reliable flow results.

First pass breath-hold 3D Gadolinium enhanced angiography of the thorax as well as respiratory navigated three-dimensional 3D SSFP scans of the heart and great vessels (125) were performed. Gadolinium enhanced angiography was preferred for the branch pulmonary artery measurements as the authors found this provided better image quality for small branch pulmonary arteries than three-dimensional 3D SSFP. For larger vessels both techniques have been shown previously to yield similar results (126). Branch pulmonary artery and aortic areas were measured as described in Chapter 8.

Areas were assessed using multi-planar reformat and indexed to body surface area (127). The ratio of the narrowest measurement in the LPA and the proximal LPA was calculated as well as the ratio of the upper descending aorta and the diaphragmatic aorta.

The presence and type of collateral vessels (aorto-pulmonary, veno-venous or arterio-venous) was recorded based on a review of Gadolinium enhanced angiography and 3D SSFP images assessed using multi-planar reformat. All analyses (flows and volumes) were performed using Viewforum EWS Version 2.0 (Philips Healthcare, Best, The Netherlands) by two members of the research team (HBR, AB), independent of each other’s analysis. Observers were blinded to the clinical data.

CVP was measured using a water manometer connected to a cannula in the internal jugular vein. The measurements were converted from cm of water to
mm of Hg. Patients who underwent MRI cardiac catheterization had direct pressure measurements of the branch pulmonary arteries with wedge pressures to calculate the trans-pulmonary gradient and, combined with MRI phase contrast flow, pulmonary vascular resistance (61) using the equation: pulmonary vascular resistance = (mean pulmonary artery pressure minus pulmonary wedge pressure) divided by (pulmonary blood flow/body surface area). Interventions under MRI guidance were not performed in this study group.

Statistics

Statistical analyses were undertaken using Stata 11 (StataCorp, Texas). Bivariate comparisons comprised paired t-tests and Wilcoxon signed rank tests as appropriate. Inter-user variability of the right ventricular volume measurements was quantified using an intraclass correlation coefficient two-way model with absolute agreement (also known as ICC(2,1)), whereby each single measurement was assessed by two authors (HBR, AB) (128). Linear regression modelling was used to quantify factors associated with change in volumetric parameters between operative stages. Variables were chosen based on clinical considerations and all were tested simultaneously (i.e. full models only were used). Partial $r^2$ values were reported to quantify the contribution of individual predictors to overall model fit. Model stability was checked using residual versus fit and leverage versus residual squared plots. Outliers were screened via calculation of Cooks distance and standardized fit betas. The functional form of predictors was assessed using augmented component-plus-residual plots. A p value of <0.157 was classified as significant within the regression models (this value maximizes model prediction, as it is based upon
penalty criteria, such as Akaike Information Criteria and Mallows Cp). Of note, all model stability and outlier checks outlined above revealed no problems.

RESULTS

Between February 2003 and July 2010, 75 patients with HLHS underwent the Norwood procedure, HF and TCPC at our institution (Figure 43). Three patients were assessed with MRI pre-HF and standard cardiac catheter pre-T CPC and one was assessed prior to HF and TCPC by standard cardiac catheter. Therefore, 71 patients underwent assessment with cardiac MRI prior to TCPC. Of the 71 patients assessed prior to TCPC with MRI (n = 66) or MRI cardiac catheterization (n = 5), 63 patients had cardiac MRI assessment prior to hemi-Fontan additionally. Five patients did not have volumetry and flow raw data available for re-analysis. The serial data of the 58 remaining patients was used for assessing remodelling before and after HF. All patients assessed in this era were deemed suitable for TCPC.
Figure 43 Patients undergoing total cavopulmonary connection between February 2003 and July 2010 at Evelina Children’s Hospital. The 71 patients indicated by (*) had pre-TCPC MRI. The 58 patients indicated by (§) were used to assess remodeling before and after hemi-Fontan. Five patients had assessment of pulmonary vascular resistance in a combined MRI – cardiac catheterization procedure.

Demographics and cardiovascular morphology for the patients are described in Table 13 and table 14. Interstage procedures are recorded in Table 15. All patients had undergone the classical Norwood procedure with creation of an aortopulmonary Damus-Kaye-Stansel anastomosis, reconstruction of the aortic arch and an insertion of a 3.0mm, 3.5 or 4.0mm modified Blalock-Taussig shunt between the innominate artery and right pulmonary artery. Subsequently, HF and fenestrated lateral tunnel TCPC was performed.
Table 13 Demographics and morphological details, n = 58

<table>
<thead>
<tr>
<th></th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>40 (69.0%)</td>
</tr>
<tr>
<td>Antenatal diagnosis</td>
<td>52 (91.2%)</td>
</tr>
<tr>
<td>Gestation &gt;37/40</td>
<td>54 (96.4%)</td>
</tr>
<tr>
<td>Normal atrial situs</td>
<td>58 (100%)</td>
</tr>
<tr>
<td>Apex to the left</td>
<td>58 (100%)</td>
</tr>
<tr>
<td>Left ventricular morphology</td>
<td></td>
</tr>
<tr>
<td>No visible/slit like LV</td>
<td>25 (43.1%)</td>
</tr>
<tr>
<td>Globular LV</td>
<td>27 (46.6%)</td>
</tr>
<tr>
<td>Borderline LV*</td>
<td>6 (10.3%)</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>4 (6.9%)</td>
</tr>
<tr>
<td>Bilateral SVC</td>
<td>6 (10.3%)</td>
</tr>
<tr>
<td>Norwood Procedure Shunt</td>
<td></td>
</tr>
<tr>
<td>3.5mm</td>
<td>48 (84.2%)</td>
</tr>
<tr>
<td>4.0mm</td>
<td>9 (15.8%)</td>
</tr>
<tr>
<td>Birth weight Mean (SD)</td>
<td>3.06 (0.45)</td>
</tr>
</tbody>
</table>

Left ventricle (LV), superior vena cava (SVC)

*Borderline LV: a left ventricle which is mildly hypoplastic, which may be considered potentially able to support the systemic circulation
**Table 14** Mean (SD) age, weight and saturations, n = 58

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Age, years</th>
<th>Weight, kg</th>
<th>Saturations, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norwood Procedure</td>
<td>0.01 (0.02)</td>
<td>3.07 (0.42)</td>
<td>-</td>
</tr>
<tr>
<td>Pre-HF MRI</td>
<td>0.44 (0.18)</td>
<td>5.80 (1.27)</td>
<td>76.5 (7.2)</td>
</tr>
<tr>
<td>HF</td>
<td>0.58 (0.20)</td>
<td>6.45 (1.47)</td>
<td>-</td>
</tr>
<tr>
<td>Pre-TCP MRI</td>
<td>2.91 (0.81)</td>
<td>13.01 (2.11)</td>
<td>82.1 (5.0)</td>
</tr>
<tr>
<td>TCPC</td>
<td>3.45 (0.89)</td>
<td>14.02 (2.13)</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 15** Interstage and associated procedures, n=58

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Pre-HF</th>
<th>At HF</th>
<th>Pre-TCP</th>
<th>At TCPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic arch*</td>
<td>4 (6.9%)</td>
<td>11 (19.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Pulmonary arteries</td>
<td>2 (3.4%)</td>
<td>4 (6.9%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Tricuspid valve</td>
<td>0 (0.0%)</td>
<td>1 (1.7%)</td>
<td>2 (3.4%)</td>
<td>11 (19.0%)</td>
</tr>
<tr>
<td>Collateral occlusion§</td>
<td>0 (0.0%)</td>
<td>2 (3.4%)</td>
<td>3 (5.2%)</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>Other^</td>
<td>2 (3.4%)</td>
<td>1 (1.7%)</td>
<td>3 (5.2%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

All pre-HF procedures were catheter procedures.

*the 4 patients who had aortic arch balloons pre-HF are included in the 11 who had an arch repair at HF; § one patient had veno-venous collaterals occluded at HF and then veno-venous collaterals and aorto-pulmonary collaterals occluded prior to TCPC; ^ pre-HF: shunt stent; atrial septal stent. At HF: re-implantation of the innominate artery. Pre TCPC: surgical relief of pulmonary vein stenosis and ligation of collateral; plication of eventration of the right diaphragm
**Ventricular Remodelling**

The volume reduction after HF resulted in a significant fall in RV cardiac index (5.5l/min/m$^2$ to 4.5l/min/m$^2$, 18% fall). Indexed RV stroke volume (iSV) remained relatively constant, but there was a significant fall in heart rate (HR). There was also a fall in RV indexed end diastolic volume (iEDV) and indexed end systolic volume (iESV) (11% and 27% respectively), resulting in an overall increase in the mean RV ejection fraction (EF) from 51% to 59%.

**Table 16** Volumetric and flow data, n=58

<table>
<thead>
<tr>
<th></th>
<th>Pre-HF MRI</th>
<th>Pre-TCPC MRI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Range</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>*Heart rate</td>
<td>113.5 (14.7)</td>
<td>83-150</td>
<td>89.3 (16.0)</td>
</tr>
<tr>
<td>*iEDV, mls/m$^2$</td>
<td>98.1 (35.5)</td>
<td>48.7-222.6</td>
<td>87.2 (22.4)</td>
</tr>
<tr>
<td>*iESV, mls/m$^2$</td>
<td>49.5 (24.4)</td>
<td>15.3-126.5</td>
<td>36.0 (12.9)</td>
</tr>
<tr>
<td>iSV, mls/m$^2$</td>
<td>48.6 (14.7)</td>
<td>19.9-105.6</td>
<td>50.9 (12.9)</td>
</tr>
<tr>
<td>*CI, l/min/m$^2$</td>
<td>5.5 (2.0)</td>
<td>2.5-13.4</td>
<td>4.5 (1.4)</td>
</tr>
<tr>
<td>*EF, %</td>
<td>51.1 (8.8)</td>
<td>28.4-72.4</td>
<td>59.3 (8.1)</td>
</tr>
<tr>
<td>RSVC iSV, mls/beat/m$^2$</td>
<td>-</td>
<td>-</td>
<td>19.8 (6.7)</td>
</tr>
<tr>
<td>(n = 53)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LSVC iSV, mls/beat/m$^2$</td>
<td>-</td>
<td>-</td>
<td>10.2 (8.6)</td>
</tr>
</tbody>
</table>
A linear regression model (Table 17) was used to look at the factors that contribute to changes in the iEDV and iESV before and after HF. The factor with the biggest effect on change in iEDV (or iESV) was the pre-HF iEDV (or iESV), accounting for two thirds of the variability within the model (partial $R^2$ 0.68), with ventricular morphology and degree of TR (assessed subjectively on cine images) pre-HF contributing to the bulk of the remainder. After adjustment for the other variables the pre-HF indexed volumes contributed on average to a 29% drop in iEDV (coefficient -0.71) and a 30% drop in iESV (coefficient -0.70), meaning that the largest absolute fall was seen in those with the most dilated ventricles.
**Table 17** Model for change in indexed end diastolic volume (n=58; \( r^2 = 0.79, \) adjusted \( r^2 = 0.75), n=58

<table>
<thead>
<tr>
<th></th>
<th>Coefficient (95% CI)</th>
<th>P value</th>
<th>Partial ( r^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Pre-HF iEDV</td>
<td>-0.71 (-0.86 to -0.57)</td>
<td>0.000*</td>
<td>0.68*</td>
</tr>
<tr>
<td>*Borderline LV morphology</td>
<td>-20.12 (-33.01 to -7.23)</td>
<td>0.003*</td>
<td>0.17*</td>
</tr>
<tr>
<td>*Moderate/severe TR on pre-HF MRI</td>
<td>16.19 (4.61 to 27.78)</td>
<td>0.007*</td>
<td>0.14*</td>
</tr>
<tr>
<td>*Globular LV morphology</td>
<td>-6.54 (-14.20 to 1.11)</td>
<td>0.09*</td>
<td>0.06*</td>
</tr>
<tr>
<td>*AP collaterals seen on pre-HF MRI</td>
<td>6.23 (-0.97 to 13.44)</td>
<td>0.09*</td>
<td>0.06*</td>
</tr>
<tr>
<td>Age at HF</td>
<td>-7.53 (-26.75 to 11.68)</td>
<td>0.43</td>
<td>0.01</td>
</tr>
<tr>
<td>Pre-HF EF</td>
<td>-0.19 (-0.73 to 0.34)</td>
<td>0.47</td>
<td>0.01</td>
</tr>
<tr>
<td>ACE-I therapy at time of pre-HF MRI</td>
<td>1.83 (-5.65 to 9.30)</td>
<td>0.63</td>
<td>0.01</td>
</tr>
<tr>
<td>Time between HF and pre-T CPC MRI, yrs</td>
<td>-0.40 (-4.80 to 4.00)</td>
<td>0.86</td>
<td>-</td>
</tr>
</tbody>
</table>

Confidence interval (CI), angiotensin converting enzyme inhibitor (ACE-I)

*Significant results

Patients with a borderline LV which is still contributing to cardiac output also appeared to have a greater degree of remodelling, with on average an additional 20ml fall in iEDV after HF. This was seen to a lesser degree in those with a globular LV morphology.
Presence of aortopulmonary (AP) collaterals pre-HF had a negative impact on remodelling, on average adding 6.2mls to the iEDV. Age at HF was not associated with a change in iEDV or iESV, nor was the use of ACE-I therapy at the time of the pre-HF scan.

The group-averaged relationship between iEDV and indexed neo-aortic stroke volume before and after HF (n=58) is described in Figure 44. The regression line of best fit for the group as a whole can be interpreted as consistent with the Frank-Starling mechanism (129), which demonstrates a shift to the left and upwards after the HF (i.e. MR1 versus MR2). This is also shown in Figure 45, whereby changes in iEDV versus stroke volume are shown for individual patients (i.e. each patient acts as their own control). An improvement in cardiac efficiency is highlighted by vectors travelling to the left of the line of identity, which occurs in the majority of patients (67%). This is consistent with the improvement in ejection fraction highlighted in Table 16.
Figure 44 Indexed right ventricular end diastolic volume plotted against indexed neo-aortic stroke volume showing an upward and leftward shift in the curve (which resembles the Frank-Starling curve) after HF, suggesting improved efficiency. Curves are calculated using fractional polynomial regression based on the 58 paired scans; solid lines represent predicted fit, dashed lines 95% confidence intervals. MRI 1 is pre-HF, MRI2 is pre-TCPC.
Figure 45 Change in loading conditions (indexed right ventricular end diastolic volume) and indexed stroke volume within individual patients (n=58) between MR1 (pre-HF) and MR2 (pre-TCPC). Each patient acts as his own control, thus the starting point (pre-HF) is situated at the reference point (0,0). An improvement in cardiac efficiency is highlighted by vectors travelling to the left of the line of identity, which occurs in the majority of patients (67%).

