2019

Recruitment, single ventricular palliation, and complex biventricular repair for patients with Hypoplastic Left Heart Syndrome

BOSTON UNIVERSITY

SCHOOL OF MEDICINE

Thesis

RECRUITMENT, SINGLE VENTRICULAR PALLIATION, AND COMPLEX BIVENTRICULAR REPAIR FOR PATIENTS WITH HYPOPLASTIC LEFT HEART SYNDROME

by

VIVIAN WU

B.S., University of California, San Diego, 2016

Submitted in partial fulfillment of the

requirements for the degree of

Master of Science

2019

Approved by

First Reader ____

Vickery Trinkaus-Randall, Ph.D.
Professor of Biochemistry

Second Reader ____

Sitaram Emani, M.D.
Associate Professor of Surgery, Harvard Medical School

ACKNOWLEDGMENTS

My sincere appreciation to my principal investigator, Dr. Sitaram Emani, for this opportunity of not only introducing me to cardiothoracic surgery, but also showing me how much expertise and determination each cardiothoracic surgeon and cardiologist contributes to ensure each child receives the best treatment. I am grateful to have witnessed and been part of all the meetings and discussions. Thank you to my immediate supervisor, Breanna Piekarski, for guiding me throughout this learning process from knowing nothing about cardiothoracic surgery to writing this thesis. Thank you to all of the HLHS patients for not only giving me the opportunity to study this topic, but also demonstrating what resilience truly is. Overall, thank you to Boston Children's Hospital's Cardiothoracic Surgery department for inspiring me to be an influential medical professional in the near future. Finally, thank you to my advisor, Dr. Trinkaus- Randall, for all your guidance as I navigated through this experience.

RECRUITMENT, SINGLE VENTRICULAR PALLIATION, AND COMPLEX BIVENTRCULAR REPAIR FOR PATIENTS WITH HYPOPLASTIC LEFT HEART SYNDROME

VIVIAN WU

ABSTRACT

Background: Hypoplastic Left Heart Syndrome is a congenital birth defect that is defined by underdevelopment of the left heart during pregnancy. This is especially dangerous as the left heart holds the systemic flow of blood- the oxygenated blood. Not enough oxygen throughout the whole body causes cyanosis, which symptoms include bluish discoloration of the skin or mucous membrane due to low oxygen saturation. Single Ventricle Palliation followed by Biventricular Conversion is the most common surgical procedural pathway to correct this defect. The goal is to convert from a single ventricle circulation during single ventricle palliation to biventricular circulation via biventricular conversion, which is the normal heart anatomy. Single Ventricle Pallation consists of three stages: Stage 1 Norwood Procedure, Bidirectional Glenn, and Fontan. Biventricular Conversion can be performed after any of the three stages. In addition, further compromise of the left ventricle includes other factors such as a thickening of fibroblast-like cells on the endocardial layer called endocardial fibroelastosis. Therefore, additional surgical procedures, also known as recruitment procedures, combat these problems. It is critical to find a correlation between a specific procedure and post surgery success in left ventricle growth and function for these patients.

Objectives: Patients with Hypoplastic Left Heart Syndrome at Boston Children's Hospital have undergone single ventricle palliation with some patients proceeding to biventricular conversion. This study aimed to study the palliation stages individually and recruitment procedures (specifically endocardial fibroelastosis resection) on the effect of left ventricle growth.

Methods: Patients with Hypoplastic Left Heart Syndrome were studied retrospectively (before 2014) and prospectively (after 2014 until December 1, 2018). Single Ventricle Palliation and Biventricular Conversion were analyzed via descriptional analysis with evidence of left ventricular growth measured by left ventricular end diastolic volume and respective z-scores. Z-scores were used to standardize end diastolic volume values across variability in age, weight, and height.

Results: A total of 55 patients underwent single ventricle palliation and 39 ended with biventricular circulation via biventricular conversion. Overall, there was a 9.29 ml increase in end diastolic volume between Bidirectional Glenn and Fontan and a 0.795 increase in end diastolic volume z-score between Fontan and Biventricular Conversion. Next, those who did not have recruitment procedures experienced a 135.6%, 48.8%, and 0% growth at Stage 1, Bidirectional Glenn, and Fontan, respectively, before directly proceeding to biventricular conversion. Those with recruitment experienced a 44.5%, 90.4%, and 83.0% growth at Stage 1, Bidirectional Glenn, and Fontan, respectively, before directly proceeding to biventricular conversion. Finally, there was a 50.2% and 62.3% in left ventricular growth at Bidirectional Glenn and Fontan, respectively, after endocardial fibroelastosis resection compared to only a 6.9% growth at Stage 1.

Conclusion: Bidirectional Glenn was the most effective palliation stage for left ventricular growth. Recruitment in patients at this stage was associated with growth that exceeds those who did not have recruitment. This stage also best demonstrates the ability and success of growing a small ventricle to be adequate for biventricular conversion. Left ventricular growth at Fontan circulation holds promising results that are a point of interest for more studies. Endocardial Fibroelastosis resection is more effective on left ventricular growth at Bidirectional Glenn and Fontan compared to Stage 1.

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LIST OF ABBREVIATIONS

ASD .... Atrial Septal Defect

BDG .... Bidirectional Glenn

BiVC .... Biventricular Conversion

BIV .... Biventricular Circulation

BTS .... Blalock-Taussig Shunt

EDV .... End Diastolic Volume

EFE .... Endocardial Fibroelastosis

HLHS .... Hypoplastic Left Heart Syndrome

HLH .... Hypoplastic Left Heart

LA .... Left Atrium

LH .... Left Heart

LV .... Left Ventricle

LV EDV .... Left Ventricular End Diastolic Volume

PDA .... Patent Ductus Arteriosus

PA .... Pulmonary Artery

RA .... Right Atrium

SVC .... Superior Vena Cava

SVP .... Single Ventricle Pallation

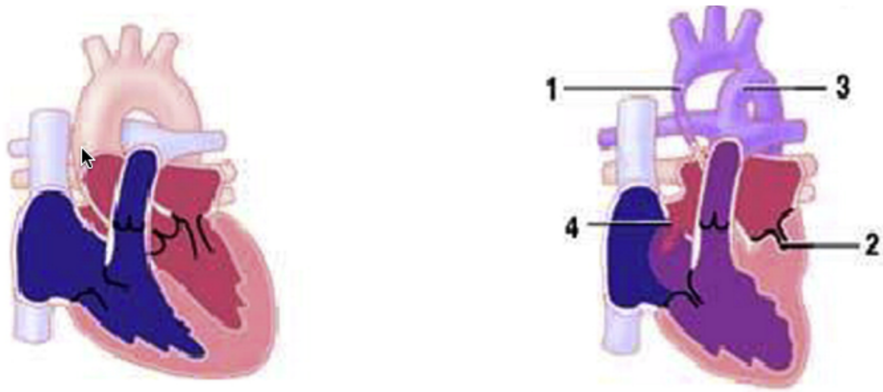
1.5V .... 1.5 Ventricular Circulation

INTRODUCTION

The goal of this study is to determine the following two things: stage in Single Ventricle Palliation (SVP) that is the most effective in stimulating left ventricular (LV) growth and stage which recruitment is the most effective, especially the impact of endocardial fibroelastosis (EFE) on LV growth. Determining which stage with the most promising LV growth can introduce discussion of critical time points to perform certain procedures that may maximize successful conversion from singular ventricular circulation to biventricular circulation (BIV) via biventricular conversion (BiVC). It is the same reasoning for purpose of recruitment effectiveness.

