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Acute abdominal pathology requiring surgical intervention in neonates and infants with congenital heart defects

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Thesis

ACUTE ABDOMINAL PATHOLOGY REQUIRING SURGICAL INTERVENTION IN NEONATES AND INFANTS WITH CONGENITAL HEART DEFECTS

by

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ABSTRACT

This retrospective study examines the association between congenital heart defects and abdominal pathology requiring surgical intervention in neonates and infants. The focus of this study was on patients admitted to Boston Children's Hospital (BCH) between January 1st, 2010 and July 31st, 2023. 936 patients having had a cardiac procedure and abdominal diagnosis of interest were admitted to BCH within the desired date range. This list of 936 patients was filtered down to 16 pateints of interest that had specifically undergone a cardiac procedure and an abdominal diagnosis requiring urgent and emergent surgical intervention. Upon the identificiation of this cohort of 16 patients, each patient's data of interest, such as demograpghic data, cardiac procedure data, abdominal procedure data, nutritional management data, and outcome data, was obtained and entered into research electronic database capture (REDCap) system. A statistical analysis was performed and results were strictly descriptive. Limitations such as the small patient population hindered the ability to

make statistical claims. Reccomendations for further studies or analyses have been provided.

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LIST OF ABBREVIATIONS

AS ..... Aortic Stenosis

ASD ..... Atrial Septal Defect

AVC ..... Atrioventricular Canal

AVSD ..... Atrioventricular Septal Defect

BCH ..... Boston Children's Hospital

CHD ..... Congenital Heart Disease

CICU ..... Cardiac Intensive Care Unit

CoA ..... Coarctation of the Aorta

CPT ..... Current Procedural Technology

CSV ..... Comma-Separated Value

D-TGA ..... D-Loop Transposition of the Great Arteries

DILV ..... Double Inlet Left Ventricle

DORV ..... Double-Outlet Right Ventricle

EMR ..... Electronic Medical Record

GA ..... Gestational Age

GI ..... Gastrointestinal

HLHS ..... Hypoplastic Left Heart Syndrome

ICU ..... Intensive Care Unit

ICU ..... Intensive Care Unit

LA ..... Left Atrium

LV ..... Left Ventricle

MRN ..... Medical Record Number

NEC ..... Necrotizing Enterocolitis

NGT ..... Nasogastric Tube

NJT ..... Nasojejunal Tube

PA ..... Pulmonary Artery

PA ..... Pulmonary Atresia

PAIVS ..... Pulmonary Atresia/Intact Ventricular Septum

PDA ..... Patent Ductus Arteriosus

PELOD ..... Pediatric Logistic Organ Dysfunction

PFO ..... Patent Foramen Ovale

PGE1 ..... Prostaglandin E1

PS ..... Pulmonary Stenosis

RA ..... Right Atrium

REDCap ..... Research Electronic Database Capture

RV ..... Right Ventricle

SES ..... Socioeconomic Status

TOF ..... Tetralogy of Fallot

VIS ..... Vasoactive-inotropic Score

VSD ..... Ventricular Septal Defect

INTRODUCTION

Congenital heart defects refer to anatomical abnormalities, presenting in the heart, that evolve during fetal development in utero. A worldwide systematic review of two hundred and sixty studies, that included over 130,000,000 live births between the years of 1970 and 2017, reported the prevalence of congenital heart disease (CHD) to be 9.41 for every 1,000 live births (Liu et al., 2019). Since these defects are occurring in about 1% of newborns, this solidifies CHD as being the most common congenital abnormality (Wu et al., 2020).

The incidence of CHD varies depending on the geographical region. Asia has been shown to have a greater occurrence of CHD when compared to both Europe and North America, with Europe seeing more encounters than the latter of the two (van et al., 2011). It is predicted that over 11,000,000 individuals throughout the world are living with CHD (Zimmerman et al., 2020). This estimated value is continuously increasing due to the fact that therapies for this disease are becoming more and more effective as knowledge within the medical field progresses (Hoffman, 1995). Although this is the case, the occurrence of congenital heart defects has continued to remain high over the past thirty years, showing that efforts in prevention of CHD have been minimally successful (Wu et al., 2020).