Tricuspid Regurgitation

To improve statistical power, TR was assessed subjectively on 2D SSFP cine images in the 58 paired MRI exams, as not all MRI exams provided enough quantitative data for TR calculation. The presence of moderate or severe TR pre-HF contributed on average an increase of 16mls to the iEDV. Quantitative data for TR calculation was available in 9 patients with moderate (20% to 40%) or severe (>40%) TR (regurgitant fraction 27.0 - 72%, mean 38%). Three of these patients (regurgitation fractions 37%, 68% and 24% respectively) underwent tricuspid valve repair at HF. To address the potential influence of
these 3 patients on ventricular remodelling, we performed a sensitivity analysis by re-running the regression model seen in Table 17. After exclusion of these 3 patients the model fit did not change significantly ($r^2$ went from 0.79 to 0.77) and neither the significance levels nor the partial $r^2$ values for individual variables changed appreciably. Similarly, the relative changes in coefficients were modest, ranging from -10% to +25%. Thus we can conclude that tricuspid valve repair did not have a significant influence on ventricular remodelling. However this must be interpreted with caution, due to the small number of patients who underwent tricuspid valve repair ($n = 3$).

**Vascular Remodelling (table 18)**

Measurement of the RPA cross-section is challenging after the HF, due to the proximity of the anastomosis to the RPA branching. Consequently, measurements of the distal RPA were not possible in all cases. The indexed LPA area increased proximally but reduced distally. The indexed RPA area also reduced after the HF. Mean differential flow pre-TCPC was 63.0% to the right and 37.0% to the left. There was a significant difference in LPA flow with reduced flow in those with the ratio of the narrowest section of the LPA to the proximal LPA < 50%. There was no correlation between the narrowest area of the LPA and superior vena cava iSV, however superior vena cava iSV correlated positively with distal RPA size (Pearson 0.550, $p = 0.004$).
**Table 18** Pulmonary artery and aortic sizes, n=58

<table>
<thead>
<tr>
<th></th>
<th>Pre-HF MRI</th>
<th>Pre-TCPC MRI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Range</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>*Distal RPA, mm²/m²</td>
<td>166.2 (76.4)</td>
<td>42.7-371.2</td>
<td>158.8 (56.7)</td>
</tr>
<tr>
<td>*Proximal LPA, mm²/m²</td>
<td>91.6 (86.2)</td>
<td>15.4-582.9</td>
<td>101.4 (53.8)</td>
</tr>
<tr>
<td>*Narrowest LPA, mm²/m²</td>
<td>72.4 (54.5)</td>
<td>8.7-282.9</td>
<td>52.1 (25.6)</td>
</tr>
<tr>
<td>*Narrowest LPA:Proximal LPA, %</td>
<td>81.2 (24.2)</td>
<td>16.9-133.3</td>
<td>55.8 (21.8)</td>
</tr>
<tr>
<td>Native aorta, mm²/m²</td>
<td>63.0 (80.4)</td>
<td>11.1-450.1</td>
<td>55.7 (61.5)</td>
</tr>
<tr>
<td>Neo-aorta sinus, mm²/m²</td>
<td>704.9 (170.7)</td>
<td>400.1-1161.7</td>
<td>680.3 (184.2)</td>
</tr>
<tr>
<td>Ascending aorta, mm²/m²</td>
<td>533.2 (155.0)</td>
<td>258.2-1001.1</td>
<td>516.4 (145.9)</td>
</tr>
<tr>
<td>Transverse arch, mm²/m²</td>
<td>425.3 (149.6)</td>
<td>189.3-877.9</td>
<td>440.9 (168.4)</td>
</tr>
<tr>
<td>Upper descending aorta, mm²/m²</td>
<td>163.6 (65.3)</td>
<td>46.4-335.7</td>
<td>177.3 (54.2)</td>
</tr>
<tr>
<td>*Lower descending aorta, mm²/m²</td>
<td>148.2 (45.5)</td>
<td>58.9-318.2</td>
<td>112.0 (31.4)</td>
</tr>
<tr>
<td>*Upper:lower descending aorta</td>
<td>1.14 (0.38)</td>
<td>0.25-2.24</td>
<td>1.63 (0.48)</td>
</tr>
</tbody>
</table>

*p<0.05 on Wilcoxon

There are limited numbers of measurements of the distal right pulmonary artery after HF due to the proximity of the HF anastomosis to the right pulmonary artery branches making measurement not possible.
We examined whether LPA size at the narrowest point (after adjustment for age) at MR1 and MR2, or change in LPA size (after adjustment for age and presence of left pulmonary arterioplasty prior to MR2) was associated with a range of anatomical and flow-related factors. Anatomical factors included: ventricular dilatation (iEDV) and proximal aortic area (neo- and native-aorta). Flow related factors included total cardiac output (pre-HF only), presence of shunt narrowing (pre-HF only) and collaterals (both aortopulmonary and veno-venous). LPA growth had a weak positive association with proximal aortic area growth; however no other factor was consistently associated with LPA narrowing.

There was no significant difference in the indexed sizes of the native aorta, transverse aortic arch and proximal descending aorta after HF, even once patients with residual coarctation requiring repair between the pre-HF and pre-TCPC MRI scans were accounted for. The indexed area of the descending aorta at the level of the diaphragm, however, significantly reduces after the HF.

**DISCUSSION**

The patient cohort observed in this study showed that serial MRI in HLHS provides comprehensive information on RV function and vascular morphology. The range of RV volumes was wide, encompassing patients with moderate or severe TR and smaller volumes in those with significant forward flow through the left heart. The reduction in volume loading after HF, with iESV and iEDV both falling as expected, led to an increase in EF, although there were no factors which predicted the increase in EF. A reduced fall in ventricular volumes was associated with significant TR as well as the presence of AP collaterals,
both of which are known to volume load the ventricle. As the majority of patients (84%) in this group had 3.5mm shunts, it was not possible to evaluate the effect of shunt size.

It was noted that nearly all of the patients with moderate or severe TR pre-HF also had moderate or severe TR pre-TCPC; persistent TR would explain this adverse remodelling and increase in iEDV (even after excluding those 3 patients who underwent TV repair as part of their HF procedure). This also suggests that the moderate or severe TR is not purely a result of annular dilatation, but an inherent abnormality of the tricuspid valve. Interestingly, age at HF was not significantly associated with greater reduction in ventricular volumes. This therefore suggests that early surgery does not appear to be indicated solely to help with the post-HF remodelling process.

Normal ranges for MRI EF have previously been described in the post-TCPC single ventricle setting (130) but we have demonstrated the impact of operative stage which should additionally be taken into account.

There was a marked discrepancy in the relative sizes of the RPA and LPA, with the proximal LPA being approximately 2/3 of the size of the RPA past the HF anastomosis. This discrepancy was more marked pre-HF. The mechanism of this is likely to be related to the change in the flow dynamics of pulmonary blood flow, e.g. from an arterial shunt in the RPA directing more of the flow into this vessel, to the lower pressure HF anastomosis redistributing the blood more evenly. Interestingly, the superior vena cava iSV positively correlated with the RPA size.
LPA stenosis is known to be a significant problem in HLHS (4). We found no significant factors affecting LPA growth in this group, though this may be because LPA narrowing in HLHS is a universal problem and because the diagnosis of HLHS in itself is a risk factor. LPA size will need close monitoring in this patient cohort and some of these patients may still require intervention to address this in the future. The timing of intervention should take into account the potential for future growth of the left pulmonary artery bed in the setting of significant proximal stenosis.

There was no aortic narrowing in any of the patients pre-TCPC. The 3D MRI images show that the areas reconstructed in the initial Norwood surgery (proximal neo-aorta, transverse arch and proximal descending aorta) did not remodel after HF. This is likely to be related to reduced compliance of these vessels secondary to the incorporated homograft tissue. As there is significant somatic growth between the two MRI scans, areas indexed to body surface area were chosen for statistical analysis. Recently, Voges et al. showed reduced aortic wall distensibility in similar areas in 40 older patients who had Norwood surgery for HLHS (131). In our patients, the aorta at the level of the diaphragm did remodel with a reduction in area/m², which is probably due to the reduced cardiac output through the aorta following HF. It must be noted however that these studies were performed under general anaesthetic and so cardiac output and systemic blood pressure may differ from the normal situation in an awake patient.
Changes in indexed neo-aortic stroke volumes versus end diastolic volumes across the whole cohort resembled the Frank-Starling relationship (Figure 44). This curve showed an upward shift comparing the pre-TCPC data with pre-HF (Figure 44 and Figure 45). The hemi-Fontan may therefore confer a benefit in RV contractility across the population. As contractility was not directly measured in this study the shift in the curve may also be attributed to other causes, such as changes in systemic vascular resistance, which were not assessed in our patients.

LIMITATIONS
Pulmonary to systemic blood flow ratio was not assessed due to technical reasons in the pre-HF patients. Therefore the relation of this to the right ventricular remodelling was not assessed. MRI scans were performed under general anaesthetic which can affect cardiac output, systemic and pulmonary vascular resistances, particularly in the single ventricle setting when the patient is supine with positive pressure ventilation.

CONCLUSION
MRI scans performed prior to HF and TCPC allow an insight into vascular and ventricular remodelling of the systemic RV. There were no factors significantly impacting growth of the LPA, however a significant reduction in RV iEDV and iESV with a constant iSV leading to an increased EF was demonstrated. The HF appears to not only volume off-load the ventricle but may also improve contractility.
SUMMARY

Background: The systemic RV in HLHS is subject to significant changes in volume loading throughout the surgical stages of palliation, particularly after the hemi-Fontan.

Methods: Fifty-eight patients had paired pre-HF and pre-TCPC MRI for assessment of changes of RV volumes, neo-aortic flow and vascular dimensions.

Results: Comparison of pre-HF and pre-TCPC MRI results showed a decrease of iEDV and iESV (98 to 87ml/m², 50 to 36ml/m² respectively) with stroke volume remaining constant (49 vs. 51mls/m²) leading to an increased RV EF (51% vs. 59%). These findings persisted after excluding the three patients who underwent tricuspid valve repair as part of their HF procedure. iEDV plotted against neo-aortic stroke volume demonstrated a Frank-Starling like curve that shifted upwards after HF. The indexed distal left and right pulmonary artery cross-sectional areas were reduced after HF.

Conclusions: In HLHS serial MRI shows increased RV ejection fraction with preserved stroke volume after HF and with significant reduction in ventricular volumes. Indexed distal LPA and RPA areas were decreased after HF.
Chapter 11 - Subjective Evaluation of Right Ventricular Systolic Function in Hypoplastic Left Heart Syndrome: How Accurate is it?


AIM

To assess subjective assessment of RV systolic function in patients with HLHS compared to objective measurement using MRI ejection fraction, and the impact that experience has on this assessment.

HYPOTHESIS

The most experienced echocardiographers will have a subjective impression of RV function that agrees closely with MRI. The level of agreement of echocardiographers with MRI results will be impacted by the training and experience of the echocardiographer.

INTRODUCTION

In day-to-day clinical practice, either in the outpatient clinic, inpatient ward or peri-operative setting, echocardiography is the mainstay of assessment of RV systolic function in HLHS. Although many qualitative techniques to determine systolic and diastolic function have been described (6), these have not been fully investigated in HLHS and are not utilised in routine clinical practice.

Additionally the echocardiographer must deal with limited views, particularly in the post-operative period, and, in the ward or outpatient clinic, the compliance of infants and young children. More simple indices such as tricuspid annular
displacement (124) and an operator dependent subjective assessment of RV systolic function, are therefore still commonly used in spite of evidence to suggest that subjective evaluation of the ventricular function in single ventricle circulations correlates poorly with MRI (130).

The current gold standard for the assessment of systemic RV function in HLHS is cardiac MRI (6), however this is a) clearly not feasible in the majority of clinical situations, b) usually requires general anaesthesia in children and c) is an investigation not readily available in all centres. In this retrospective study, we sought to evaluate the accuracy of subjective assessment of RV systolic function in HLHS, as well as investigating whether this was determined by operator experience.

**METHODS**

All patients with HLHS undergoing cardiac MRI under general anaesthetic were included in the study. Patients were excluded if parental consent was not given or if there was cardiovascular instability during the MRI scan, precluding additional time for echocardiography. Data was prospectively acquired but retrospectively analysed for this study.

**MRI Acquisition**

Two-dimensional SSFP cine imaging orientated to the short axis of the RV was used to calculate ventricular volumes using the disc summation method as described in Chapter 8. MRI EF was categorised as used in our clinical department: good function (greater than or equal to 50%), moderate function (40-49%) and poor function (less than 40%).
**Echocardiogram Acquisition**

Echocardiograms were undertaken immediately after the MRI scan under the same general anaesthetic to avoid potential physiological changes. Subcostal, apical, long and short axis views were obtained, whenever acoustic windows permitted. Two dimensional cine images (no colour) were anonymised and reviewed by a range of observers working within the department of congenital heart disease, with varying levels of experience of echocardiography in this patient group. Observers were blinded to the MRI results. Each observer was asked on the basis of the images to categorise global RV systolic function as good, moderate or poor.

**Observer Grouping**

Observers were grouped by experience level: senior house officers in paediatric cardiology with less than 6 months exposure to echocardiography (n=5), junior congenital heart disease trainees with less than 3 years of training (n=6), senior congenital heart disease trainees with more than 3 years of training (n=5), cardiac physiologists (n=5) and consultant paediatric cardiologists (n=7).

**Statistical analysis**

Observers were scored based on the concordance of their visual assessment of RV systolic function on echocardiogram with MRI EF. i.e.: 0 concordant, 1 if a single functional echocardiographic grade different and 2 if functional echocardiographic grade differed by 2 compared to the MRI scan. For example, if an MRI EF was ‘good’ (greater than 50%) and the observer rated it as poor echocardiographically, this was considered as two grades different. Each
observer was given a total score (calculated from the total of grades different); this was then averaged for each observer experience group. Thus a low score means that there was a high level of agreement between the echocardiographic assessment and MRI and a high score indicates less agreement between the echocardiographic and MRI methods. To evaluate variability in assessment in each observer group, an inter-class correlation co-efficient was calculated within each observer group (two-way random, absolute agreement).