Hypoplastic Left Heart Syndrome (HLHS)

Among congenital defects in neonates, heart defects prove the most common with 3-12 per 1000 births with the risk rising two-fold for premature infants (Gładki et al., 2015). One major congenital heart defect is Hypoplastic Left Heart Syndrome (HLHS). HLHS affects boys more than girls (two thirds of cases occur in boys) and is the most common cause of cardiac-related death in the first month of life (Toebbe et al., 2013) It is defined as the general underdevelopment of the left ventricle and its dependent structures such as the mitral valve, aortic valve, and preductal and ductal aorta (Mettler & Pigula, 2016). In addition, pulmonary and systemic ventricles for biventricular circulation are often compromised for severe HLHS patients, which left ventricular hypoplasia and/or valve atresia are hallmarks (Banka et al., 2014).



Example of a normal heart	Example of Hypoplastic Left Heart Syndrome

1. Hypoplastic ascending aorta and aortic arch.
2. Hypoplastic left ventricle.
3. Large patent ductus arteriosus supplying the only source of blood flow to the body.
4. Atrial septal defect allowing blood returning from lungs to reach the single ventricle.

Figure 1. Comparison between a normal heart and a heart with HLHS (Toebbe et al., 2013). Patent ductus arteriosus (PDA) is a connection between pulmonary artery and aorta that is usually closed shortly after birth. A persistent opening indicates mix of pulmonary and systemic blood. Atrial Septal Defect (ASD), an opening between the atrium, is further mixing of the systemic and pulmonary blood that causes problems such as cyanosis.

With the left ventricle's function compromised, these neonates will commonly be seen in severe respiratory distress, respiratory acidosis, and cyanosis immediately after birth (Mettler & Pigula, 2016). The following are two surgical pathways to attempt to combat HLHS: single ventricle palliation (SVP) and biventricular conversion (BiVC).

Single Ventricle Palliation (SVP)

There are three stages of SVP. Stage I is the Norwood Procedure, stage II is the Bidirectional Glenn (BDG), and stage III is the Fontan. SVP's objective is to utilize the right heart as both pulmonary and systemic circulation to alleviate obstruction of left heart's blood flow when left heart is compromised. Stage 1 Norwood Procedure is often performed shortly after birth for survival. This procedure encompasses all of the following steps but not necessarily in this order: Blalock-Taussig shunt (BTS), side to side anastomosis between aorta and pulmonary valve, aortic arch augmentation with a piece of pulmonary homograft, and atrial septectomy (Mettler & Pigula, 2016). Atrial septectomy allows blood from the LA to enter RA and this increase in total volume of blood in to the RV will leave through the augmented aortic arch and to the body. BTS provides additional pulmonary blood flow to prevent cyanosis.

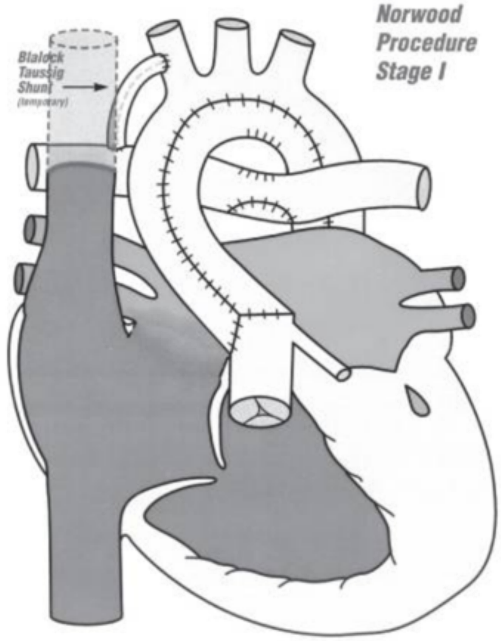


Figure 2. Stage I: The Heart after Norwood Procedure is Performed. Increased systemic flow by this procedure relieves the hypoplastic left heart (HLH) from working excessively to provide an adequate amount of blood to the body. BT Shunt ensures blood volume to pulmonary blood flow is still sufficient (Human, 2009)

The interstage mortality rate between Norwood procedure and stage II palliation is of significance; it remains as high as 8% to 12% (Oster et al., 2016). Due to the statistics, performing stage II BDG early may seem tempting to solve this high interstage mortality; however, it is proven that performing early BDG on patients younger than two months of age resulted in a reoperation rate of 17%. Therefore, stage II BDG is postponed for a neonate until after three months of age (Mettler & Pigula, 2016).

The purposes of stage II BDG is to further decrease the amount of blood going through the ventricles and shunt it towards the lungs in hopes of increasing oxygen saturation. The goal of this procedure is to connect the superior vena cava (SVC) to the pulmonary artery (PA) so that the blood flow from the head circumvents the right ventricle and to the lungs. To do so, the azygous vein is severed, the pulmonary remnant of BTS is excised, and the pulmonary arteriotomy is enlarged to accommodate the SVC. After the SVC is clamped at its insertion into the RA, anastomosis is performed with a suture between SVC and PA (Mettler & Pigula, 2016).

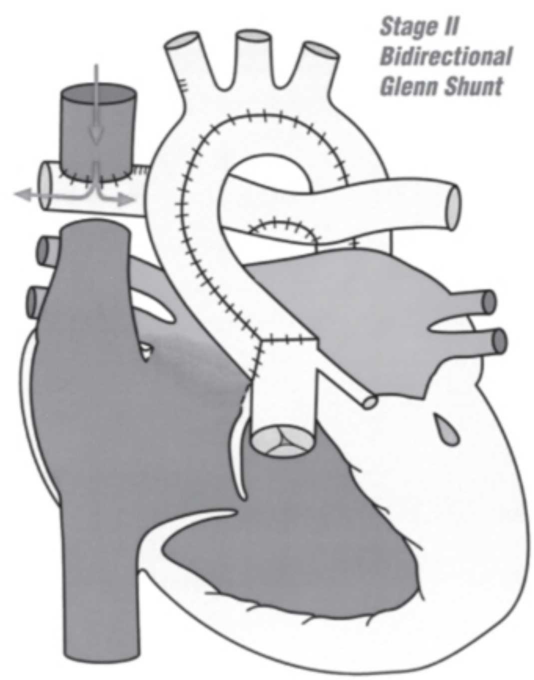


Figure 3. Stage II: The Heart after BDG is performed.
By attachment of SVC to PA, the blood from the head bypasses RA and flows directly to the lungs. More blood is shunted towards the lungs to increase saturation and relieves the demands on the heart.

The final stage of SVP is stage III Fontan. The goal of this procedure is to divert all systemic venous return to the pulmonary circuit- allowing a physiologic septation of circulation. The are two types of Fontan- extracardiac and lateral tunnel; however, extracardiac Fontan is preferred as it is more hemodynamically efficient (Mettler & Pigula, 2016). The lateral tunnel of a Fontan is a baffle (or tunnel) that connects the inferior vena cava (IVC) to SVC through the right atrium so the deoxygenated blood from the lower part of the body circumvents the RA, but still leads to the PA. The extracardiac tunnel is a conduit that connects RV to PA, which follows the natural path of blood flow.