The process of screening for cardiac congenital abnormalities is invariably necessary amidst regular obstetric anatomic ultrasounds during the course of the second trimester (H. Y. Sun, 2021). Early diagnosis of congenital heart defects is an extremely important factor when working to prevent disadvantageous consequences regarding the health of an individual. Methods for identifying structural cardiac anomalies both prenatally and postnatally include, but are not limited to, fetal echocardiograms, regular echocardiograms, electrocardiograms, chest X-rays, pulse oximetry, and cardiac catheterization (R. Sun et al., 2015).

When discounting extracardiac congenital abnormalities, the rate of prenatal diagnosis for CHD was 66% (Landis et al., 2013). Although more than half of CHD cases are diagnosed prenatally, there are still a large number of cases that are diagnosed postnatally as well. Individuals that make it through their first year of life have a 96% chance of reaching the age of sixteen, which further solidifies the importance of CHD screening (Onuzo, 2006).

Unfortunately, more than 50% of supposedly healthy newborns with congenital heart anomalies, undergoing conventional examination, are asymptomatic due to the fact that severe heart abnormalities are difficult to detect (Richmond & Wren, 2001). This

places emphasis on making sure experienced individuals are performing postnatal examinations using effective means of screening.

Embryology of Heart Development

The development of an embryo is a process that requires the necessary presence of oxygen and nutrients. The cardiovascular system is one of the first organ systems to develop allowing the embryo to receive these much needed gaseous and nutritional supplements. The formation of the heart, and its accessories, involves cellular communication which ensures that its structure evolves properly and at the appropriate time. If anything were to interfere with this process then a congenital heart defect can come to fruition (Mathew & Bordoni, 2024).

In order to fully understand the implications of congenital heart defects, it is important to understand embryology and how evolution of the heart occurs. The determinants of how severe a congenital heart defect depends on which stage of gestation the embryologic disturbance occurs, how extensive the disturbance is, and how well the embryo is able to alleviate that defect. The exact cause of congenital heart defects is unknown but it is acknowledged that they occur when a developmental flaw arises between the third and eighth weeks of

pregnancy, which is the period of time when the main components of the cardiovascular system develop (Villavicencio-Guzmán et al., 2023).

During gastrulation, an imperative developmental process beginning around the third week of pregnancy, the formation of the primitive streak takes place. The primitive streak is a groove at the caudal end, not to be confused with the cranial end, of the epiblast which is an epithelial cell layer. These same epiblast cells migrate down into the primitive streak and eventually form the endoderm, mesoderm, and ectoderm germ layers. (Muhr et al., 2024).

Certain organs, such as the heart, kidneys, and axial skeleton, develop from mesoderm progenitor cells which grow into marked mesodermal branches. These branches are chorda, extraembryonic, intermediate, lateral, and paraxial mesoderm (Ferretti & Hadjantonakis, 2019). The lateral plate mesoderm will differentiate into a somatic (also known as parietal) layer and a splanchnic (also known as visceral) layer (Muhr et al., 2024). The splanchnic layer of the mesoderm will begin to form vascular structures that create blood-islands during a period termed vasculogenosis. These blood islands lead to the development of an area called the cardiogenic field (Mathew & Bordoni, 2024). This cardiogenic field, also known as the cardiogenic area, at the cranial end of the embryo is where the heart

begins to evolve. The cardiogenic area leads to the formation of two cords known as the cardiogenic cords in which a lumen begins to appear. These two cardiogenic cords come together to form one single primitive heart tube leading to the development of five regions which include the truncus arteriosus, bulbus cordis, primitive ventricle, primitive atrium, and the sinus venosus (Biga et al., 2019). Figure 1 shows a depiction of these major developmental steps.