An important clinical consideration is the ability of echocardiography to accurately detect reduced RV systolic function. If an RV EF of <50% assessed by MRI is regarded as ‘reduced function’ sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of subjective echocardiographic function were calculated for each observer group. Echocardiographically assessed moderate or poor RV function was used to define ‘reduced function’.

All echocardiograms were graded for quality by the author and Dr A Bell. Scans were graded from 1 (poor quality) to 4 (excellent quality). The inter-class correlation co-efficient was performed to assess inter-observer variation for grading of the quality of echocardiograms (two-way random, absolute agreement).

RESULTS
Twenty-eight patients with HLHS underwent an echocardiogram under the same general anaesthetic as MRI between July 2007 and January 2009. All patients had MRI and echocardiogram images available for analysis. The
demographics and MRI results are shown in Table 19. Twenty-three (82%) of patients had an MRI EF of greater than or equal to 50%, 4 (14%) had an MRI EF 40-49% and 1 (4%) had an MRI EF less than 40%. The median MRI EF for the whole group was 59% (33-78%).

### Table 19 Patient demographics and MRI results as median (range)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number (%)</th>
<th>Age, months</th>
<th>Weight, kg</th>
<th>Sats, %</th>
<th>iEDV, mls/m²</th>
<th>iESV, mls/m²</th>
<th>iSV, mls/m²</th>
<th>iCO, l/min/m²</th>
<th>EF, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-NW</td>
<td>14 (50%)</td>
<td>3</td>
<td>5.0</td>
<td>78</td>
<td>92</td>
<td>47</td>
<td>46</td>
<td>4.8</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2-5)</td>
<td>(3.4-6.8)</td>
<td>(72-98)</td>
<td>(48-113)</td>
<td>(16-57)</td>
<td>(26-60)</td>
<td>(2.2-6.7)</td>
<td>(33-63)</td>
</tr>
<tr>
<td>Post-HF</td>
<td>11 (39%)</td>
<td>27.5</td>
<td>12.9</td>
<td>84</td>
<td>79</td>
<td>32</td>
<td>51</td>
<td>4.3</td>
<td>62.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(24-49)</td>
<td>(10.4-15.4)</td>
<td>(70-89)</td>
<td>(54-173)</td>
<td>(15-77)</td>
<td>(34-96)</td>
<td>(3.6-10)</td>
<td>(43-78)</td>
</tr>
<tr>
<td>Post-Fontan</td>
<td>3 (11%)</td>
<td>104</td>
<td>29.0</td>
<td>92</td>
<td>70</td>
<td>23</td>
<td>46</td>
<td>3.1</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(76-111)</td>
<td>(23.6-32.5)</td>
<td>(92-95)</td>
<td>(52-75)</td>
<td>(20-29)</td>
<td>(29-50)</td>
<td>(2.7-4)</td>
<td>(60-70)</td>
</tr>
</tbody>
</table>

When evaluating the echocardiograms, concordance with MRI EF was generally poor, although there was a trend towards improved concordance with increasing experience (Figure 46). Consultant paediatric cardiologists assessed the grade of function concordant with MRI in 58.2% of patients, compared to 55% of senior trainees, 47.1% of cardiac physiologists, 47.6% of junior trainees and 31.4% of senior house officers.
Concordance within each observer group also improved with increasing experience from 0.674 (0.440-0.831) in residents to 0.876 (0.789-0.936) in consultant cardiologists. Sensitivity, specificity, positive predictive value and negative predictive value (based on group averages) are shown in Table 20. Overall, observers were sensitive to poor function (i.e. detected poor function well), but demonstrated poor specificity (i.e. underrated good function), although there was improvement with increasing experience.
Table 20 Specificity, sensitivity, positive and negative predictive values

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attendings</td>
<td>0.86</td>
<td>0.55</td>
<td>0.29</td>
<td>0.95</td>
</tr>
<tr>
<td>Senior fellows</td>
<td>0.80</td>
<td>0.54</td>
<td>0.27</td>
<td>0.93</td>
</tr>
<tr>
<td>Junior fellows</td>
<td>0.89</td>
<td>0.45</td>
<td>0.26</td>
<td>0.95</td>
</tr>
<tr>
<td>Cardiac physiologists</td>
<td>0.92</td>
<td>0.45</td>
<td>0.27</td>
<td>0.96</td>
</tr>
<tr>
<td>Residents</td>
<td>0.96</td>
<td>0.26</td>
<td>0.26</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Based on the ability of subjective echocardiographic assessment to detect ‘reduced function’ (function rated as ‘moderate’ or ‘poor’) using magnetic resonance imaging derived ejection fraction of less than 50% as the standard.

Twenty-one (75%) of echocardiograms were rated as having good to excellent quality clips – all loops were included to reflect the normal clinical situation of varying quality of images. It was noted that concordance in those with less than good to excellent quality images was lower than those with good to excellent clips (Table 21).

Table 21 Clip quality and concordance

<table>
<thead>
<tr>
<th></th>
<th>Clips</th>
<th>Total discordance</th>
<th>Average discordance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate/Poor</td>
<td>7</td>
<td>178</td>
<td>25.4</td>
</tr>
<tr>
<td>Excellent/Good</td>
<td>21</td>
<td>312</td>
<td>14.9</td>
</tr>
</tbody>
</table>

Each clip was marked 0 for same as MRI, 1 for 1 grade different from MRI, and 2 for 2 grades different from MRI. Total discordance calculated from sum of all observers for each clip.
DISCUSSION

We have shown that visual assessment of RV systolic function has only a limited correlation with MRI EF, but that this appears to improve with increasing levels of experience. This variation with experience has obvious clinical implications, especially in the situation where it may be a more junior member of the medical team undertaking and interpreting the echocardiogram. It highlights the importance of recognising the skills and limitations of those undertaking echocardiography in this patient group and the need to ensure appropriate supervision, education and clinical review.

There was a tendency for operators to under-rate function compared to MRI - this was more marked in the less experienced and reflected by the highest sensitivity and lowest specificity seen in the most junior group compared to the most experienced (Table 20). Subjective assessment may also be affected by differences seen in regional wall motion, as can be seen in those with different residual left ventricular morphologies (83). It is essential that multiple views from a range of echocardiographic windows are obtained, although this will be limited in the immediate post-operative period. Additionally this study required review of echocardiograms away from the patient bedside, however this too is analogous to many clinical situations where images may be reviewed either remotely or in clinical review meetings.

The improvement seen with increasing experience is likely to be due to increased training and exposure to echocardiograms, though as MRI is used widely within our unit this may be due to greater exposure to MRI and potentially a better understanding of the correlation between the two. Despite
this, concordance with MRI in the most experienced group was only 58.2%, which highlights the limitations of subjective echocardiographic assessment of systolic function. This emphasises the need for more robust and objective echocardiographic tools to assess function at the bedside in these patients. Methods using tissue Doppler imaging and speckle tracking are currently being investigated by several groups (83,97,132,133) and may prove useful in this group.

LIMITATIONS
The majority of patients had MRI EF in the normal range. This is likely to represent a degree of selection bias, as those with very poor function are at greater risk of mortality (5). We included all patients at any surgical stage due to the small numbers of patients involved and to reflect clinical practice, but acknowledge that there is a potential influence of different loading conditions. There are inherent problems in comparing a 2D technique such as echocardiography where assessment of function is based on myocardial motion, to a 3D technique utilising measurement of volume changes (MRI). MRI RV EF does not necessarily reflect systolic function, but has been used here as a surrogate in the absence of other proven reliable measures. Additionally, the authors acknowledge that they have compared a continuous variable (MRI EF using arbitrary cut-offs) to a categorical variable.

CONCLUSIONS
This study has shown that subjective assessment of RV function in HLHS is limited but improves with increasing experience. This has important clinical implications as junior staff perform the majority of assessments, particularly in
the immediate post-operative period and emphasises the importance of on-going training and supervision. Objective echocardiographic measures to reliably measure RV function in these patients are required. Ideally these would be simple, reproducible and not altered by the patient’s operative stage, loading conditions or morphological subtype.
SUMMARY

Background: The geometry and heterogeneity of the single RV in HLHS make reliable and reproducible echocardiographic assessments of systolic function challenging. Functional echocardiographic parameters of RV function can be used, though subjective evaluation of RV function is still utilized on a day-to-day basis. We sought to evaluate subjective echocardiographic assessment of RV systolic function and the role of experience by comparison to cardiac MRI.

Methods: A retrospective analysis of prospectively acquired data. Children with HLHS underwent routine pre-operative cardiac MRI and echocardiography under the same general anaesthetic. Echocardiograms were reviewed and members of the congenital heart disease team with differing echocardiography experience subjectively graded RV systolic function as good, moderate or poor. This grading was compared to MRI derived ejection fraction.

Results: Twenty-eight patients at different palliative stages were included in the study. Twenty-eight observers were divided into 5 experience categories (from congenital heart disease junior trainees to attending cardiologists). Overall there was improved concordance between subjective echocardiographic assessment and MRI ejection fraction with increasing level of experience; maximal concordance was however, only 58.2%.

Conclusions: Subjective echocardiographic assessment of RV systolic function in HLHS is generally poor, but does improve with experience. Thus the development of easy and reproducible objective echocardiographic tools is essential.
AIM

To review the values of tissue Doppler derived time intervals and indices in patients with HLHS at the different operative stages, as compared to the normal paediatric population.

HYPOTHESIS

Echocardiographic time intervals and derived indices will correlate with measures of cardiac function based on MRI.

The use of echocardiographic parameters based on time intervals will be of value through all surgical stages.

INTRODUCTION

Measurement of systolic and diastolic time intervals, by either pulsed Doppler or tissue Doppler imaging (TDI) (134), has been undertaken in HLHS. Derived indices, such as the MPI and S:D ratio, have been proposed as useful measures of RV function in HLHS (88,90-92,94) and for the RV in adults (135). The S:D ratio was increased in children with idiopathic dilated cardiomyopathy compared to controls (136). With respect to the RV, TDI has an advantage over pulsed blood pool Doppler techniques for the calculation of such indices because all of the components can be measured on a single trace and reference data from the paediatric population is available (137,138). TDI has
the potential to identify pre-symptomatic changes in cardiac function (52,139).

Due to the fibre orientation in the RV, the ability of TDI to assess longitudinal function makes it particularly suited to the RV (6).

There are limitations to the data currently available with respect to TDI in HLHS. Firstly, many reports predate the publication of normal TDI time interval data in the paediatric age range, which demonstrated the major impact of heart rate (137). This has the potential to confound comparisons between children of different ages and stages of surgical palliation. Secondly, echocardiographic indices, such as MPI or S:D ratio have been compared to subjective measures, such as qualitative assessment of RV function or measures from a single echocardiographic plane (93,94), which may themselves be inaccurate. MRI is currently regarded as the most accurate and reproducible technique for measuring ventricular volumes and blood flow. This technique is used for pre-operative assessment of HLHS at our institution (41,105).

The aims of this paper are twofold. The first is to present prospectively acquired TDI data from a cohort of patients with HLHS at different stages of surgical palliation using heart-rate specific z-scores calculated from published reference ranges. This is to allow comparison of patients across operative stages and avoids the confounding effect of heart rate. Secondly, the absolute values and z-scores of TDI derived indices were correlated with objective measures of cardiac performance including MRI derived RV ejection fraction, indexed ventricular volumes and aortic flow. Where possible, TDI indices were also correlated with other measures of RV systolic and diastolic function such as
flow acceleration of the tricuspid regurgitant jet and invasive pressure measurements.

METHODS

Study Population

Patients with HLHS were studied between July 2007 and December 2010. Patients were subdivided according the timing of their study in relation to operative stage. To facilitate correlation with other imaging techniques, where possible patients were studied immediately following cardiac MRI. In these patients the study was performed under the same anaesthetic as the MRI scan for consistency.

Echocardiography - Pulsed Tissue Doppler

Pulsed wave tissue Doppler was performed using age appropriate probes (S5-1, S8-3, S12-4) and was analysed offline using a single measurement. From an apical 4 chamber view, the sample volume was placed at the level of the tricuspid annulus on the RV free wall (124). The Doppler sweep speed was set to “high”, maximising the frame rate to optimise measurement of time intervals. If the patient was under general anaesthetic for MRI scanning or ventilated on the intensive care unit, a temporary cessation of ventilation avoided respiratory impact on the trace. Patients breathing spontaneously had measurements made in expiration. Measured time intervals included R-R interval, IVCT, ET and IVRT. MPI was calculated as described previously (140) as well as the systolic time (ST), diastolic time (DT), filling time (FT) and S:D ratio were measured as described in Chapter 8.
Other Echocardiographic Parameters – Systolic function

In patients with measurable tricuspid regurgitation, the change of velocity over time of the regurgitant jet (dV/dT) was measured as previously described (87,141). The slope of the tricuspid regurgitant jet was measured between 1 and 3m/s on a continuous wave Doppler trace. The peak s’ wave velocity was also recorded from the pulsed tissue Doppler trace acquired as described above. Peak s’ wave velocities were converted to z-scores using published paediatric data (138).

Other Echocardiographic Parameters – Diastolic function

The tricuspid valve inflow pattern was also recorded from the standard four chamber view using pulsed wave Doppler. The E wave velocity was measured from this and the e’ measured from the pulsed tissue Doppler trace acquired as described above. The E to e’ (E/e’) ratio was calculated.

Magnetic Resonance Imaging

MRI scans were performed as clinically indicated, including short axis steady state free precession cine stack for volumetry and neo-aortic phase contrast flow. RV end diastolic volume, RV end-systolic volume, ejection fraction, stroke volume and cardiac output were calculated according to published methodology (142). Cardiac output and stroke volume calculated from RV volumetry reflect all blood leaving the ventricle, whether as antegrade flow into the neo-aorta or retrograde flow as tricuspid regurgitation. In order to assess true effective antegrade flow from the ventricle, neo-aortic forward flow was measured. Tricuspid regurgitation fraction was calculated from (right ventricular stroke volume – neo-aortic forward flow) / right ventricular stroke volume. Tricuspid
regurgitant fractions of >10% were regarded as significant. Measured variables were indexed to body surface area (124). In patients with a cavopulmonary anastomosis, it is our routine clinical practice to measure CVP at the time of MRI which, in the absence of pulmonary arterial obstruction, we recorded to reflect filling pressures. Full catheterisation data is only obtained selectively if the CVP is raised, either reflecting obstruction to pulmonary blood flow, increased pulmonary vascular resistance or ventricular dysfunction.