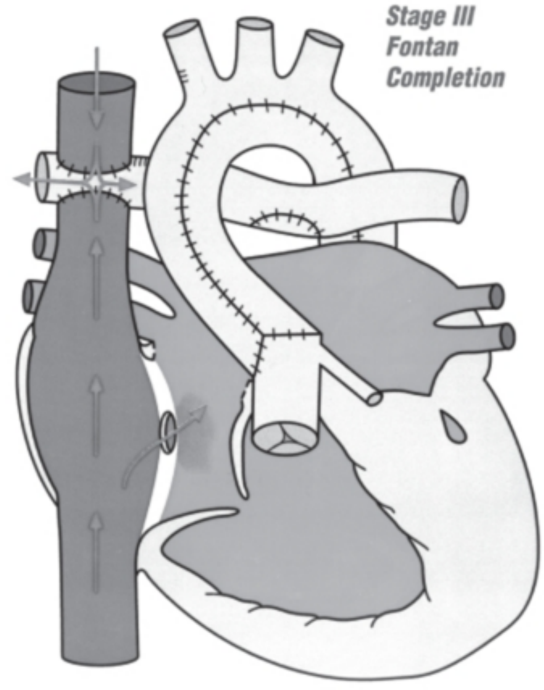


Figure 4. Stage III: The Heart after Fontan is performed. A physiological septation is established with the RH pumping blood received from LA and venous return from SVC and IVC flows directly in to PA.

Biventricular Conversion (BiVC)

Biventricular conversion (BiVC) is the conversion of SVP to biventricular circulation. The objective for BiVC is to avoid SVP's long-term complications. Some of these complications for Fontan circulation are arrhythmias, thromboembolic events, hepatic dysfunction, protein-losing enteropathy, exercise intolerance, and neurocognitive defects (Kalish et al., 2013). To convert from single ventricular circulation to biventricular, there must be a re-establishment of separate LV and RV outflow tract. Biventricular conversion can be performed after any stage of SVP as long as the LV meets the criteria in size and function; echocardiographic measures of a larger LV EDV, LV-to-RV stroke volume ratio, and mitral-to-tricuspid inflow ratio have indicated a higher association with successful BiVC (Banka et al., 2014). Therefore, procedures for conversion vary for different patients. Example of some procedures performed for BiVC are takedown of the aortopulmonary anastomosis and/or reconnecting SVC from the PA to the RA (after BDG) (Emani et al., 2012) .

Staged LV Recruitment

Staged LV Recruitment strategy is a combination of surgical techniques that can complement the Norwood procedure, BDG, or Fontan, or as separate methods. The purpose of this strategy is to promote LV growth with the preparation of ultimately establishing a functional biventricular circulation through BiVC. Growing and increasing the LV size will increase the chance of success and sustained biventricular circulation. Some of the techniques applied are resection of endocardial fibroelastosis (EFE), mitral valvuloplasty, aortic valvuloplasty, and atrial septal defect restriction (Emani et al., 2012).

Endocardial Fibroelastosis (EFE) is the thickening of the endocardial layer composed of spindle shaped fibroblast-like cells among abundant collagenous tissue and elastic fibers (Ursell et al., 1984). EFE is a crucial threat because it restricts growth of the LV. Furthermore, fetal imaging proves that EFE development is associated with distended, poorly contractile LV in HLHS patients (Shimada et al., 2015). Therefore, EFE resection is an important method associated in enhancing a patient's potential LV growth.

Heart valves are important in managing blood pressure and blood flow and when compromised, the outflow tract is obstructed. In HLHS, mitral atresia/stenosis and aortic atresia/stenosis are common diagnosis. The potential danger caused by faulty valves is high, especially because LH retains systemic flow. Therefore, mitral and aortic valvuloplasties are valve repair techniques designed to promote sufficient blood flow and pressure in LH. These methods for valve repair are part of the LV recruitment strategy because repaired valves help increase flow and pressure to the LV, which will cause the cardiac muscles to stretch and enlarge the hypoplastic LV.

A type of atrial septal defect (ASD) restriction often performed is fenestrated ASD. Fenestrated ASD uses a fenestrated pericardial patch (4-mm fenestration) to establish separate atriums (RA and LA) compared to Norwood procedure where RA and LA functioned as one large atrium via atrial septectomy. By restricting ASD, blood entering the LA would flow in to LV; thus, the force of blood flow will put pressure on the LV, which will promote LV growth. The reasoning behind ASD restriction via fenestrated ASD and not total ASD occlusion is if full occlusion happens, RA pressure would increase; this would cause pulmonary blood flow leading to the RA to backtrack, leading to pulmonary edema. With fenestration, some flow from RA can enter LA to relieve the pressure.

METHODS

Study Design

This is a prospective and retrospective analysis for children who were presented to Boston Children's Hospital with a diagnosis of HLHS. There are a total of 55 patients; 25 are retrospective patients and 30 are prospective patients. Retrospective study is defined as children who have completed Biventricular Conversion at Boston Children's Hospital in 2014 or before. Prospective study is defined as children who were presented from 2014 to December 1, 2018. Hospital records presented in database were analyzed for demographics, diagnosis, details of surgical procedures, cardiac magnetic resonance imagine (MRI) measurements, and echocardiographic (ECHO) measurements. However, only ECHO measurements were used for Left Ventricle End Diastolic Volume (LV EDV) and respective Z-scores for this study. ECHO measurements were taken immediately before a procedure and right before the next procedure. There may also be more ECHO measurements between this time but are not relevant to this study. Primary outcomes measures were changes in z-scores for LV EDV as this was a better measurement for comparison across the sample of HLHS patients with variation in age, weight, and height. Secondary outcomes include current status- alive on a biventricular circulation, deceased, takedowns, and/or transplants- and re-operation after BIV conversion.

Biventricular Conversion Procedure

Agreement to BiVC was performed after meticulous assessment from primary cardiologist and cardiothoracic surgeons at Boston Children's Hospital. Some factors considered include normal ventricular function, adequate AV valve size and function, and low end diastolic pressures (Oladunjoye et al., 2018).

Descriptional Statistics

Descriptional analysis was performed using measures of central tendency, with median solely used. Since obtained z-scores are from patients with different ages, heights, and weights at each palliation procedure, median was used to ensure outliers did not skew final measures. Categorical variables include palliation procedures and EFE resection at each palliation stage; continuous variables are median z-scores. Use of descriptional statistics over analytical statistics for HLHS (N=55) was due to observing the trend of recruitment procedures' efficacy at growing the LV to arrive at our desired destination: BIV Conversion for ultimate biventricular circulation. This also allows following the secondary outcomes of patients who have undergone both recruitment procedures and BIV Conversion to create an overall picture of what a child presented to us could possibly expect his or her surgical journey to be like. Furthermore, descriptional analysis assists with focusing on the impact of EFE and if it indeed is a significant factor in hindering LV growth, which could hinder the success of BiVC.

RESULTS

Patient Characteristics

Out of a total of 55 patients, 25 are retrospective patients and 30 are prospective patients. Retrospective patients have undergone BIV Conversion in 2014 or before and prospective patients are presented from 2014 and onwards. All 55 patients have had ECHO performed to measure LV EDV and its respective z-score at and in between each SVP procedure.