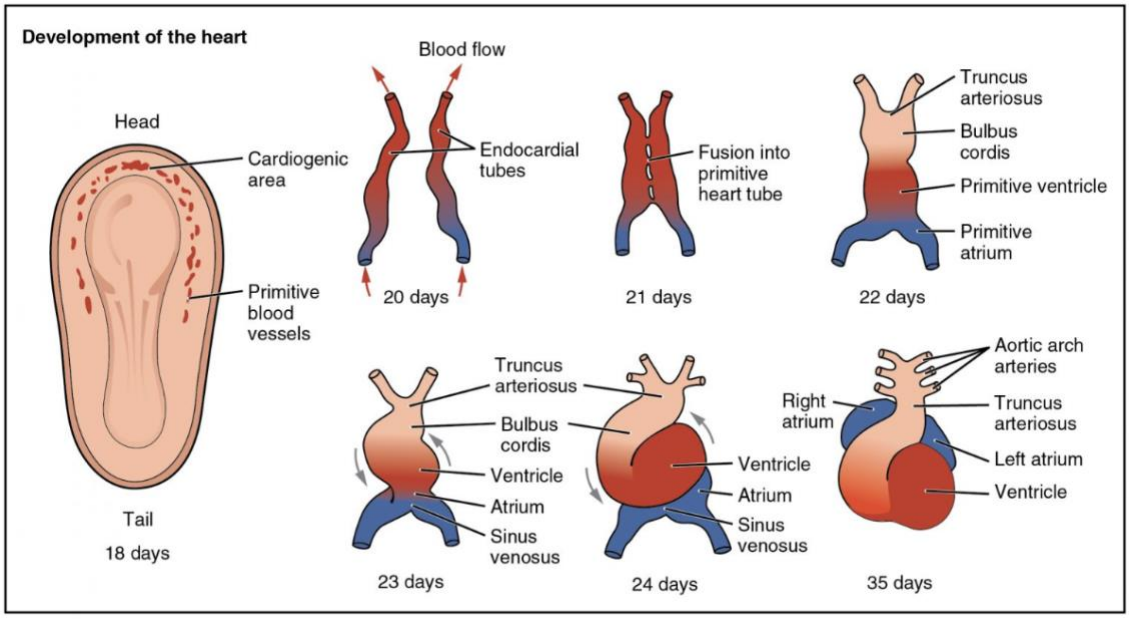

Figure 1. Embryogenic Development of the Heart. Figure taken from Biga et al., 2019.

As can be seen in Figure 1, the primitive heart tube elongates and begins to fold into an S shaped structure. This forces the heart

chambers and major vasculature to align in a manner very similar to an adult heart. The continuation of the heart development includes the formulation of valves, septa, and chambers. By the end of week five, division of the atria and ventricles is complete. During weeks five through eight the atrioventricular valves develop, and during weeks five through nine the semilunar valves develop (Biga et al., 2019). The heart is now finally divided into four distinct chambers and its major associated vasculature has formed. Figure 2 illustrates the division of the heart into its four described chambers.

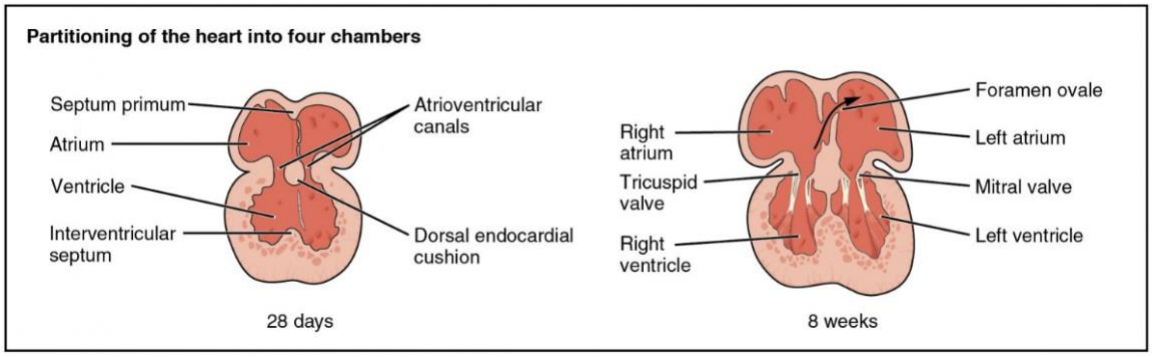

Figure 2. Division of the Heart Chambers. Figure taken from Biga et al., 2019.

For simplicity, when gastrulation occurs, a single-layered embryo develops into a three-layered structure made up of an endoderm, mesoderm, and ectoderm. These three germ layers eventually evolve

into the body's organs and organ systems, a process termed organogenesis. Specifically, it is the mesodermal layer that will eventually give rise to the heart (EISENBERG et al., 2004). Any imperfection that occurs, which could be caused by a plethora of factors, will give rise to a defect leading to the overall development of CHD. Understanding this concept of heart embryologic development is crucial in order to discern how congenital heart defects arise and could potentially lead to further progress in the prevention of CHD.