**Data analysis**

The range of heart rates, highest in the neonatal period and lower in older patients, complicates analysis of echocardiographic time intervals. Previous authors have corrected IVCT and IVRT by dividing the measured value by the square root of the R-R interval: normal ranges have been produced by this method (93,137). In this paper time intervals are presented as absolute values, corrected for heart rate and as z-scores (137). The additional consideration in HLHS is identifying an appropriate comparison group for time intervals. Normal TDI time intervals and z-scores have been published but these relate to the structurally normal heart (137). In HLHS, the RV pumps systemic arterial blood. The normal RV TDI time intervals relate to a low pressure RV; and those from the LV relate to a ventricle pumping systemic pressure and so may be more appropriate, although the morphology and myoarchitecture of the LV is different from the RV. For time intervals, the ranges obtained from the normal mitral valve annulus and tricuspid valve annulus are almost identical (137). We have elected to compare HLHS patients with the TDI values from the normal tricuspid valve annulus in the calculation of z-scores. The TDI results were correlated with MRI derived ejection fraction and cardiac output indexed to body surface
area. In addition, we correlated MPI and S:D ratio with other measures of systolic function (peak s’ wave velocity and dV/dT of the tricuspid regurgitant jet) and filling pressures (E/e’ ratio and CVP measurement).

**Statistical Analysis**

Pearson correlations were calculated between variables. Due to potential confounding, correlation with MRI derived variables was performed as the whole group and without patients with significant tricuspid regurgitation (regurgitant fraction >10%). Patients with significant residual forward flow through the native aorta were also excluded from correlation with MRI derived variables, as this also impacts on RV volumetry and neo-aortic flow. Comparison of heart rate specific z-scores for each measure over four time points (pre-Norwood, pre-HF, post-HF and post TCPC) was performed using one way analysis of variance; point estimates at individual time points were via marginal means with 95% confidence intervals. The statistical package was Stata v11 (StataCorp).

**RESULTS**

A total of 90 echocardiographic studies were performed in 69 patients. Of these, 76 studies were judged of sufficient quality to be included in the analysis. Forty-nine (63.6%) studies had been performed under general anaesthesia to allow correlation with MRI findings. Patient characteristics are shown in Table 22.
Mean (standard deviation) time intervals, and MPI are shown in Table 23, with MRI results in Table 24. Median MRI ejection fraction was 55.9% (range 35.4-79.3%). Measurement of E/e’ was not possible in all patients (particularly younger patients with high heart rates) due to fusion of the Doppler E and A signals. Measurement of dV/dT was only possible in patients with measureable tricuspid regurgitation. Significant tricuspid regurgitation was noted in six studies (median regurgitant fraction 12%, range 10.1-32.5%). No significant neo-aortic regurgitation was noted in any patient.

### Table 22 Patient demographics, mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>Pre-Norwood (n = 10)</th>
<th>Pre-HF (n = 28)</th>
<th>Post-HF (n = 21)</th>
<th>Post-TCPC (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at echo, years</td>
<td>2.7 days (2.1)</td>
<td>0.33 (0.13)</td>
<td>2.3 (0.8)</td>
<td>9.8 (2.1)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>3.1 (0.3)</td>
<td>5.2 (1.1)</td>
<td>11.7 (2.4)</td>
<td>31.8 (11.8)</td>
</tr>
</tbody>
</table>
### Table 23: Pulsed Tissue Doppler Parameters, mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>Pre-Norwood</th>
<th>Pre-HF</th>
<th>Post-HF</th>
<th>Post-TCPC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 9</td>
<td>n = 28</td>
<td>n = 21</td>
<td>n = 17</td>
</tr>
<tr>
<td>Frame rate, Hz</td>
<td>169.7 (64.1)</td>
<td>173.4 (65.2)</td>
<td>184.4 (67.5)</td>
<td>189.2 (69.9)</td>
</tr>
<tr>
<td>RR interval, ms</td>
<td>400 (52)</td>
<td>517.1 (87.3)</td>
<td>652.4 (121.7)</td>
<td>778.8 (128.1)</td>
</tr>
<tr>
<td>IVCT, ms</td>
<td>44.0 (15.0)</td>
<td>56.4 (21.5)</td>
<td>81.0 (25.7)</td>
<td>78.2 (38.9)</td>
</tr>
<tr>
<td>ET, ms</td>
<td>192 (46.4)</td>
<td>240 (36.2)</td>
<td>256.2 (47.1)</td>
<td>248.8 (40.3)</td>
</tr>
<tr>
<td>ST, ms</td>
<td>233.3 (43.6)</td>
<td>296.4 (45.0)</td>
<td>337.1 (55.4)</td>
<td>327.1 (57.6)</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>43 (19.5)</td>
<td>56.4 (21.1)</td>
<td>71.4 (23.1)</td>
<td>68.8 (30.1)</td>
</tr>
<tr>
<td>Filling, ms</td>
<td>124 (36.8)</td>
<td>164.3 (56.9)</td>
<td>243.8 (79.0)</td>
<td>382.9 (125.1)</td>
</tr>
<tr>
<td>DT, ms</td>
<td>166.7 (33.5)</td>
<td>220.7 (64.4)</td>
<td>315.2 (82.6)</td>
<td>451.8 (137.0)</td>
</tr>
<tr>
<td>MPI</td>
<td>0.51 (0.28)</td>
<td>0.48 (0.18)</td>
<td>0.62 (0.22)</td>
<td>0.63 (0.28)</td>
</tr>
<tr>
<td>S:D ratio</td>
<td>1.46 (0.49)</td>
<td>1.46 (0.49)</td>
<td>1.13 (0.31)</td>
<td>0.79 (0.27)</td>
</tr>
<tr>
<td>dV/dT</td>
<td>-</td>
<td>8340 (4572)</td>
<td>4479 (1707)</td>
<td>5876 (1545)</td>
</tr>
<tr>
<td>E/e’</td>
<td>-</td>
<td>11.1 (2.9)</td>
<td>10.6 (4.5)</td>
<td>8.7 (3.5)</td>
</tr>
<tr>
<td>Peak s’</td>
<td>6.6 (1.2)</td>
<td>5.7 (1.3)</td>
<td>6.1 (1.7)</td>
<td>6.5 (2.1)</td>
</tr>
<tr>
<td>Peak s’ z-score</td>
<td>-0.6 (0.2)</td>
<td>-0.8 (0.2)</td>
<td>-3.2 (1.1)</td>
<td>-3.2 (1.0)</td>
</tr>
</tbody>
</table>

All values are presented in the format previous published data (137)
Table 24 MRI Data, mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>Pre- Norwood (n = 0)</th>
<th>Pre-HF (n = 19)</th>
<th>Post-HF (n = 13)</th>
<th>Post-TCPC (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>iEDV, mls/m²</td>
<td>-</td>
<td>85.2 (14.3)</td>
<td>79.1 (12.5)</td>
<td>73.8 (12.7)</td>
</tr>
<tr>
<td>iESV, mls/m²</td>
<td>-</td>
<td>39.9 (11.3)</td>
<td>30.2 (9.7)</td>
<td>32.7 (7.4)</td>
</tr>
<tr>
<td>iSV, mls/m²</td>
<td>-</td>
<td>45.3 (8.7)</td>
<td>48.7 (5.9)</td>
<td>41.1 (10.2)</td>
</tr>
<tr>
<td>iCO, l/min/m²</td>
<td>-</td>
<td>4.7 (0.9)</td>
<td>4.1 (0.5)</td>
<td>2.8 (0.6)</td>
</tr>
<tr>
<td>iAo, mls/m²</td>
<td>-</td>
<td>44.6 (7.8)</td>
<td>45.2 (7.8)</td>
<td>38.8 (7.4)</td>
</tr>
<tr>
<td>TR %</td>
<td>-</td>
<td>2.4 (3.7)</td>
<td>6.8 (9.4)</td>
<td>3.7 (5.3)</td>
</tr>
<tr>
<td>MRI EF, %</td>
<td>-</td>
<td>54.0 (9.0)</td>
<td>62.6 (8.1)</td>
<td>55.3 (8.1)</td>
</tr>
<tr>
<td>CVP, mmHg</td>
<td>-</td>
<td>-</td>
<td>10.9 (2.3)</td>
<td>11.3 (2.9)</td>
</tr>
</tbody>
</table>

Patients with forward flow through the left heart (n = 11) were excluded from the MRI analysis due to the effect on volumetry of this

**Presentation of results**

Figure 47 shows the values of heart-rate corrected IVCT in HLHS plotted against age including normal reference ranges (137) from the tricuspid valve annulus in the normal heart.
Figure 47 Normal ranges for the normal tricuspid valve annulus are shown for comparison (137) (solid black line – mean corrected IVCT, dashed black lines – +/- one standard deviation). All values are significantly prolonged compared to the normal data (Bonferroni corrected p values all <0.05). Cross – pre-Norwood, closed diamond – pre-HF, closed triangle – post-HF, closed circle – post-TCPC

Figure 48 demonstrates the clear impact of heart rate on ET in our patient group with normal reference values (137) from the tricuspid valve annulus in the normal heart.
Figure 48 Normal ranges for the normal tricuspid valve annulus are shown for comparison (137) (solid black line – mean ET, dashed black lines – +/- one standard deviation). Cross – pre-Norwood, closed diamond – pre-HF, closed triangle – post-HF, closed circle – post-TCPC

Figure 49 shows the S:D ratio first by (a) operative stage then plotted against (b) heart rate with normal reference ranges from the tricuspid valve annulus(137). At all operative stages the S:D ratio shows no systematic deviation from the normal range for heart rate. Figure 50 demonstrate the heart rate specific z-scores for (a) IVCT, ET and ST, (b) IVRT and DT and (c) MPI and S:D ratio.
Figure 49 The S:D ratio decreases with operative stage (a), however by representing the S:D against heart rate (b), it is clear that this decrease is heart rate related, and the data actually follows the normal pattern. Normal ranges for the normal tricuspid valve annulus are shown for comparison (137) (solid black line – mean S:D ratio, dashed black lines – +/- one standard deviation). Cross – pre-Norwood, closed diamond – pre-HF, closed triangle – post-HF, closed circle – post-TCPC.
Figure 50 ANOVA analysis of z-scores calculated from data for the normal tricuspid valve annulus (137) at each surgical stage for heart rate corrected (a) IVCT, ST and ET (b) IVRT and DT and (c) MPI and S:D ratio demonstrating the significant prolongation of IVCT and IVRT and therefore the MPI (although with some overlap with the normal range).

Correlation of echocardiographic indices with MRI parameters

The correlations of echocardiography derived MPI z-score and heart rate specific S:D ratio z-score with MRI derived right ventricular ejection fraction, indexed right ventricular cardiac output and indexed neo-aortic forward flow are shown in Table 25. The only statistically significant correlation was between
MPI z-score and MRI derived right ventricular ejection fraction (Pearson 0.437, p < 0.05). When patients with a tricuspid regurgitant fraction of >10% were excluded the correlation between MPI z-score and MRI derived right ventricular ejection fraction was no longer significant (Table 25).

**Table 25** Pearson correlation values for parameters: whole group and without patients with severe tricuspid regurgitation

<table>
<thead>
<tr>
<th></th>
<th>Whole Group</th>
<th>Patients with a tricuspid regurgitation fraction &lt;10%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S:D ratio z-score</td>
<td>MPI z-score</td>
</tr>
<tr>
<td>MRI EF</td>
<td>-0.249</td>
<td>0.437*</td>
</tr>
<tr>
<td>iCO</td>
<td>0.201</td>
<td>-0.171</td>
</tr>
<tr>
<td>iAo</td>
<td>0.205</td>
<td>-0.106</td>
</tr>
</tbody>
</table>

*p < 0.05

Patients with forward flow through the left heart (n = 11) were excluded from this correlation due to the effect on volumetry of this

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**Correlation of MPI z-score and S:D ratio z-score with other measures of systolic and diastolic function (Table 26)**

MPI z-score did not correlate with dV/dT, s’ velocity z-score, CVP or E/e’ ratio. Heart rate specific S:D ratio z-score did not correlate with dV/dT, peak s’ velocity z-score or E/e’ ratio. There was a negative correlation between heart rate specific S:D ratio z-score and CVP (Pearson -0.451, p < 0.05).
Table 26 Pearson correlation values for MPI z-score and S:D z-score against measures of systolic and diastolic function

<table>
<thead>
<tr>
<th></th>
<th>dV/dT</th>
<th>Peak s' velocity z-score</th>
<th>E/e' ratio</th>
<th>CVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPI z-score</td>
<td>-0.191</td>
<td>-0.217</td>
<td>0.094</td>
<td>0.152</td>
</tr>
<tr>
<td>S:D z-score</td>
<td>-0.284</td>
<td>0.026</td>
<td>-0.159</td>
<td>-0.451*</td>
</tr>
</tbody>
</table>

*p < 0.05

DISCUSSION

Functional assessment of the systemic RV in the context of HLHS is important to guide clinical management, particularly the detection of pre-symptomatic ventricular dysfunction. Systolic dysfunction early in life has been shown to be an important determinant of patient outcome (5). Objective assessment of RV function in HLHS is difficult and age-related changes in heart rate may confound measurements and derived indices.

Assessment of myocardial velocities, time intervals and derived indices by TDI is readily performed in this patient group on a single Doppler trace. Measurement of systolic time by TDI does not depend on the presence of tricuspid regurgitation, in contrast to continuous wave Doppler (94,143), thus avoiding selection bias. Our data demonstrates that measurement of TDI time intervals is reproducible in HLHS. At all ages and surgical stages, the HLHS group has heart rate adjusted IVCT and IVRT which are prolonged compared to the normal heart, although there is overlap with the normal range (Figure 50). The prolongation of IVCT and IVRT appears more marked at later surgical stages. In contrast the heart rate specific ET z-score is normal at all surgical
stages, which is also the case for total systolic and diastolic times. The prolonged IVCT and IVRT are likely to reflect the abnormal loading conditions of the systemic RV. Such prolongation is seen in other settings such as in anthracycline cardiomyopathy, chronic heart failure and pulmonary hypertension (144-146). It is not clear in HLHS whether the prolonged IVCT and IVRT reflect adaptation or an evolving disease process.