Table 1. Patient Characteristics (N=55). 55 patients are separated as retrospective and prospective and by sex. HLHS affects males more than females.

Variable	Value
Retrospective, n (%) Prospective, n (%)	25 (45) 30 (54)
Sex, n (%) Male Female	 37 (67) 18 (33)

Overview of Patients' Palliation Journey

Overall, all 55 patients (n=55) had Stage 1 Norwood Procedure, as it is essential for HLHS patients' survival. 44 patients (n=44) of the 55 had BDG. Lastly, 10 patients (n=10) of the 55 have had Fontan operation. With choosing to focus on population at each stage of SVP, there is an inevitable overlap of patients. Some patients will have undergone all procedures- Stage 1, BDG, Fontan, and BiVC- and will, therefore, be counted as one patient at each stage.

Table 2. Overview of Patients' Palliation Journey. All patients had Stage 1 Norwood Procedure, 80% had a BDG, and 10% had a Fontan. 71% of the 55 patients ultimately had BiVC with 38% of this specific population in need of at least one re-operation.

Variable	Value
SVP, n(%)	
Stage 1 Fontan: BiVC:	55 (100) 4 39
BDG Fontan: BiVC:	44 (80) 4 28
Fontan Fontan: BiVC:	10 (18) 4 6
Biventricular Conversion (BiVC) total, n (%)	39 (71)
Re-operations, n (%)	21 (38)*

*Calculated out of 39 of those who had BiVC

Thirty-nine of the 55 patients at Stage 1 ended their surgical journey with BiVC (ultimate biventricular circulation) while 4 out of the 55 ended as Fontan completion (remaining on single ventricular circulation). The median of recruitment procedures from Stage 1 to BiVC was one, with a range of 0 to 2.

Furthermore, out of the 44 patients that have had BDG, 4 patients stayed on Fontan circulation and 28 patients proceeded to BiVC. The median of recruitment procedures from BDG to BiVC was one, with a range of 0 to 4.

Lastly, of the 10 patients that have had Fontan operation, 6 proceeded to BiVC with a median of one recruitment procedure.

Table 3. SVP Recruitment Summary. Median and range number of recruitment procedures at each stage were recorded to note the tendency of when recruitment is usually done before having BiVC.

SVP: Palliation Stage Recruitment to BiVC, n (%)	Value
Stage 1 Median Recruitment: Range of Recruitment:	55 (100) 1 0-2
BDG Median Recruitment: Range Recruitment:	44 (80) 1 0-4
Fontan Median Recruitment:	10 (18) 1

BIV Conversion

In total, 39 HLHS patients (out of 55) ultimately had BiVC. Outcomes after BiVC are as following: 8 patients deceased and 31 patients survived. Of the 31 patients, 2 patients had heart transplants, 2 patients had a biventricular takedown back to single ventricle circulation, and 21 patients had re-operations (53.8%).

Table 4. BIV Conversion Outcomes. 8 patients deceased and 31 patients survived after BiVC.

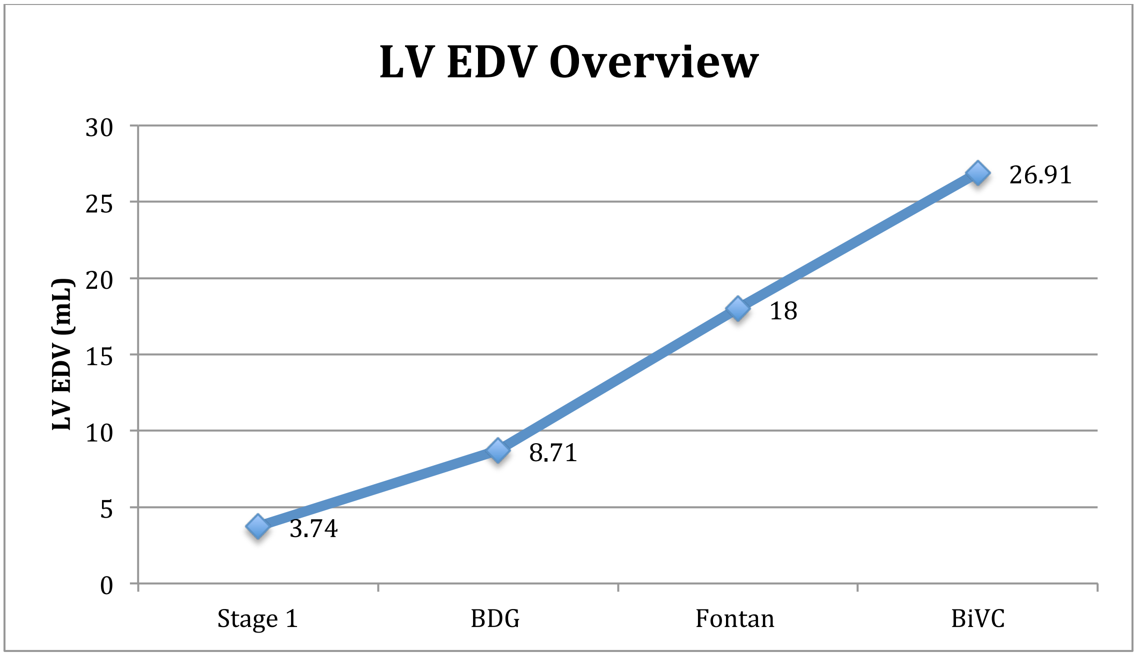
Outcomes, n (%)	Value
Deceased, n(%)	8 (21)
Alive, n(%) Transplant: Takedown from biventricular	31(79) 2 (0.06)*

circulation to single ventricle circulation:	2 (0.06)*
Re-operations:	21(68)*

*Calculated out of 31 patients alive

Trajectory of LV Growth

Overall, LV EDV and z-score increases at each sequential palliation stage. Median LV EDV increased from 3.74 ml to 8.71 mL, 18.0 ml, and finally 26.91 ml at Stage 1, BDG, Fontan, and BiVC, respectively. LV EDV median z-score increased from -2.78 to -2.65, -1.86, and finally -0.81 at Stage 1, BDG, Fontan, and BiVC, respectively. The most improvement in LV EDV happens between BDG and Fontan, with a difference of 9.29 ml. The most improvement in z-score happens between Fontan and BiVC, with a difference of +0.795.