CHD Risk Factors

As described, the progress that has been made within the medical community in regard to congenital heart defects has been substantial. Both the detection of congenital heart defects and the quality of life of those with CHD has improved greatly. Although the formation of the heart while in utero has been studied extensively, the exact cause of CHD needs to be investigated further, as it is relatively unknown. What is known is that there are risk factors that make the occurrence of congenital heart defects more likely ("The Molecular Basis of Congenital Heart Disease," 2007).

One study focused on the comparison of outcomes in children with CHD that had undergone a noncardiac procedure, identifies many

associated risk factors. This retrospective analysis of 14,031 patients with CHD highlights that 94% of children had at least one chronic codition in addition to CHD. Neonates only experiencing CHD had the highest mortality rate at 15.6% but, children that had CHD as well as one other chronic condition had a higher mortality rate when compared to patients with CHD only. Risk factors such as socioeconomic status (SES), type of chronic condition, race, and age were major risk factors that increased not only mortality but postoperative length of stay as well (Valencia et al., 2022).

Recent efforts in understanding the role genetic (inherited) risk factors play in one's development of CHD have been successful. Although this is the case, there is still a need to fully understand environmental (non-inherited) risk factors and the part they play in the development of congenital heart defects. (Giraldo-Grueso et al., 2020). These non-inherited risk factors that have been studied include teratogens, maternal age, maternal diabetes, and abnormal hemodynamics (Suluba et al., 2020). Though this is not a comprehensive list, these are a few of the many environmental factors that have been shown to play a role in the formation of congenital heart defects. These inherited and non-inherited factors described, along with others, will be reviewed throughout this section.

Inherited Risk Factors

It has been approximated that there are somewhere around 400 genes associated with congenital heart defect pathology. When these genes, that encode for transcription factors and biological processes such as cell signaling, are mutated it can impinge on the embryologic development of the heart and other anatomical structures (Williams et al., 2019). One article reports that the inherited risk of CHD occurrence can range from 3% to 20%, which is conditional on the type of lesion that forms. Figure 3 represents the risk associated with different types of congenital heart lesions. It should also be noted that women with CHD are two times as likely to pass the congenital heart defect on to their offspring when compared to men (Nees & Chung, 2020).

Lesion	Father affected (%)	Mother affected (%)	One sibling affected (%)	Two siblings affected (%)
ASD	1.5–3.5	4–6	2.5–3	8
AVSD	1–4.5	11.5–14	3–4	10
VSD	2–3.5	6–10	3	10
AS	3–4	8–18	2	6
PS	2–3.5	4–6.5	2	6
TOF	1.5	2–2.5	2.5–3	8
CoA	2–3	4–6.5	2	6
HLHS	21	21	2–9	6
D-TGA	2	2	1.5	5

Figure 3. Inherited Risk of Occurrence of Congenital Heart Defect. (AS) Aortic Stenosis, (ASD) Atrial Septal Defect, (AVSD) Atrioventricular Septal Defect, (CoA) Coarctation of the Aorta, (D-TGA) D-Loop Transposition of the Great Arteries, (HLHS) Hypoplastic Left Heart Syndrome, (PS) Pulmonary Stenosis, (TOF) Tetralogy of Fallot, (VSD) Ventral Septal Defect. Figure taken from Nees & Chung, 2020.

Other genetic factors such as chromosomal aneuploidy, which has a positive correlation with maternal age (a non-inherited factor), increases the risk of one's offspring to develop a congenital heart defect. The most common chromosomal aneuploidy, trisomy 21 (Down syndrome), is very closely associated with CHD. It is stated that CHD is discovered in anywhere from 40% to 50% of patients with trisomy 21. The most common congenital heart defects associated with

trisomy 21 are patent ductus arteriosus (PDA), atrioventricular septal defect (AVSD), VSD, ASD, and TOF (Nees & Chung, 2020).

Non-Inherited Risk Factors

Environmental risk factors can be broken down into many subgroups. Two major subgroups of environmental risk factors are parental characteristics and parental recreational drug exposures. Maternal age, maternal diabetes, and socioeconomic status are a few very important paternal characteristics. It has been described that mothers that are older in age are at an increased risk to have a child with an atrial septal defect (ASD), tetralogy of Fallot (TOF), or a ventricular septal defect (VSD). When investigating the role of diabetes, it seems that pre-gestational diabetes is connected to many congenital heart defects including but not limited to ASD, double-outlet right ventricle (DORV), TOF, VSD, and pulmonary atresia (PA). Hyperglycemia has shown to be the driving factor in these developments. As far as SES goes, one study investigated the association between SES and TOF but found no statistical significance. Although this is the case, paternal unemployment and a low paternal level of education have shown to have a correlation with CHD development (Patel & Burns, 2013).