The MPI is, on average, higher in patients with HLHS at all surgical stages, but overlaps with the normal range (Figure 50) without evident change between surgical stages. The high MPI is due entirely to prolonged IVCT and IVRT given the normal heart rate adjusted ET across surgical stages (Figure 48 and Figure 50). With respect to S:D ratio, our data confirms that if heart rate is not taken into account then the S:D ratio is different in HLHS patients at different surgical stages, with the highest values seen in younger patients (Figure 49). However, heart rate is a major determinant of S:D ratio (137) and when heart rate specific z-scores are computed, the heart rate specific S:D ratio is within normal limits across all surgical stages (Figure 50). Thus, adjustment of S:D ratio for heart rate is essential for longitudinal and cross-sectional comparison of data to avoid misinterpretation of differences or changes of this index.

MPI and S:D ratio have been proposed as markers of systolic or diastolic dysfunction in previous studies of HLHS (90-94). Our study was designed to include data from MRI and invasive pressure measurements where possible, to provide an objective means of assessing the usefulness of these indices in the functional assessment of patients with HLHS. MPI z-score did not correlate with dV/dT, s’ velocity z-score, MRI derived indexed right ventricular cardiac
output or indexed neo-aortic forward flow. Furthermore, neither the E/e’ ratio nor CVP correlated with MPI z-score. This is in contrast to the study of Williams et al. (92) where there was a weakly positive correlation between MPI and cardiac catheter end diastolic pressure. There was a positive correlation between MPI z-score and MRI derived ejection fraction. This positive correlation was surprising because higher MPI values have been associated with worse ventricular function (6). A possible influence is the presence of significant tricuspid regurgitation (>10%), and when these patients were excluded there was no significant correlation. Thus, MPI does not appear to be a surrogate for any of the other direct measures of cardiac performance in this study.

The heart rate specific S:D ratio z-score did not correlate with dV/dT, peak s’ velocity z-score or MRI derived right ventricular indexed cardiac output, neo-aortic forward flow or MRI derived ejection fraction. Thus there was no significant correlation with any of the other measures of systolic cardiac performance. This differs from the report of Friedberg et al. (94) where a high S:D ratio (uncorrected for heart rate) was seen in patients with subjectively poor RV systolic function. In our patient group, there was no correlation of S:D ratio z-score with E/e’ ratio, but there was a negative correlation with CVP. Our measured CVPs were within a close range (6-15mmHg) and were all acceptable for a cavopulmonary connection. This merits further investigation in patients with both normal and abnormal filling pressures.
LIMITATIONS

Our study population included children up to the age of 11 years and our results may not be able to be extrapolated to older children or young adults. Although relatively easy to perform, it will not always be possible to obtain analysable traces in all patients. This study was cross-sectional and the utility of echocardiographic indices when applied longitudinally was not investigated.

CONCLUSIONS

In children with HLHS, isovolumic contraction and isovolumic relaxation times are significantly prolonged compared to normal. The values and trends of ejection time, systolic time and diastolic time are no different from the normal population when age-related changes in heart rate are taken into account. Differences in the S:D time ratio between surgical stages can be accounted for by heart rate alone. MPI is elevated across all surgical stages due to the prolonged IVCT and IVRT. Neither MPI z-score nor S:D z-score significantly correlated with MRI or other echocardiographic indices of systolic or diastolic function with the exception of a negative correlation between CVP and S:D ratio z-score.
SUMMARY

Background: Tissue Doppler indices can be used to assess systolic and diastolic function. They have previously been proposed to be of use in the assessment of patients with HLHS. Patients with this condition undergo three operations over the first few years of life, subjecting the systemic right ventricle to different loading conditions. We sought to assess tissue Doppler indices in these patients.

Methods: Patients at different stages of HLHS palliation were studied prospectively using tissue Doppler imaging of the right ventricular free wall, with simultaneous cardiac MRI in the majority.

Results: Fifty-seven patients were included in the study. Both IVCT and IVRT were prolonged compared to the normal left and right ventricle: median (range) z-scores for tricuspid annulus 1.9 (-1.2 to 9.3) and 1.3 (-2.0 to 5.5) respectively. When adjusted for heart rate, the ejection, systolic and diastolic times in HLHS were not significantly different from published normal data. The MPI was increased at all surgical stages in HLHS. Neither the MPI nor heart rate specific S:D time ratio z-score correlated with MRI ejection fraction or indexed cardiac output when the confounding effect of significant tricuspid regurgitation was taken into consideration.

Conclusion: The prolongation in isovolumic relaxation and contraction times may be due to adaptation or reduced myocardial performance. Differences in the S:D time ratio between surgical stages can be accounted for by heart rate alone. Neither MPI z-score nor S:D z-score correlated with MRI or other echocardiographic indices of systolic or diastolic function with the exception of a negative correlation between central venous pressure and S:D ratio z-score.
Chapter 13 - Novel Speckle Tracking Methods for the Assessment of Right Ventricular Systolic Function in Hypoplastic Left Heart Syndrome

AIM
To review novel speckle tracking techniques which are not dependent on geometric assumptions in patients with HLHS, using MRI ejection fraction as a reference.

HYPOTHESIS
Speckle tracking techniques may provide a useful, simple and reproducible method for screening and longitudinal follow-up of systolic performance in patients with HLHS.

INTRODUCTION
Speckle tracking technology has been well described in the assessment of the LV (146) however assessment models for the RV remain a challenge. The RV has a very anterior position in the chest with a relatively thin wall with many trabeculations, thus making acquisition and then contour definition challenging. Additionally, the RV has a complex geometry that cannot be assessed using the same assumptions as the LV. The simple application of a LV model to the RV in HLHS is further complicated by the impact of the residual hypoplastic LV (83,88). In this study we investigated simple speckle tracking techniques that were independent of geometry and could be applied to all the different RV morphologies in HLHS and correlated these to cardiac MRI derived RV ejection fraction.
METHODS

Study Population
Patients with HLHS were studied between July 2007 and December 2010. Patients were subdivided according the timing of their study in relation to operative stage. To facilitate correlation with other imaging techniques, where possible patients were studied immediately following cardiac MRI. In these patients, the study was performed under the same anaesthetic as the MRI scan for consistency.

Echocardiographic Acquisition
Standard subcostal and apical 4 chamber views were acquired using a Philips IE 33 ultrasound system (Philips Inc, Andover, Mass., USA) using age and size appropriate probes (S5-1, S8-3, S12-4). Post-processing was performed off-line on a Philips Excelera workstation (Philips Inc, Andover, Mass., USA).

Tricuspid annular descent (TAD) – Three points were placed on a standard apical four chamber view (one either side of the tricuspid annulus on the RV free wall and interventricular septum, and a third at the apex of the RV). Displacement of each of the annular points as well as the descent of the plane formed by the two tricuspid annular points was measured. This displacement was then expressed as a percentage of the displacement of the distance from the plane to the apical point (Chapter 8). The ratio of the free wall to septum descent was also measured.
Inferior strain – Two points were placed on the diaphragmatic surface of the RV on a standard subcostal four chamber view, one towards the tricuspid annulus and the other towards the apex. Strain and time to peak strain (indexed to RR interval) of this cord was then calculated (Chapter 8).

Four cord strain/shortening – Four points were placed on a standard apical 4 chamber view. One point was placed either side of the annulus, as described above, and two further points halfway down the RV, one on the interventricular septum and the other on the RV free wall. Strain of the free wall and septum and shortening of the annular and apical cords was calculated (chapter 8). The ratios of the free wall to septum strain and of annular to apical shortening were calculated, along with the mean and total strain. The time to peak strain/shortening of each cord was noted and indexed to the RR interval.

MRI acquisition

MRI scans were performed under general anaesthetic in younger children or children who were unable to lie still and perform breath holds. MRI scans were performed on a Philips 1.5 Tesla Achieva Scanner (Philips Healthcare, Best, Netherlands). MRI examination was performed as clinically indicated, but all included acquisition of SSFP short axis cine stack and phase contrast neo-aortic flow as described in Chapter 8. All scans were reanalysed on a Viewforum EWS Version 2.0 workstation (Philips Healthcare, Best, The Netherlands).
**Statistical analysis**

Each of the echocardiographic parameters was correlated with MRI derived ejection fraction. Inter and intra-observer variability was assessed using two-way random intra-class coefficients with absolute agreement.

**RESULTS**

Forty-five studies were performed in 37 patients (8 patients had two studies performed at different time points). Images were adequate for analysis in 41 patients, four cord assessment in 42 and inferior cord in 36 patients. All but one study was performed under general anaesthetic. Patient demographics and basic MRI results are shown in Table 27.

**Table 27** Demographics of study patients, median (range)

<table>
<thead>
<tr>
<th></th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at study, years</td>
<td>2.0 (0.2-13.7)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>9.7 (3.4-45.9)</td>
</tr>
<tr>
<td>Saturations, %</td>
<td>80 (69-98)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>Post Norwood</td>
<td>20</td>
</tr>
<tr>
<td>Post hemi-Fontan</td>
<td>21</td>
</tr>
<tr>
<td>Post TCPC</td>
<td>4</td>
</tr>
<tr>
<td>LV morphology</td>
<td></td>
</tr>
<tr>
<td>Slit or no LV</td>
<td>17</td>
</tr>
<tr>
<td>Borderline LV</td>
<td>10</td>
</tr>
<tr>
<td>Globular LV</td>
<td>18</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>59.5 (35.4-79.3)</td>
</tr>
<tr>
<td>&gt;15% tricuspid regurgitation fraction</td>
<td>2</td>
</tr>
</tbody>
</table>
There was a significant positive correlation between MRI EF and tricuspid annular descent. The ratio of free wall to septal point descent was significantly negatively correlated to MRI EF, with a higher ratio associated with a lower MRI EF. Of the strain and shortening of the 5 cords, only apical shortening was significantly correlated to MRI EF with a more negative strain associated with a higher MRI EF. The mean and total of the four cord strain and shortening was also significantly associated with a higher MRI EF. There was no correlation between inferior cord strain and MRI EF, nor any of the time to peak strain (indexed to RR interval) for any of the cords.

Figure 51 TAD against EF by operative stage
**Figure 52** TAD against EF by LV morphology

**Figure 53** FW:septal ratio against EF by operative stage
Figure 54 FW:septal ratio against EF by LV morphology

Figure 55 Apical shortening against EF by operative stage
**Figure 56** Apical shortening against EF by LV morphology

**Figure 57** Total strain against EF by operative stage

**Figure 58** Total strain against EF by LV morphology
The dataset was too small to statistically compare the various techniques by surgical stage and residual LV morphology, but the above graphs show the correlations with patients at different surgical stages and with different LV morphologies. Interuser variability for MRI is described in Appendix 4 and for the echo measures in Table 28. There was reasonable intra and interclass agreement for TAD, but moderate to poor agreement for the four cord and particularly, inferior strain.
Table 28 Intraclass coefficient for echo analysis

<table>
<thead>
<tr>
<th></th>
<th>Intraclass coefficient (Intra-observer)</th>
<th>Intraclass coefficient (Inter-observer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAD %</td>
<td>0.542 (-1.40-0.790)</td>
<td>0.583 (0.189-0.815)</td>
</tr>
<tr>
<td>Lateral descent</td>
<td>0.678 (0.357-0.857)</td>
<td>0.765 (0.484-0.903)</td>
</tr>
<tr>
<td>Septal descent</td>
<td>0.874 (0.711-0.948)</td>
<td>0.864 (0.646-0.948)</td>
</tr>
<tr>
<td>Midpoint descent</td>
<td>0.838 (0.634-0.933)</td>
<td>0.850 (0.652-0.940)</td>
</tr>
<tr>
<td>Free wall strain</td>
<td>0.617 (0.254-0.831)</td>
<td>0.316 (-0.140-0.664)</td>
</tr>
<tr>
<td>Septal strain</td>
<td>0.451 (-0.002-0.748)</td>
<td>0.809 (0.571-0.922)</td>
</tr>
<tr>
<td>Annular shortening</td>
<td>0.601 (0.223-0.823)</td>
<td>0.398 (-0.04-0.717)</td>
</tr>
<tr>
<td>Apical shortening</td>
<td>0.551 (0.160-0.797)</td>
<td>0.312 (-0.88-0.654)</td>
</tr>
<tr>
<td>Inferior strain</td>
<td>0.253 (-0.291-0.686)</td>
<td>0.384 (-0.19-0.762)</td>
</tr>
</tbody>
</table>

DISCUSSION

The ideal tool for screening for significant RV dysfunction should be quick, simple and reproducible. Speckle tracking techniques are quick and utilise standard views that are easily obtained in daily practice by even the most inexperienced echocardiographer. The methods described here are relatively independent of geometry and go some way to avoiding the application of an LV model to the RV.

There appears to be reasonable inter and intraclass reliability for TAD but less so for the four cord and inferior strain analysis which may explain the lack of correlation for these parameters. This may be because placement of points for TAD is less user-dependent than for the four cord method.
Of the single measurements, TAD and apical shortening correlated significantly with MRI EF, suggesting that they may therefore be used as screening tools in clinical situations such as post-operatively and in clinic to identify patients who require further investigation for systolic dysfunction. The ratio of free wall to septal strain also was significantly correlated with MRI EF for the group as a whole, which is interesting as this is a composite measure which would be expected to be significantly different in those with a globular LV compared to those with a slit-like LV.

The mean and total of the four cord strains also correlated with MRI EF in the whole group, but again is a composite measure that is potentially affected by the different residual LV morphologies. The direction of correlation for TAD, apical shortening and total as well as mean strain is unsurprising with increased levels correlating with a higher MRI EF. A higher ratio of free wall to septal strain (suggesting a greater difference between the two, generally seen in those with a globular LV) appears to be associated with a lower MRI EF. As discussed in Chapter 14, loading conditions as well as residual LV morphology could affect this ratio and this should be looked at with a larger group of patients.