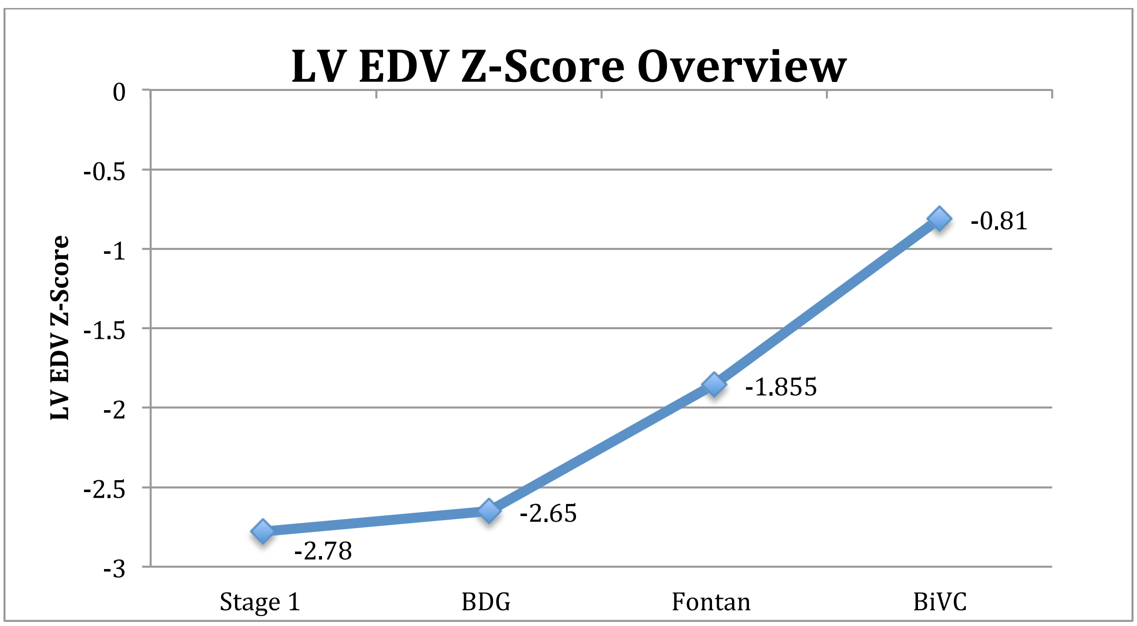


Figure 5. LV EDV and Z-score Overview throughout HLHS Journey. LV EDV had greatest improvement from BDG to Fontan with an increase of 9.29 ml. Z-score's best improvement was between Fontan to BiVC with an increase of 0.795.

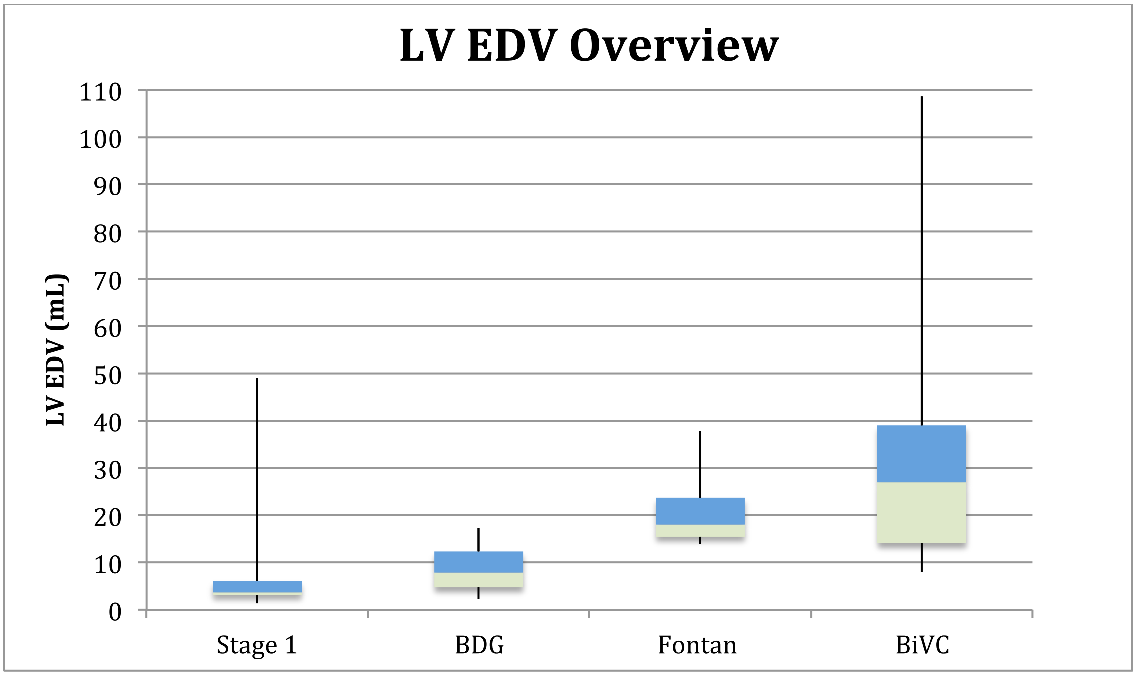


Figure 6. LV EDV Overview with interquartile range (IQR). Besides at BDG, the dispersion of most LV EDV values settles above the median. BiVC has the largest dispersion for these values while BDG has the smallest.

Recruitment Procedures

Similar to above, choosing to focus on population at each stage for recruitment procedures performed will entail overlap. He or she may have had undergone recruitment procedures in both Stage 1 and BDG, but will be counted as one patient at each stage.

Recruitment procedures are done either in complement with the palliation surgery or separately. Twenty-three patients had recruitment in Stage 1, 29 patients for BDG, and 5 patients for Fontan.

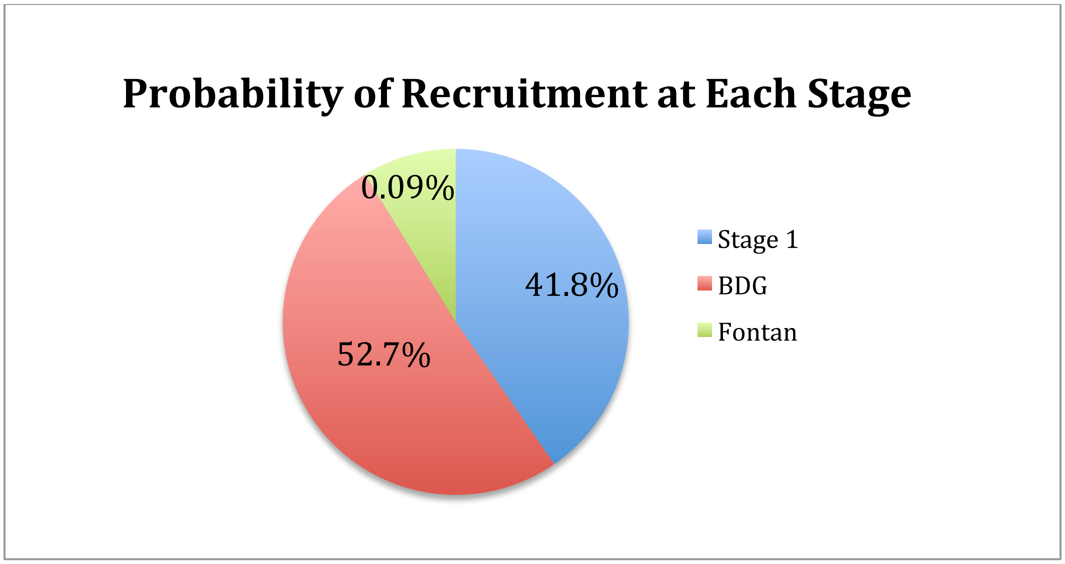


Figure 7. Probability of Recruitment at Each Palliation Stage.
About half of the patients had at least one recruitment procedure at BDG. Majority of the patients have recruitment procedures done at BDG, followed by Stage 1 and then Fontan.