Under the subgroup of parental recreation drug exposures falls alcohol, other illicit substances such as marijuana and cocaine, and cigarette smoking. Maternal alcohol use during pregnancy has been associated with increased risk for CHD in offspring. A study investigating the relationship between CHD and alcohol related diagnostic codes during pregnancy found that infants born to a mother with an alcohol related diagnostic code were more likely to develop CHD (2.86%) when compared to infants born to mothers not related to one (1.55%) (Harvey et al., 2022). Another study reported that prenatal exposure to cocaine was associated with a significantly higher risk for developing a congenital heart defect (Lipshultz et al., 1991). In contrast, maternal marijuana use has not been found to be associated with the development of congenital heart defects but a connection between the two, specifically VSDs and marijuana use, has been described (Patel & Burns, 2013). Lastly, maternal cigarette smoking during pregnancy has been investigated and was shown to be positively correlated with the formation of septal defects, tricuspid atresia, and DORV (Bolin et al., 2022).

Single Ventricle Congenital Heart Defects

One predictor variable being evaluated within this study is single ventricle congenital heart defects. Single ventricle heart defects refer to hearts that only have one functioning ventricle. This occurs when one of the ventricles is underdeveloped or not powerful enough to function properly. This type of heart defect is termed a congenital heart defect when it occurs prenatally. Single ventricle congenital heart defects, although rare, are responsible for an estimated 5 out of every 100,000 congenital heart defects in newborn babies (*Single Ventricle Defects | Boston Children's Hospital*, n.d.).

There are several types of congenital heart defects that fall under the category of single ventricle defects. HLHS, where the left ventricle, mitral valve, aortic valve, and aorta do not develop properly, is one variation. Other variations include tricuspid atresia, DORV, Ebstein anomaly, double inlet left ventricle (DILV), and atrioventricular canal defect. Prenatally, single ventricle heart defects can be identified starting around the 18th week of gestation. Postnatally, identification of a single ventricle heart defect can occur for a list of reasons. Common presentations of someone with a single ventricle defect are heart murmurs, cyanosis, and hypotension. These symptoms may not be

identified immediately at the time of birth if blood flow is adequate (Heaton & Heller, 2024).

In healthy offspring without any heart defects, the circulation of blood occurs in series. As we can see in Figure 4., blood from the vena cava enters the right atrium (RA) where it then moves to the right ventricle (RV). From there, it is pumped through the pulmonary artery (PA) and into the lungs where it becomes oxygenated. Next, it gets delivered to the left atrium (LA) and is passed on to the left ventricle (LV). Lastly, the oxygenated blood enters the aorta where it can be pumped throughout the rest of the body to deliver the much needed oxygen to the body’s tissues to prevent tissue death (Rao, 2021).