LIMITATIONS
This study compared speckle tracking parameters to MRI derived ejection fraction. EF is a measure of volume change, and not deformation and is artificially high in significant TR. This study group contained very few patients with impaired ventricular function, which makes description of correlation in patients with impaired systolic function difficult.
CONCLUSION

Certain speckle tracking techniques do correlate with MRI EF, but not all are consistently reproducible. TAD seems to offer the best reproducibility and may be a good screening tool for RV dysfunction in HLHS.
SUMMARY

Background: RV dysfunction is a clinically significant poor prognostic factor in patients with HLHS. Visual assessment is poor and related to experience. Speckle tracking software has allowed the development of simple tools for the screening for right ventricular dysfunction that are independent of the complex right ventricular geometry.

Methods: Patients at different stages of HLHS palliation undergoing echocardiography under the same anaesthetic as cardiac MRI were studied. Displacement of points placed either side of the tricuspid annulus and the plane of the tricuspid annulus along with strain of cords placed on the free wall, septum and across the apex and annulus were correlated to MRI derived EF. A cord placed on the inferior wall from a subcostal view was also correlated to MRI EF.

Results: TAD and the ratio of the free wall to septal descent correlated with MRI EF. The only single cord to correlate with MRI EF was the shortening of the apical cord, but the total and mean strain (derived from all four cords) also correlated, with a more negative strain associated with a higher MRI EF.

Conclusion: TAD and apical cord shortening appear to be quick and easy tools which are independent of the RV geometry to screen for ventricular dysfunction. However there is limited reproducibility for apical cord shortening, likely due to more variation in the placement of points, suggesting that TAD may be the best technique of those assessed in this study.
Chapter 14 - The Impact of Left Ventricular Morphology on Echocardiographic Indices of Systolic and Diastolic Function in Hypoplastic Left Heart Syndrome

**AIM**
To assess echocardiographic indices (tissue Doppler and speckle tracking) in patients with different morphological sub-types of HLHS.

**HYPOTHESIS**
The morphology of the residual left ventricle in HLHS will impact on echocardiographic indices.

**INTRODUCTION**
HLHS is characterized by severe stenosis or atresia of the aortic and mitral valves, which renders the left heart incapable of supporting the systemic arterial circulation. Within this clinical spectrum there are two dominant morphologies. The first is mitral and aortic atresia, where the LV is typically slit-like and may be difficult to visualise at all. The second group, often with mitral stenosis and aortic atresia, typically have a globular and echogenic LV. Reports of the impact of LV morphology on RV function in this context are contradictory (88,91,147). The thickened septum in the group with the globular LV has been suggested to negatively impact on RV EF (91,147), RV fractional area change and myocardial performance index (91). However other studies have not shown any impact of LV morphology on RV myocardial performance index, tricuspid annular plane systolic excursion and RV fractional area change following completion of the Fontan circulation (88).
Previous work using speckle tracking in HLHS has applied a ‘left ventricular’ model to the RV (83). There are, however, considerable differences between right and left ventricular geometry coupled with great heterogeneity within this group of patients. We report a prospective study of HLHS patients with different LV morphologies investigated using echocardiographic techniques, including speckle tracking and tissue Doppler imaging. The primary aim of the study was to investigate the effect of LV morphology on the mechanics of the systemic RV. Secondary aims of the study included comparison of MRI derived RV EF and tricuspid regurgitation fraction (TR%) in the different morphological groups.

**METHODS**

Ethical and institutional approval was obtained. Patients with aortic and mitral atresia or stenosis with normal cardiac connections were included. Patients with unbalanced atrioventricular septal defects and abnormal connections were excluded, as were patients with a ‘borderline’ LV (a mildly hypoplastic LV, but still palliated through the Norwood operation). Patients were then divided based on the morphology of the residual LV into two groups: those with a slit-like LV or no visible LV as defined in Chapter 8.

Echocardiograms were acquired prospectively between July 2007 and December 2010 using age appropriate probes (S5-1, S8-3, S12-4) on the Philips IE 33 ultrasound system (Philips Inc, Andover, Mass., USA). All scans were analysed offline using Philips Q lab 7.0 on an Excelera workstation (Philips Inc, Andover, Mass., USA).
In patients where an MRI scan was performed contemporaneously with the echocardiogram, neo-aortic stroke volume was measured using phase contrast flow and RV volumes were measured from short-axis cine acquisitions by tracing the endocardial border (excluding major trabeculations) in end diastole and end systole. RV EF was then calculated from RV end diastolic volume minus RV end systolic volume divided by the end diastolic volume. Tricuspid regurgitant fraction was calculated from the RV stroke volume (end diastolic volume minus end systolic volume) minus neo-aortic flow expressed as a percentage of the RV stroke volume.

**Tissue Doppler**

Tissue Doppler traces were obtained from the RV free wall and interventricular septum according to published guidance (124). Time intervals were recorded as in Chapter 12. Tissue Doppler time intervals were converted where applicable to heart rate related z-scores as we have described previously (132). Tissue Doppler peak e’, a’ and s’ velocities were recorded as well as the time to peak s’ velocity. Tissue Doppler velocities are influenced by age (138) and so all measurements were converted to age-specific z scores according to the data of Eidem et al. (138).

**Speckle Tracking - Chord Analysis**

Currently, there are no speckle tracking software analysis packages that have been specifically developed for the RV. The Q lab 7.0 2D strain analysis package designed for the LV did not permit accurate tracking of the abnormally shaped RV in our patient groups, nor would it permit exclusion of specific segments that did not track optimally. Thus, for the purposes of this study we
elected to use a simple speckle tracking approach based on the placement of individual chords in the RV free wall and interventricular septum as described in Chapter 8 and Figure 61.

**Figure 61** The placement of the chords in the myocardium mid-way between the epi and endocardium along the free wall and septum in a patient with a slit like LV (left - group 1) and in a patient with a globular LV (right – group 2). The graph below shows the strain over time.

**Speckle Tracking - Tricuspid Annular Displacement (Chapter 8 and Figure 62)**
Points were placed either side of the tricuspid annulus and a further point at the apex of the RV. The displacement of each point was measured, as well as the displacement of the plane formed by the two points either side of the annulus.
Figure 62 The placement of points either side of the tricuspid annulus and at the RV apex in a patient with a slit like LV (left - group 1) and in a patient with a globular LV (right – group 2). The graph below shows the displacement of these points over time.

**Statistical Analysis**

Two major types of analysis were performed. The first was an analysis of echocardiographic parameters relating to the RV free wall and septum within an individual patient (paired t-test). The second analysis was a comparison of echocardiographic parameters between the groups of patients with slit-like LV (Group 1) and those with echogenic globular LV (Group 2) (unpaired t-test). The comparisons between groups involved conversion of data to z-scores where appropriate (132,137,138). Correlations between the difference in time to peak strain and time to peak s’ between the free wall and the septum, expressed as a percentage of the RR interval and MRI derived tricuspid regurgitation fraction, were evaluated.

**RESULTS**

Seventy-four patients with HLHS between July 2007 and December 2010 were included, 32 in group 1 (slit like or no LV) and 42 in group 2 (globular LV). The
median (range) of age was 1.8 years (0.001-14.6 years) and median (range) weight was 7.3kg (2.46-68kg). Twelve patients were assessed prior to the Norwood procedure, 22 had completed the Norwood procedure, 19 were post hemi-Fontan and 21 had completed total cavopulmonary connection. In 43 patients (20 group 1 and 23 group 2), MRI data obtained contemporaneously with the echocardiogram was available. Table 29 shows that there were no significant differences in MRI derived ejection fraction or tricuspid regurgitation fraction between the two groups.

**Table 29 Patient Groups, median (range)**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 20)</th>
<th>Group 2 (n = 23)</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI ejection fraction, %</td>
<td>60.2 (44.5-70.0)</td>
<td>54.3 (35.4-79.3)</td>
<td></td>
</tr>
<tr>
<td>MRI derived TR, %</td>
<td>1.2 (0-53.7)</td>
<td>0.0 (0-32.5)</td>
<td>NS</td>
</tr>
<tr>
<td>MRI derived TR &gt;10%</td>
<td>4 patients</td>
<td>3 patients</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Comparisons within group 1 (slit-like LV)**

Within group 1, the peak s’ velocity, peak strain and displacement of the tricuspid annulus was significantly greater for the RV free wall than the septum (Table 30, Figure 63).
Table 30 Systolic Function

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (Slit–like LV)</th>
<th>Group 2 (Globular LV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RVFW</td>
<td>Septum</td>
</tr>
<tr>
<td>Peak s+§</td>
<td>5.3 (3.2-8.1)*</td>
<td>4.6 (2.5-7.2)</td>
</tr>
<tr>
<td>Peak s’ z-score+</td>
<td>-3.1</td>
<td>-1.7</td>
</tr>
<tr>
<td></td>
<td>(-5.0 to -0.7)*</td>
<td>(-4.2 to 0.9)</td>
</tr>
<tr>
<td>Peak 2D strain (%)+§</td>
<td>-19.6</td>
<td>-14.4</td>
</tr>
<tr>
<td></td>
<td>(-34.3 to -6.3)</td>
<td>(-41.4 to -0.4)*</td>
</tr>
<tr>
<td>TAD point displacement</td>
<td>7.7 (3.5-16.4)</td>
<td>5.6 (2.2-10.6)</td>
</tr>
</tbody>
</table>

All values are median and range, *significant difference between Group 1 and 2, + significant difference between free wall and septum within group 1, § significant difference between free wall and septum within group 2

Figure 63 The differences in strain between the RV free wall and septum between the two groups. Group 1 – slit/no discernible LV; group 2 – globular LV

With respect to diastolic function the a’ velocity z-score was significantly lower for the RV free wall compared to the septum and the E/e’ ratio z-score was higher based on values from the RV free wall than the septum (Table 31, Figure 64). The IVCT and IVRT were significantly longer for the ventricular septum.
compared to the RV free wall (Table 32) and the MPI was higher based on septal measurements than the RV free wall (Table 33).

Table 31 Diastolic Function

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RVFW</td>
<td>Septum</td>
</tr>
<tr>
<td>$e'$ velocity$</td>
<td>7.4 (3.8-11.1)</td>
<td>8.5 (4.3-13.4)*</td>
</tr>
<tr>
<td>$a'$ z-score$</td>
<td>-2.4</td>
<td>-1.3</td>
</tr>
<tr>
<td>$e'$ velocity$</td>
<td>(3.7 to -0.3)*</td>
<td>(4.8 to 0.1)</td>
</tr>
<tr>
<td>$a'$ z-score+$</td>
<td>5.0</td>
<td>5.2</td>
</tr>
<tr>
<td>$E/e'$</td>
<td>7.0 (5.7-18.7)</td>
<td>6.7 (0.0-16.3)*</td>
</tr>
<tr>
<td>$E/e'$ z-score+$</td>
<td>3.2</td>
<td>0.3</td>
</tr>
</tbody>
</table>

All values are median and range, *significant difference between Group 1 and 2, + significant difference between free wall and septum within group 1, § significant difference between free wall and septum within group 2.

Figure 64 The differences in $E/e'$ ratio between the right ventricular (RV) free wall and septum between the two groups. Group 1 – slit/no discernible LV; group 2 – globular LV.
**Comparisons within group 2 (globular LV)**

The peak s’ velocity, 2D strain and tricuspid annular point displacement was higher for the RV free wall than the septum (Table 30, Figure 63). Diastolic measurements including e’ and a’ velocity were lower from the septum than the RV free wall (Table 31). The E/e’ ratio was higher using tissue Doppler values.
from the septum than the RV free wall (Table 31, Figure 64). The absolute IVCT was higher for the septum than the RV free wall but this was no longer significant when corrected for heart rate. IVRT was significantly longer for the septum compared to the RV free wall. Systolic time was significantly higher for the RV free wall than the septum but the reverse was true for diastolic time (Table 32). The MPI calculated from the septum was significantly higher than that calculated from the RV free wall (Table 33) and the S:D ratio was higher from the RV free wall compared to the ventricular septum.

**Comparisons between group 1 and group 2 - RV free wall values**

The peak s’ velocity (and derived z-score) from the RV free wall was significantly lower in group 1 compared to group 2 (Table 30). The RV free wall e’ and a’ velocities were significantly lower in group 1 compared to group 2 (Table 31). The RV free wall ejection time and systolic time were significantly longer in group 1 patients than group 2, but MPI and S:D ratio were no different between groups 1 and 2.

**Comparisons between group 1 and group 2 – septal values**

Peak septal strain was significantly lower for group 2 than group 1 (Table 30, Figure 63). The septal e’ velocities were lower in group 2 than group 1 but this lost significance when converted to z-scores (Table 31). The E/e’ ratio calculated from septal velocities was higher in group 2 than group 1 (Table 31, Figure 64). The septal IVCT, ejection time and systolic time were longer in group 1 than group 2 (Table 32). The S:D ratio z-score was lower in group 2 than group 1 but there was no significant difference in the MPI between the groups (Table 33).
**Tricuspid Regurgitation and wall to wall delay**

In order to assess a potential role for timing of the contraction of the free wall versus the septum between the two groups, we investigated this relationship. There was no correlation between the difference in free wall time to peak strain and the septum time to peak strain (corrected for RR interval) and tricuspid regurgitation, nor for the difference between the free wall and septum time to peak s’. When looking at wall to wall delay (septal time to peak s'/time to peak septal strain as a percentage of the RR interval minus FW time to peak s'/time to peak FW strain as a percentage of the RR interval), there was no significant difference between the two groups.

**Loading Conditions**

Strain is recognised to be load dependent (148), however Petko et al have described no change in global strain pre- and post-HF operation (96). There is significant volume unloading of the RV after the hemi-Fontan procedure when the systemic shunt is removed and superior cavopulmonary connection created. Although not reaching statistical significance (only small numbers in each group), the volume unloading appeared to influence strain values for the free wall and the septum (Figure 65), with the difference between the free wall and septum more exaggerated after HF.
The differences between the right ventricular free wall strain and septal strain in the two morphological groups prior to and after HF. There were no significant differences in the free wall or septal strain values in either group when comparing pre- and post-HF.