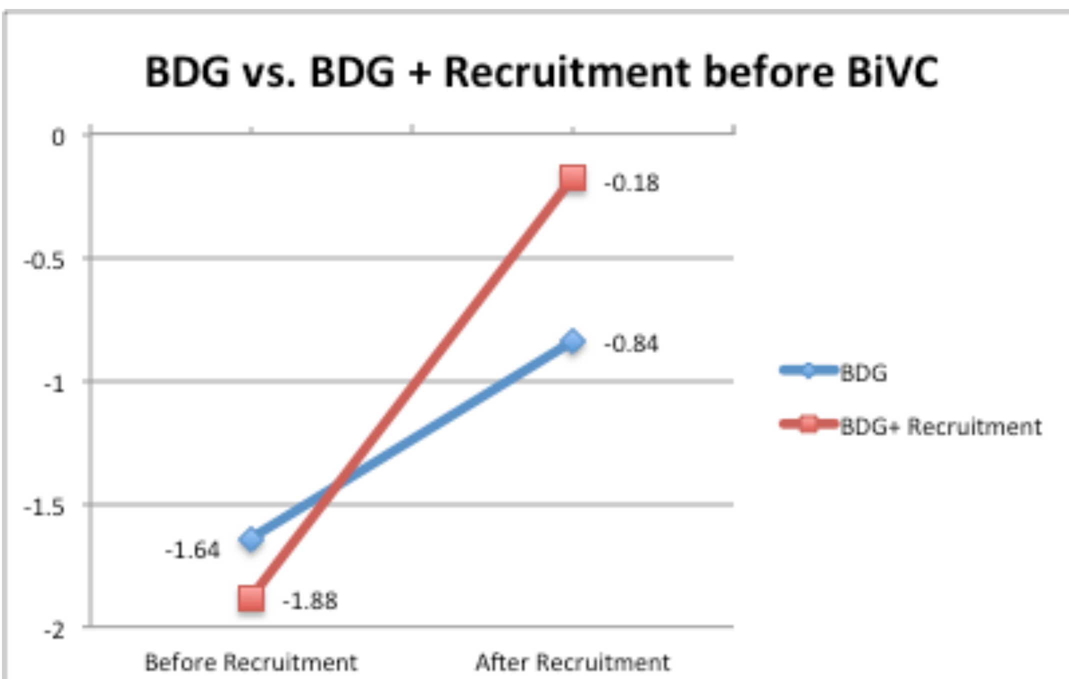
Recruitment Effectiveness

Recruitment effectiveness was observed at each stage by comparing median z-scores between patients who went straight to BiVC compared with patients who had LV recruitment procedures before BiVC. Z-score data was collected directly before a patient undergoes respective palliation surgery and immediately before BiVC.

Patients at Stage 1 who went straight to BiVC had a 135.6% increase in LV EDV z-score. Patients at Stage 1 who had recruitment procedures before BiVC had a 44.5% increase in LV EDV z-score.

Patients at BDG who went straight to BiVC had a 48.8% increase in LV EDV z-score compared to a 90.4% increase for patients who had recruitment procedures at BDG before BiVC.

Finally, the Fontan patient who went directly to BiVC had 0% increase LV EDV z-score while there was an observed 83.0% increase for Fontan patients with recruitment procedures before BiVC.



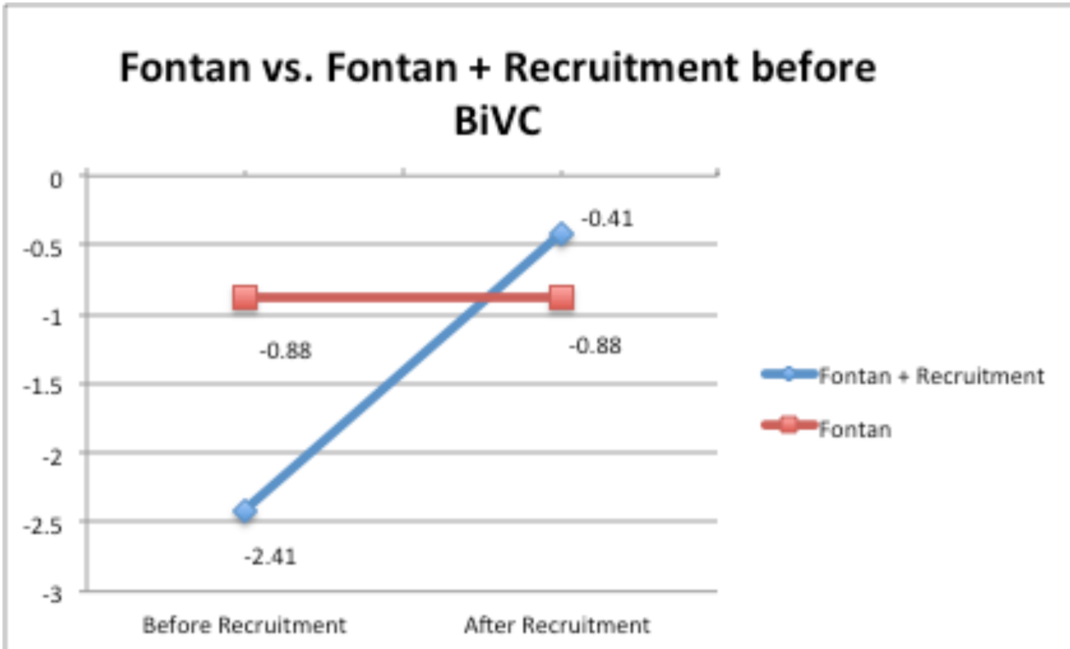


Figure 8. Recruitment Effectiveness. To measure the effectiveness of recruitment on LV growth, patients that had Stage 1 Norwood, BDG, and Fontan were compared with other patients who had same procedures except with recruitment all before directly going to BiVC. Recruitment effectiveness was most prominent at BDG.

Specifics of LV Recruitment Procedures

LV Recruitment procedures consist of EFE Resection, ASD restriction (ASD Fenestration), and valve work (aortic and mitral valvuloplasty). Thirty-one out of the 55 patients of patients had EFE Resection (56.4%), 28 had ASD fenestration (50.9%), and 39 had valve work (70.9%). Patients can have multiple recruitment procedures done simultaneously. These numbers also include patient overlap for the same reasoning as he or she may have had undergone recruitment procedures in both Stage 1 and BDG, but will be counted as one patient at each stage.

Table 5. Breakdown of Recruitment Procedures

Recruitment Procedure, n (%)	Value
ASD Fenestration	28 (51)
Valve Work (AV/MV repair/replacement)	39 (71)
EFE Resection	31 (56)

EFE Resection

Percent of LV growth was calculated by median z-scores taken at the following time points: directly before EFE resection and right before the next procedure. It was then categorized by palliation stage when EFE resection was performed- Stage 1, BDG, and Fontan- but also included BiVC to further explore the significance and correlation of EFE and LV growth. A 6.9% increase, 50.2% increase, 62.3% increase, and 206.1% increase in LV EDV z-score after EFE resection at Stage 1, BDG, Fontan, and BiVC, respectively.