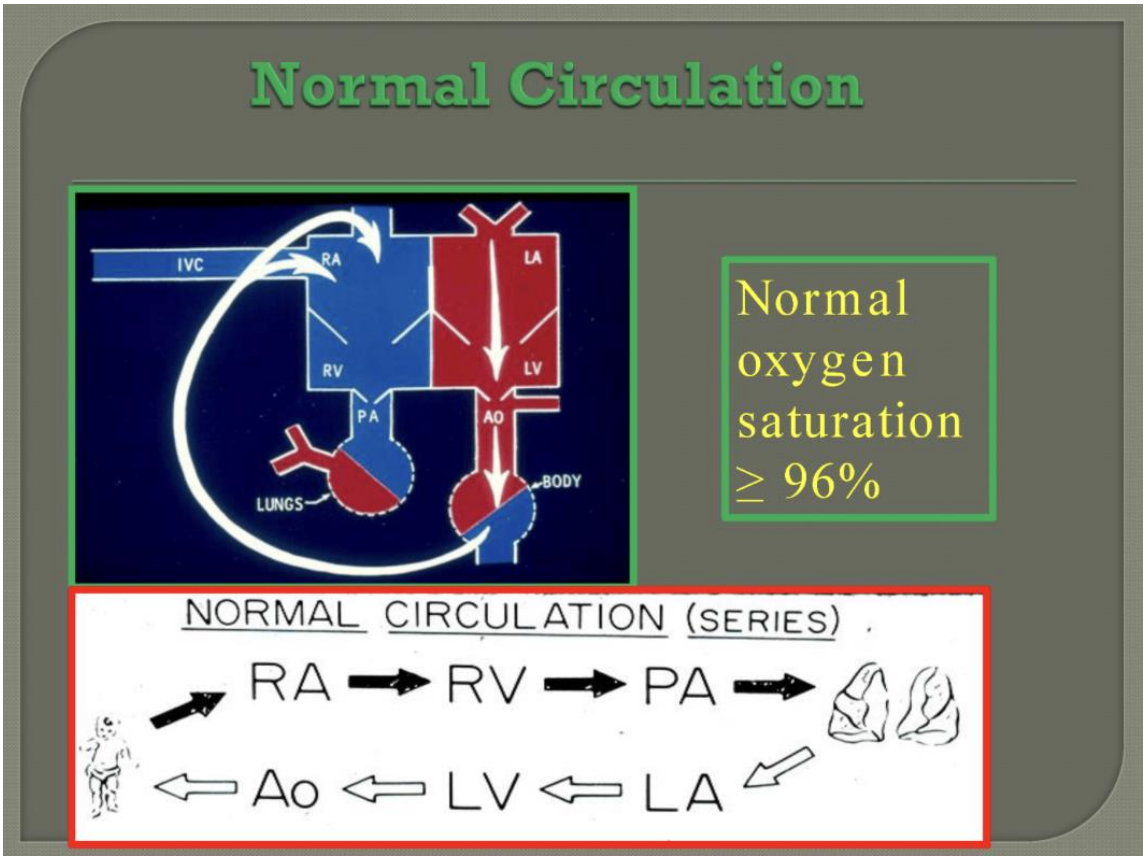

Figure 4. Circulation of 96% O_2 Saturated Blood in a Healthy Individual Without Heart Defects. Figure taken from Rao, 2021.

When comparing an individual with healthy circulation to an individual with a single ventricle heart defect, in the defective heart, the systemic blood flow mixes with pulmonary blood flow resulting in decreased oxygen saturation. This occurs because the single ventricle is feeding both the systemic blood flow and pulmonary blood flow. Figure 5 illustrates what occurs in certain single ventricle heart defects. It can be seen that blood coming from the lungs and blood

coming from the body mixes, resulting in decreased oxygen saturation in the blood coming from the lungs. It is reported that oxygen saturation within these cases can vary from 75% to 85% but it all depends on the ratio of pulmonary blood flow (Qp) to systemic blood flow (Qs) (Rao, 2021).

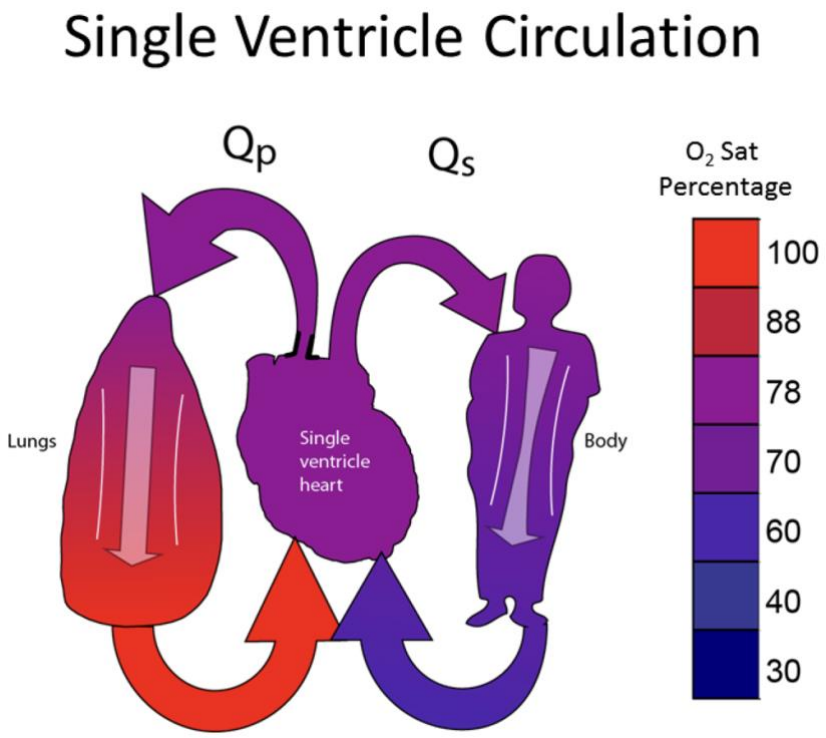

Figure 5. Circulation of Blood in a Single Ventricle Defected Heart. Figure taken from Rao, 2021.