DISCUSSION

The data we present address the impact of the morphology of the LV on systolic and diastolic function of the RV in the context of HLHS. Our subdivision into two groups, one of which is characterised by a hypoplastic, slit-like LV and the other by a globular, echogenic LV encompasses the majority of patients with HLHS seen in clinical practice. Our data show that some trends are similar irrespective of the morphologic group. For example the peak s’ velocity, 2D peak strain and tricuspid annular displacement were higher at the RV free wall than at the septum. For both groups, the IVCT and IVRT tended to be more prolonged for the ventricular septum than the RV free wall. In consequence, the calculated MPI was higher when septal readings were used compared to the RV free wall. Thus, for either morphology, measurements from the RV free wall and ventricular septum cannot be used interchangeably.
However, there are major differences between the slit-like LV (Group 1) and globular LV (Group 2) morphologies in many functional aspects (Table 30, Table 31, Table 32 and Table 33). Peak s’, e’ and a’ z-scores of RV free wall measurements were lower in group 1 patients than group 2. Septal strain, ejection time and S:D ratio were lower in group 2 than group 1. Taken together, these measurements suggest that in group 2 the RV free wall is “compensating” for poor septal contraction with enhanced performance of the free wall of the RV.

Mechanical dyssynchrony has previously been reported in patients with HLHS (95-97). Although we have documented differences in regional echocardiographic measurement, MRI derived RV ejection fraction or tricuspid regurgitant fraction was not significantly different between groups 1 and 2. This may reflect the relatively enhanced performance of the RV free wall in patients with a globular LV. The difference in time to peak strain or peak s’ between the RV free wall and septum also did not correlate with tricuspid regurgitation.

In the normal heart, ventricular-ventricular interaction is important in RV biomechanics and the generation of RV systolic pressure (23,149). Although this interaction is important, it may be considered that the interaction with a thickened, globular LV may detrimentally impact on RV mechanics more than absence of a ventricle. In patients with pulmonary atresia with intact ventricular septum, contractility and left ventricular efficiency was decreased compared with those with tricuspid atresia and no high pressure right ventricle (150). The subjective impression in those with a globular, thickened LV is that the septum
is ‘tethered’. It is therefore unsurprising that strain in this region is reduced with reduced tissue Doppler velocities. Petko et al. have described higher regional strain with a shorter wall to wall delay in the mitral atresia/aortic atresia group compared to other subtypes (83).

**LIMITATIONS**

The ideal study in this patient group would be to follow-up individual patients longitudinally to assess RV mechanics through the successive stages of surgical palliation. Such a study would take a considerable amount of time to accumulate sufficient data and our cross-sectional approach was adopted to provide a realistic time for data collection. This does mean that patients at all ages and stages of palliation are included. Echocardiographic methods are known to be influenced by age, heart rate and loading conditions, and where appropriate we have tried to use suitable z-scores to facilitate comparisons (132,137,138). Z-scores are based on normal subjects, but there is no ‘normal’ HLHS data to compute condition specific z-scores.

**CONCLUSION**

Right ventricular ejection fraction and tricuspid regurgitation fraction appear similar in patients with slit-like and globular LV morphology. Tissue Doppler and speckle tracking techniques highlight major differences in regional wall motion between the groups. The impact of such differences on the long-term performance of the systemic RV merits further study.
SUMMARY

**Background:** In HLHS some patients have a slit-like or no discernible LV cavity, whereas others have a hypertrophied, globular LV. The impact of LV morphology on tissue Doppler and speckle tracking parameters was investigated.

**Methods:** Echocardiograms were prospectively acquired on children with HLHS with contemporaneous cardiac MRI scans where possible. Tissue Doppler and speckle tracking parameters were measured from a standard four chamber view.

**Results:** Seventy-four studies between July 2007 and December 2010 were included, 32 in group 1 (slit like or no LV) and 42 in group 2 (globular LV). In 43 patients (20 group 1 and 23 group 2) MRI data was available. MRI ejection fraction and tricuspid regurgitation fraction were no different between the two groups. Septal strain and septal annular displacement were significantly lower than the right ventricular free wall in both groups, although this was most marked in the globular LV group. Septum e’ velocity was significantly lower in those with a globular LV as was septal IVCT corrected for heart rate.

**Conclusion:** LV morphology did not appear to impact on MRI RV EF or tricuspid regurgitation fraction. There are significant differences in tissue Doppler and speckle tracking parameters of systolic and diastolic function between patients with a slit-like LV and those with a globular LV. The long-term significance of these differences needs to be further investigated with a longitudinal study.
Chapter 15 - Future Directions 1: MRI Cardiac Catheterisation with Dobutamine Stress in Patients with Hypoplastic Left Heart Syndrome

AIM
To assess the feasibility of MRI cardiac catheterisation with dobutamine stress in patients with HLHS and compare a small group to the normal adult RV and LV.

HYPOTHESIS
The response to dobutamine stress will be different to the normal adult RV and LV reflecting the chronic preload deprivation of the Fontan circulation.

INTRODUCTION
Initial survival after TCPC is good, however as these patients get older there is often reduced exercise tolerance. The systemic RV is known to fail over time (151), but impaired exercise tolerance can be seen in patients with apparently normal systolic function. The impact of diastolic dysfunction and Fontan physiology (152) (84) has not been fully established.

MRI is considered the gold standard for the assessment of RV function as well as giving detailed anatomical information. Cardiac catheterisation allows invasive pressure measurements, but functional information is limited. MRI cardiac catheterisation involves MRI coupled with invasive pressure measurements and reduces the required radiation dose (66).
Dobutamine is frequently used in adult patients during MRI to assess wall motion abnormalities at stress and has also been used in patients with congenital heart disease such as those with tetralogy of Fallot (153). It has been safely used in our institution for several years in paediatric patients with branch pulmonary stenosis as assessment prior to liver transplantation. Measuring pressures, ventricular volumes and function at rest and two levels of stress may give further information about TCPC physiology and an insight into why patients with seemingly good systolic ventricular function develop exercise intolerance.

**METHODS**

Patients with HLHS after TCPC referred for MRI cardiac catheterisation were included. Patients underwent cardiac catheterisation and MRI scanning in the specially designed MRI catheter suite. Catheters were inserted under fluoroscopic guidance. A catheter was positioned in the lateral tunnel and another in the systemic ventricle. Baseline heart rate, systolic ventricular pressure, end diastolic pressure and lateral tunnel pressure were recorded. The patient was then moved into the MRI scanner.

Phase contrast flow sequences were used to assess flow in the branch pulmonary arteries, superior and inferior caval veins and aorta. SSFP cine imaging was used to obtain a short axis stack across the RV and volumetry was calculated as described in Chapter 8. All volumes were indexed to BSA.

A dobutamine infusion at 10mcg/kg/minute was commenced. After 10 minutes, repeat measurements were recorded from the lateral tunnel and RV and the
short axis stack and aortic flow were repeated. If the patient remained haemodynamically stable with no arrhythmias, then the dobutamine infusion was increased to 20mcg/kg/minute. After 10 minutes at this level, the pressures, ventricular volumetry and aortic flow were repeated. Dobutamine was then discontinued, the catheters were withdrawn and once the patient had returned to baseline status, the MRI scan was completed as clinically indicated. Dobutamine was discontinued at any point if there was haemodynamic instability or arrhythmias. The pattern in the change in volumes was compared to early data on normal stress MRI in a group of adult patients, comparing it to the normal systemic LV and normal sub-pulmonary RV (Kutty et al., in press).

RESULTS
Four patients with HLHS referred for reduced exercise tolerance underwent cardiac catheterisation; demographics are shown in Table 34. Table 35 summarises the changes seen which are also demonstrated in Figure 66, Figure 67, Figure 68, Figure 69, Figure 70 and Figure 71. In all patients, iEDV fell at 10 and then further at 20mcg/kg/min of dobutamine. iESV also fell at the first level of stress. There was a further fall in iESV at the second level of stress in 3 out of 4 patients. ISV decreased 3 patients at 10mcg/kg/min and further at 20mcg/kg/min, but in one patient ISV increased at the first level then fell to below the rest ISV at the second level of stress. Heart rate increased in all patients and iCO also increased at the first stage of stress in all patients. At 20mcg/kg/min, iCO fell in one, rose in another and remained constant in two. EF increased in all patients at the first level of stress, and again at the second stage of stress to a lesser extent in three patients. In one patient there was a slight fall in EF at the second level of stress.
The volumetric response to stress in both the normal RV and LV is very similar. Heart rate increases with each level of stress. EDV remains constant at the first level then rises at the second level of stress. ESV falls at both levels, meaning SV first increases then falls, but to a level higher than at rest. CO increases at both levels and EF rises also, the second increase being not as marked as the first.

**Table 34 Patient demographics**

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Time after TCPC (years)</th>
<th>Weight (kg)</th>
<th>Saturations (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>5.9</td>
<td>3.5</td>
<td>21.5</td>
<td>95%</td>
</tr>
<tr>
<td>Patient 2</td>
<td>9.3</td>
<td>6.7</td>
<td>20.0</td>
<td>95%</td>
</tr>
<tr>
<td>Patient 3</td>
<td>11.6</td>
<td>8.9</td>
<td>45.9</td>
<td>98%</td>
</tr>
<tr>
<td>Patient 4</td>
<td>9.2</td>
<td>5.7</td>
<td>26.5</td>
<td>98%</td>
</tr>
</tbody>
</table>
Figure 66 Heart rate response in the normal RV and LV and the mean in the HLHS group (normal heart rate is clearly same for LV/RV so is represented soley by ‘normal RV’ line)

Figure 66 shows the heart rate response in the normal adults and patients with HLHS. In both groups there is an increase in heart rate between the two stages of stress. The HLHS group appear to have a larger increase between rest and stress than the normal adult group, although this may be related to age rather than the physiology.
Figure 67 *iEDV response in the normal RV and LV and the mean in the HLHS group*

Figure 67 shows the response of iEDV to stress. In both groups there is a fall between the levels of stress, with the normal LV and RV following a similar pattern. The HLHS group have a more marked fall from rest to the first level of stress and then a further fall, of a similar magnitude to the normal hearts between the first and second level of stress.
Figure 68 iESV response in the normal RV and LV and the mean in the HLHS group

The change in iESV can be seen in Figure 68 and is very similar to that of the normal RV and LV.

Figure 69 iSV response in the normal RV and LV and the mean in the HLHS group
As there was a more dramatic fall in iEDV (compared to the normal group) with a similar fall in iESV, the HLHS group had a fall in iSV (as opposed to the increase seen in normal hearts). The HLHS group then had a further fall in iSV as seen in the normal group, but from a lower starting point.

![Graph showing cardiac output increase](image)

**Figure 70** iCO response in the normal RV and LV and the mean in the HLHS group

The cardiac index increased in all groups due to the increase in heart rate. A similar rate of rise was seen in the HLHS group, despite a fall in iSV due to a larger increase in heart rate. Whereas the normal patients increased their cardiac index further, due to a smaller fall in iSV and increased heart rate, the HLHS group plateaued.
Figure 71 EF response in the normal RV and LV and the mean in the HLHS group

Figure 71 shows little difference in EF between the normal and HLHS patients. There is a slight increase in EF at the last stage of stress in the normal group compared to the HLHS group. There were variable changes in lateral tunnel pressures and RV end diastolic pressures at the different levels of stress. In all patients RV pressure increased at the first level of stress, remained constant at the second level of stress in 2 patients, rose in one and fell in another. The changes are summarised in Table 35.

Table 35 Response to stress

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>iEDV</th>
<th>iESV</th>
<th>iSV</th>
<th>iCO</th>
<th>EF</th>
<th>LT</th>
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<th>EDP</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>↑↑</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↑↑</td>
<td>↑↑</td>
<td>-</td>
<td>↑↑</td>
<td>- -</td>
</tr>
<tr>
<td>2</td>
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<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
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<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
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<tr>
<td>3</td>
<td>↑↑</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↑↑</td>
<td>↑↑</td>
<td>-</td>
<td>↑↑</td>
<td>-</td>
<td>- -</td>
</tr>
<tr>
<td>4</td>
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<td>↓↓</td>
<td>↑↑</td>
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<td>↑↓</td>
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</tr>
</tbody>
</table>
All patients tolerated dobutamine infusion at both levels of stress without haemodynamic instability or arrhythmias. There were no major complications from the MRI or catheterisation.

DISCUSSION

The circulation in subjects with normal hearts and patients who have undergone TCPC are fundamentally different. Normal hearts have both a sub-systemic and sub-pulmonary ventricle with reserve to increase cardiac output under stress. Following TCPC, the systemic ventricle derives venous return from blood which has passed through the series circuit of the systemic arterial, systemic venous and pulmonary circulations. This means that the systemic ventricle following TCPC tends to have a chronically reduced preload compared to the normal heart (154).

Pump failure in the normal circulation leads to abnormally high ventricular filling pressures in contrast to the situation following TCPC, where filling pressures may not increase due to deprivation of venous return. Furthermore, the functionally single systemic ventricle has normally been subjected to different loading conditions through successive surgical stages. Volume loading occurs after the initial shunt operation, but creation of a superior cavopulmonary connection leads to abrupt volume reduction. The net result of the surgical stages is that there is an increase mass to volume ratio.

In the absence of fenestration flow, the filling of the RV after TCPC is entirely dependent on pulmonary venous return. Pulmonary venous return is
dependent on pulmonary blood flow, which is in turn influenced by factors including PVR and size of the branch pulmonary arteries.

The main differences between the patients with HLHS and the normal hearts were in EDV and therefore SV. As there was a decrease in SV, the CO could only be maintained by an elevation in heart rate. This decrease in EDV at stress could be representative of the decreased preload in the post TCPC circulation. If the decreased exercise tolerance is due to decreased ventricular filling, then it is possible that agents that can manipulate pulmonary blood flow and pulmonary venous return, such as pulmonary vasodilators may be of use to many children after TCPC, including those with ‘normal’ PVR. There is currently ongoing work at this institution building on this preliminary data, exploring these physiological responses to stress in patients with single ventricles.
AIM
To assess the feasibility of modelling the systemic RV in patients with HLHS and compare to the normal LV.

HYPOTHESIS
It will be technically feasible to model RV geometry, filling patterns and vortex formation in patients with HLHS.

That the use of such techniques will provide additional insights into cardiovascular physiology.