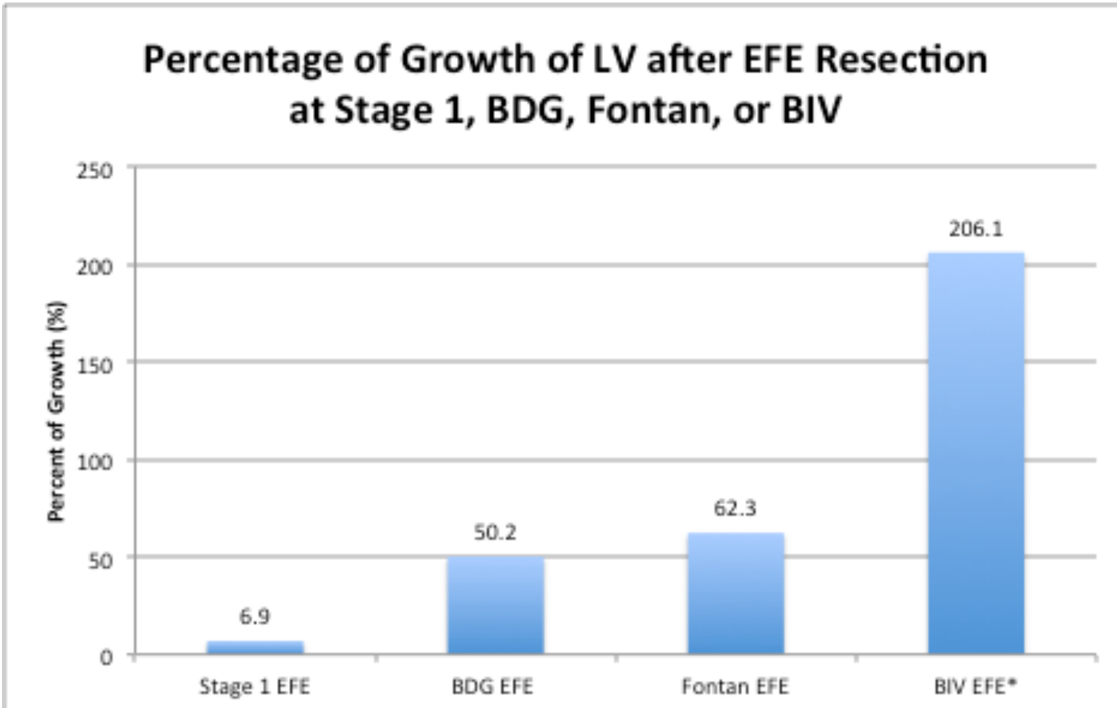


Figure 9. Percentage of Growth after EFE Resection at SVP and BiVC. To judge if EFE was truly hindering LV growth, z-scores before and after EFE resection were measured and categorized to be either at Stage 1 Norwood, BDG, Fontan, or BiVC. Most LV growth occurs after EFE resection at BDG and Fontan compared to stage 1.

Re-operations:

Twenty-one patients had re-operations after BiVC. Re-operation for mitral valve replacement and mitral valve repair was the most common. Two of the 21 patients had biventricular takedown back to SVP.

DISCUSSION

In this report, we explore the overall trajectory of surgical care for HLHS patients at Boston Children's Hospital while observing significant characteristics of this population at each stage- Stage 1, BDG, Fontan, BiVC. LV Recruitment was further evaluated to observe its impact on LV growth and function. EFE resection, a specific procedure part of staged LV Recruitment, was also discerned to show that EFE could hinder LV growth. All data recording for both prospective and retrospective patients ended on December 1, 2018.

The main findings of this study is listed as the following:

- BDG is the most critical stage in the SVP pathway
- EFE Resection is most effective (or correlates to the most LV growth) at BDG and Fontan compared to Stage 1

Limitations

The decision to focus on population at each stage of SVP even if our patient population will overlap is to pinpoint what happens at that particular stage. This includes LV recruitment effectiveness on LV growth and characteristics that predict re-operations after BiVC, which both are measured by LV EDV and respective z-scores. Using this information, connections can be seen on how each stage affects the next (ie. BDG affecting Fontan results) or how it relates to previous stage (ie. how did Stage 1 help BDG be more successful). Overall, main conflict with data collection is attempting to obtain data, especially patients who were referred from outside hospitals. ECHO measurements are often missing. To address data quality, patients were included only if LV EDV and respective z-scores were measured prior and after each surgical stage. Even if one of the two measurements were included, patients were excluded from data analysis at that stage.

Another limitation to the study is the definition of true HLHS. True HLHS patients do not have ventricular septal defects (VSD). Patients who do have HLHS but have VSDs are considered HLHS variants. Therefore, for the purpose of focusing on LV growth potential at each stage, HLHS variants were not excluded. This may affect the generalizability of the results of this study for true HLHS patients but still gives a good oversight of the effects after each palliation procedure.

LV EDV and Z-Scores

In Figure 6, the dispersion of LV EDV values at BDG in relationship to that of Fontan is important to highlight. There is a larger LV EDV variance at Fontan, particularly above the median, than at BDG. This indicates that there must be significant improvements in LV growth after BDG to not only reflect a higher median EDV at Fontan, but also the increase in ratio of EDV values above the median. Thus, this reiterates the potential BDG holds to grow the LV.

Recruitment Effectiveness

Although there is a median of recruitment procedures of one for all stages to BiVC, the difference in range is most drastic in BDG (0 to 4) compared to Stage 1 (range of 0 to 2) (Table 3). This shows that LV growth at BDG has the most potential because more recruitment procedures are being approved and performed, which relates to opportunities to stimulate LV growth. Through recruitment, it is only shown at BDG to be able to push for the most LV growth, with evidence that those who had recruitment at this procedure had a LV growth that exceeds those who did not have recruitment- 90.4% vs. 48.8% (Figure 8).

Next, a median recruitment of one at Fontan matches expectation; those who are on Fontan circulation usually do not proceed to BiVC. Therefore, the ability to do so indicates that at Fontan, there are still possibilities of LV growth that meet the criteria for BiVC. Growth after recruitment on Fontan was 83.0%, close to growth of that of BDG patients (90.4%).

Overall, recruitment effectiveness is best demonstrated at BDG. BDG patients with recruitment also experienced 45.9% more LV growth than patients at Stage 1 with recruitment and 7.4% more LV growth than patients at Fontan with recruitment (all going directly to BiVC) (Figure 8). One limiting factor for these results can be due to having two and three times the amount of patients (16 patients) than BDG (8 patients) and stage 1 (5 patients), respectively; thus, more data obtained can assist accuracy and reliable results.

Outcomes

All patients at BDG with no recruitment had an outcome of BIV circulation with no re-operations. Contrarily, outcomes for patients with recruitment are as the following:

4 patients had 1 re-operation after BiVC, 2 patients had 2 re-operations after BiVC, 1 patient had 3 re-operations after BiVC, 5 patients on BIV circulation without re-operations, 2 deceased, and 2 transplanted. There is a positive correlation between number of recruitments and re-operations after BiVC.

Table 6. Outcomes of BDG With and Without Recruitment

Outcomes of BDG with Recruitment	Number of Patients
BiVC with No Re-operations	5
BiVC with 1 Re-operation	4
BiVC with 2 Re-operations	2
BiVC with 3 Re-operations	1
Deceased	2*
Transplanted	2*

*Patients also had re-operations before death or transplant

Outcomes of BDG with No Recruitment	Number of Patients
BiVC with No Re-operations	4

Stage 1 shows an opposite trend. Patients who did not have recruitment before going directly to BiVC experienced 91.1% more growth than patients who have recruitment and went directly to BiVC. It is usually expected if no recruitment is needed, then LV for these patients must be larger than that of patients who need recruitment; On the contrary, the z-scores at the beginning of stage 1 between both groups are similar (median z-score of -2.91 for no recruitment and -2.98 for recruitment patients). LV growth has yet to achieve its full potential because children tend to undergo stage 1 in their first week of life (Roeleveld et al., 2018). Therefore, LV growth for one child might be more than the other.