INTRODUCTION
There is no significant evidence base for the majority of interventions and medication in congenital heart disease and, due to the wide heterogeneity of the patients it is not always possible to predict the response of a particular patient to a particular therapeutic strategy. With respect to HLHS, for example, there is conflicting clinical data on agents such as pulmonary and systemic vasodilators (155). It would therefore be ideal to have a patient specific model which could be used to estimate the effect of various interventions.
METHODS

Data acquired from patients with HLHS as part of this project was used in a collaboration with computer scientists, engineers and mathematicians within King’s College London to produce patient specific cardiac models. A geometric model was created using manual segmentation of the 3D SSFP MRI sequence and a fibre model. The tricuspid inflow Doppler was used to simulate filling with validation from myocardial velocities and displacements from tissue Doppler and MRI cine images.

The vortex formation and distribution of kinetic energy was studied in these patients compared to the normal LV (model obtained from MRI and echocardiographic data on a child with a structurally normal heart who underwent a cardiac MRI for clinical reasons).

RESULTS

Four patients with HLHS were studied along with a normal left ventricle in a healthy child. All patients were studied prior to hemi-Fontan and in two patients data prior to TCPC was available. Vortex ring formation from incoming blood was seen. The pattern and shape were different, with the first patient having a single large vortex that filled the upper part of the cavity that then expanded to the apex. Asymmetric vortex formation was seen in the other three patients and in one patient there was an additional vortex. Two vortices were associated with biphasic inflow and associated with less energy loss.

Additionally, the shape of the ventricular cavity was also important in the fluid dynamics. Patient 1 had a more dilated, globular RV with the vortex expanding
circumferentially before travelling from base to apex. This was in contrast to the patients with a more elliptical RV, which had a pattern that was more similar to the LV with asymmetric vortex formation encouraging longitudinal flow. Figure 72 shows the differences in the patterns between the globular RV and a normal LV. The larger single vortex can be seen in the HLHS RV on the left with more circumferential displacement compared to the longitudinal deformation in the normal LV on the right.

**Figure 72** Difference in vortex patterns between the RV in HLHS (left) and a normal LV. The blue (minimum) to white (maximum) scale refers to speed and the blue (minimum) to red (maximum) scale to displacement

**DISCUSSION**

It is possible to create patient specific models that give insight into the flow dynamics within the ventricles of the normal and diseased heart. The RV in HLHS has a sub-optimal cavity shape for energy loss, which is further compounded by dilatation and the loss of a biphasic filling pattern. It may be
possible in the future to alter data input to the model to assess possible changes from different interventions.
Chapter 17 - Conclusions

An increasing number of children with HLHS are surviving to Fontan completion (34,156). As these children get older they will require close monitoring for RV dysfunction, which is seen over time in those with a systemic RV (157). Ongoing assessment of these patients is challenging, with techniques either being relatively inaccessible and expensive (MRI) or based on adult or LV assessment (echocardiography). Imaging in non-compliant children is compounded by the complex geometry of the single RV (6), which in turn is complicated by the varying degrees of residual left ventricular morphology. This thesis has sought to better understand the systemic RV in HLHS throughout the palliative stages using MRI and both simple and advanced echocardiographical techniques.

The systemic RV in HLHS is subjected to widely differing volume loads throughout the stages of surgical palliation (4). The Norwood procedure results in a RV pumping the entire cardiac output. This is reduced after HF, which has been demonstrated through the analysis of cardiac MRI scans prior to and after HF. Additionally, there appears to not only be a reduction in volume loading, but an increase in contractility. The extent of the volume reduction after HF was associated with tricuspid regurgitation (less volume reduction) and LV morphology (greater volume reduction in those with a larger residual LV).

The size of the residual LV appears to have an impact on cardiac mechanics, with lower septal strain in those with a globular, hypertrophied LV compared to those with no discernible or a slit-like LV. It is not clear whether these altered
mechanics affect outcome in HLHS and further longitudinal studies are required. The varying size of the residual LV affects the shape of the RV contributing to the high heterogeneity in this patient group. This heterogeneity makes standard echocardiographic assessment tools (predominantly designed for the LV) challenging to apply in this setting. The current clinical gold standard for assessment of RV systolic function is considered to be cardiac MRI.

The main measure of function derived from cardiac MRI is EF based on volumetry. EF is a pure measure of volume change and not of intrinsic myocardial contractility or diastolic function, and therefore can be artificially elevated in significant tricuspid regurgitation or be within the normal range in diastolic dysfunction. Assessment of patients using MRI prior to and after HF showed an increase in median EF, showing that a flat ‘normal’ range of EF in this population is not necessarily valid. Our study of subjective visual assessment of RV systolic function in HLHS showed that although experience improves concordance with MRI derived ejection fraction overall concordance is poor.

The challenge has therefore been to develop objective measures of function for the RV in HLHS in the setting where the only gold standard is a poor surrogate for systolic and diastolic function. Application of speckle tracking techniques showed a correlation with MRI derived ejection fraction, with a trend towards lower apical strain and speckle derived tricuspid annular displacement in patients with lower EF, but with no clear cut-off and a degree of variability of the values. Investigation of tissue Doppler derived time interval parameters
demonstrated significant differences from the normal heart in both isovolumic contraction and isovolumic relaxation times (and emphasised the need to correct for heart rate), but it is not clear whether these differences reflect adaptation or maladaptation of the systemic right ventricle.

To conclude, assessment of the systemic RV in HLHS is essential but very challenging. The current clinical gold standard only assesses volume change and can give no insight into diastolic function or dyssynchrony, but does demonstrate the ventricular and vascular changes occurring after the different stages of palliation. Speckle tracking shows some correlation with MRI derived EF and may be a useful clinic screening tool for referral of patients for further investigations. Tissue Doppler time interval assessment shows significant differences from the normal heart, but it is not clear whether these represent a systemic RV trying to adapt or ventricular dysfunction.
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APPENDIX 1 – ETHICAL APPROVALS

Four submissions were made to the ethics committees for approval and amendments made to two ethical approvals already in place.

Pathophysiology of the Systemic Right Ventricle

09/H0804/62: Guy’s Hospital Ethics Committee

The first submission was ethical approval for studying patients with a systemic right ventricle (MRI, echocardiography and in some, catheter data). It was proposed that patients were divided into two groups.

Group 1 – Patients with a systemic RV referred for MRI or MRI catheter as part of their routine care (all age groups).

Group 2 – Patients with a systemic RV actively recruited for an MRI catheter that was not part of their routine clinical care, in order to study them in more detail (adult patients only).

Ethical approval was granted for both groups described above. Patients recruited in group 1 would undergo their routine MRI or MRI catheter with the addition of dobutamine stress and also echocardiography at rest and at stress at the time of the MRI.

Patients recruited in group 2 would undergo an MRI catheter with dobutamine stress as well as echocardiography at rest and at stress. Approval was granted for all data to be shared with the cardiac modelling team at Oxford University.
Advanced Echocardiography in Congenital Heart Disease
09/H0802/116: St Thomas’ Hospital Ethics Committee
A submission was made to use the echocardiography archive (Excelera, Philips Healthcare and Echopac, GE) as a research database. Permission was granted for all echocardiograms on the archive to be used for research purposes within the department. No specific consent was required. This application was made so that echocardiograms obtained in routine clinical care could be analysed, thus increasing the number of patients included in the echocardiographic part of the study.

MRI of cadaveric human hearts from hospital postmortems
10/H0802/28: St Thomas’ Hospital Ethics Committee
Fibre tracking in the heart can currently only be practically carried out in the still heart, although work is in progress to improve fibre tracking in the living person. An application was submitted to perform fibre tracking on cadaveric cardiac specimens from patients undergoing a hospital postmortem (adults and children). Knowledge of fibre orientation would be essential for the computer models of the systemic RV, as well as giving information on fibre changes with age and, potentially, in congenital heart disease.

Retrospective Review of Cardiac MRI in Congenital Heart Disease
08/H0810/058: Lewisham Hospital Ethics Committee
Ethical approval was already in place for the study of the notes and MRI scans of patients with congenital heart disease. This was used to analyse the MRI scans and outcomes of patients with HLHS.
**Advanced Imaging Techniques in Congenital Heart Disease**

*07/Q0704/3: Guy’s Hospital Ethics Committee*

A time extension was made for this ethical application, which gives approval to perform an echocardiogram under the same general anaesthetic as an MRI scan in patients with congenital heart disease.

**MRI Sequence Development in Paediatric Patients**

*10/H0802/65: St Thomas’ Hospital Ethics Committee*

An ethical submission was made to perform and develop MRI sequences under the same general anaesthetic as a clinical scan in children referred for an MRI or MRI catheter under general anaesthetic. Patients could be involved if a) they gave consent, b) the total scanning time did not exceed the clinical slot, c) the patient was stable enough and d) if they were not already enrolled in another study requiring extra time under general anaesthetic.
APPENDIX 2 – NORMALISATION OF VALUES IN PAEDIATRICS

Normal ranges of most echocardiographic parameters have been established in the adult population. Children with congenital heart disease present a two-layered problem: the hearts are not structurally normal and, particularly in cases where there is a systemic RV, normal ranges cannot necessarily be applied. Adult ranges can also not generically be applied to the paediatric population, as many are heart rate dependent and some may be related to size (in paediatrics this is often adjusted for by using body surface area, BSA). For every parameter, it is important to assess for the impact of growth – both physical and age-related – as well as heart rate. There may also be gender and race-related factors.

The American Society of Echocardiography has recently published guidelines on this subject. It was recommended that “when normative data are available, the measurements of cardiovascular structures should be expressed as Z scores using the Haycock formula (158) to calculate BSA (124)”. The Haycock formula is expressed as:

$$\text{BSA (m}^2\text{)} = 0.024265 \times \text{weight (kg)}^{0.5378} \times \text{height (cm)}^{0.3964}$$

Roberson et al. (159) performed tissue Doppler in 634 children, from the age of 1 day to 18 years, and have derived z-score tables for myocardial velocities in the positions described above. They found that the s’ wave correlated best with age at all three sites. The e’ correlated best with age for the septum and tricuspid valve sites, but best with heart rate at the mitral valve site. The a’ correlated best with heart rate at all three sites.
APPENDIX 3 - REPEATABILITY

Echocardiography

Inter and intra-observer variability of all measures was assessed using two-way random intra-class coefficients with absolute agreement on twenty cases. Echocardiographic inter-observer variability was assessed by two observers (the author and Dr. J Simpson) and intra-observer by a single observer (the author) analysing the twenty cases more than a week after the initial analysis. Both observers were blinded to the original analysis.

Inter and intrauser variability for echocardiography is shown in Table 36. Intraclass coefficients for most tissue Doppler derived time intervals were very good. IVRT for both the free wall and the septum showed the most variation of the time intervals. Tissue Doppler velocities also showed good agreement, although speckle tracking parameters showed only moderate agreement.

Table 36 Intraclass coefficient for echo analysis

<table>
<thead>
<tr>
<th>Tissue Doppler Times</th>
<th>Intraclass coefficient (Intra-observer)</th>
<th>Intraclass coefficient (Inter-observer)</th>
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<td>Free wall RR interval</td>
<td>0.999</td>
<td>0.998</td>
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<tr>
<td>Free wall IVCT</td>
<td>0.904</td>
<td>0.821</td>
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<td>FW ET</td>
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<td>Free wall IVRT</td>
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<td>Septal RR interval</td>
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<tr>
<td>Septal ET</td>
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<td>0.936</td>
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<tr>
<td></td>
<td>Free Wall</td>
<td>Septum</td>
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<tr>
<td>----------------------</td>
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<tr>
<td>Septal IVRT</td>
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<td>Tissue Doppler</td>
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<td>velocities</td>
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<tr>
<td>Free wall peak s</td>
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<td>0.933</td>
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<tr>
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<tr>
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<td>Septum</td>
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<td>0.809</td>
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</table>

Ejection time (ET), isovolumic contraction time (IVCT), isovolumic relaxation time (IVRT), tricuspid annular descent (TAD)
**Magnetic resonance imaging**

Inter and intra-observer variability of the right ventricular volume measurements was quantified using an intra-class correlation coefficient two-way model with absolute agreement. Each single measurement was assessed by two observers (the author and Dr. A Bell).

The intra-class coefficient for MRI analysis was 0.945, 0.952, 0.926, 0.885, and 0.999 for end diastolic volume, end systolic volume, stroke volume, ejection fraction and neo-aortic stroke volume respectively.
List of Abbreviations

1D – one dimensional
2D – two dimensional
3D – three dimensional
AA – aortic atresia
AS – aortic stenosis
AV – atrioventricular
AVSD – atrioventricular septal defect
BSA – body surface area
CD – chest drain
CVP – central venous pressure
CW – continuous wave
DF – diastolic filling
DORV – double outlet right ventricle
dP/dT – change in pressure by time
DT – diastolic time
ECG - electrocardiogram
EF – ejection fraction
EFE – endocardial fibroelastosis
EP – ejection period
ET – ejection time
FAC – fractional area change
FT – filling time
HF – hemi-Fontan
HLHS – hypoplastic left heart syndrome
ICP – isovolumic contraction period
(i)EDV – (indexed) end diastolic volume
(i)ESV – (indexed) end systolic volume
(i)SV – (indexed) stroke volume
(i)CO – (indexed) cardiac output
IRAS – integrated research application system
IRP – isovolumic relaxation period
ITU – intensive therapy unit
IVC – inferior caval vein
IVC(T) – isovolumic contraction (time)
IVR(T) – isovolumic relaxation (time)
LPA – left pulmonary artery
LV – left ventricle
MA – mitral atresia
MAPCAS – major aortopulmonary collaterals
MHC – myosin heavy chain
MPI – myocardial performance index
MRI – magnetic resonance imaging
MS – mitral stenosis
NICOR - National Institute for Cardiovascular Outcomes Research
NPV – negative predictive value
NSF – nephrogenic systemic fibrosis
PLE – protein losing enteropathy
PPV – positive predictive value
PVR – pulmonary vascular resistance
PW – pulsed wave
Qp:Qs – pulmonary to systemic blood flow ratio
RPA – right pulmonary artery
RV – right ventricle
SD – standard deviation
S:D – systolic to diastolic time ratio
SENSE – sensitivity encoding
SSFP – steady state free precession
ST – systolic time
SVC – superior caval vein
TAD – tricuspid annular displacement
TAPSE – tricuspid annular plane excursion
TAPVD – total anomalous pulmonary venous drainage
TCPC – total cavopulmonary connection
TDI – tissue Doppler imaging
TGA – transposition of the great arteries
TOF – tetralogy of Fallot
TR – tricuspid regurgitation
TV – tricuspid valve
UK – United Kingdom
USA – United States of America