Outcomes at stage 1 for no recruitment patients are as following: 2 patients on BIV circulation with no re-operations, 1 patient with 1 re-operation after BiVC, 1 patient deceased, and 1 patient on a 1.5 ventricular circulation (1.5V). 1.5V, also known as "one and one-half ventricle repair", is when pulmonary ventricle (RV) is recruited to manage part of the systemic venous return, as there is RV hypoplasia and dysfunction (Chowdhury et al., 2005). Outcomes for recruitment patients are as following: 4 patients with 1 re-operation after BiVC, 1 deceased, and 3 patients with no re-operation after BiVC. The positive correlation between number of recruitments and re-operations after BiVC is consistent at this stage.

Table 7. Outcomes for Stage 1 Norwood With and Without Recruitment

Outcomes for Stage 1 with Recruitment	Number of Patients
BiVC with No Re-operations BiVC with 1 Re-operation Deceased	3 4 1

Outcomes for Stage 1 with No Recruitment	Number of Patients
BiVC with No Re-operations BiVC with 1 Re-operation	2 1

BiVC to 1.5V Deceased	1 1*

*Patient had a takedown from BIV to SVP

At the other end of the spectrum, optimal time for Fontan surgery is considered to be between 2 and 3 years of age because older age at Fontan completion has been associated with worse exercise capacity and hemodynamics, aorticventricular valve regurgitation, and deteriorating diastolic function (Lytrivi et al., 2011). Outcomes for Fontan with recruitment are the following: 2 deceased and 3 patients with no re-operations after BiVC. The only outcome for Fontan and no recruitment is deceased. These results do not indicate the same trend of positive correlation between numbers of recruitments to re-operations, but does indicate correlation between death and Fontan with recruitment. With the side effects of Fontan being well known, recruitment performed may worsen the effects and compromise LV function.

Table 8. Outcomes for Fontan With and Without Recruitment

Outcomes for Fontan with Recruitment	Number of Patients
Deceased BiVC with No Re-operations	2* 3

*1 patient had 1 re-operation after BiVC

Outcomes for Fontan without Recruitment	Number of Patients
Deceased	1

Re-operations:

Patients that did not have recruitment at stage 1 and ended with BIV circulation without re-operation displayed an initial LV EDV median z-score of -2.91. Compared to patients with the same outcome but who had recruitment, the initial LV EDV median z-score was -2.78. Since their z-scores are similar, it can be assumed that a z-score within this range indicates association with no- reoperation after BiVC. The median z-score for those who did have re-operation after BiVC is -3.18. A more negative z-score indicates a smaller left ventricle; Therefore, an assumption is that the smaller the left ventricle is at stage 1 undergoing recruitment procedures, the higher the association with re-operation after BiVC.

At BDG, the results were opposite from that of stage 1. The more negative the z-score is at BDG operation, the more likely it is associated with no re-operation after BiVC. A median z-score of -5.11 was observed. The median z-scores associated with re-operation after BiVC for both recruitment and no recruitment patients were -1.42 and -1.64, respectively. Therefore, a range between a z-score of -1 and -2 could be a point of interest associated with re-operation. The assumption at BDG comparing a z-score of -5.11 to -1.42 and -1.64 indicates that the smaller the left ventricle is, the increase in association with no re-operation after BiVC. Overall, BDG is the ideal situation; it shows that we can truly grow the left ventricle from an abnormally small left ventricle (z-score of -5.11) with minimal side effects.

At Fontan, the outcomes are either BIV circulation with no re-operation or deceased. A more positive z-score (-0.44 and -0.88 for recruitment and no recruitment patients, respectively) has an association with death. A more negative z-score (-2.66 for recruitment patients) is associated with BIV circulation with no re-operation. This is similar to the results from BDG.

EFE

The highest percentage of LV growth after EFE resection is at BiVC (Figure 9). There is a 206.1% in LV growth compared to 6.9%, 50.2%, and 62.3% at Stage 1, BDG, and Fontan, respectively. For SVP, EFE resection is most effective at BDG and Fontan compared to Stage 1. Although BiVC had a higher increase in LV growth compared to BDG and Fontan, the more accurate conclusion for Figure 9 about EFE resection's effectiveness would be at SVP. This is due to the inconsistency of time points for data collection at BiVC. BiVC is the end procedure for many of the patients and measurements taken to evaluate impact of EFE resection were before BiVC and prior to re-operation. If there were no re-operation, the latest ECHO before December 1, 2018 would be used to assess for results. Therefore, the time period between BiVC and re-operation and/or latest ECHO on file varies significantly across all patients. Measurements were taken this way to observe the full potential of LV growth after EFE resection. Compared to SVP, time period between data collection procedures do not have as much variance because procedures are performed usually around recommended ages - stage 1 Norwood procedure in the first week of life, BDG at 4-6 months of life, and Fontan at 2-4 years of age (Roeleveld et al., 2018).

Furthermore, another limitation is EFE resection is often times being performed with valve work and /or ASD fenestration. There may be a possibility of a particular combination of the three techniques that may influence LV growth more significantly. Nonetheless, this data overall shows that EFE truly hinders LV growth and more so at subsequent palliation stages.

Conclusion

In conclusion, BDG is the most critical stage for LV growth. LV EDV shows the most improvement and recruitment is the most effective at BDG. Furthermore, we are able to show the recruitment procedures were able to affect growth of the small LV that exceeds LV growth with no recruitment (Figure 8). However, recruitment done at BDG is also strongly associated with an increase in re-operations. This can be due to the interplay of age and time recruitment is performed; these patients may be at an age that potential for adaptability and resilience is at its highest, but can act as a double-edged sword when this vulnerability causes the most side effects.

EFE resection is most effective at BDG and Fontan compared to stage 1,which indicates EFE is strongly correlated with increased hindrance of LV growth potential in the long-term. EFE resection's promising results help reevaluate perspective on the importance of this recruitment procedure at the later stages despite knowing SVP's long-term negative effects on the heart. Recruitment and EFE resection at Fontan has also been impressive. With an 83.0% and 62.3% in improvement for LV EDV z-score for recruitment and EFE resection, respectively, there remains potential for LV growth at Fontan.

Further Studies

Further points that can be explored are predictive factors besides LV EDV and respective z-scores for estimating LV growth, combinations of recruitment techniques that draw a bigger difference in LV enlargement, and patterns in surgical techniques that are correlated with reduced number of re-operations. More investigation can also be drawn to Fontan and successful LV growth. Although long-term effects on Fontan circulation are proven, the LV growth potential at this stage should be explored and weighed with risks. More detailed studies on correlation between BDG and LV growth, such as predictive factors and patterns between patients, are also subjects that may be of interest. The amount of re-operations at BDG are also worthy to be noted. Moreover, another suggestion for further study is to analyze the results of true HLHS patients. Not only will it improve the application of this study to HLHS patients, it can more accurately pinpoint specific significant factors that may have gone unnoticed.

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