A novel repair mechanism for single ventricle heart defects that is becoming more and more common is the use of a biventricular

repair. A biventricular repair involves reconstructing a single ventricle defective heart to have two working ventricles. BCH is at the forefront of this innovative form of surgery with their Complex Biventricular Repair Program where medical professionals will look to see if individuals with single ventricle heart defects are good candidates for a biventricular repair. If they are not, depending on the case, a traditional repair route can be taken through the use of Fontan, Glenn, or Norwood procedures (*Complex Biventricular Repair | Boston Children's Hospital*, n.d.; *Complex Biventricular Repair Program | Boston Children's Hospital*, n.d.).

A large number of patients with single ventricle defects do have both ventricles present but one being smaller than the other causes the heart to not function properly. Individuals with severe congenital heart defects usually undergo single ventricle palliation (Fontan, Glenn, or Norwood procedures for example) while children with more mild defects may be treated through the use of biventricular repair. Figure 6 shows anatomical variations that patients undergoing biventricular repairs may experience. The image conveys that these patients can be grouped into three categories that are not mutually exclusive since some patients may experience conditions in more than one category (Davies et al., 2023).

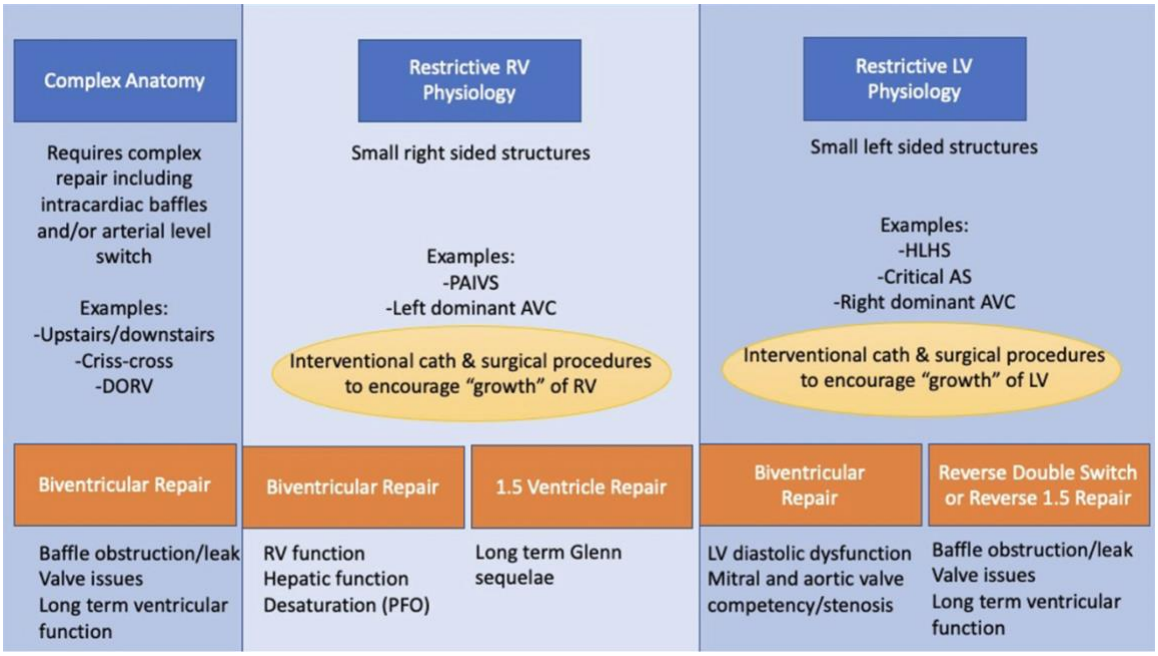

Figure 6. Anatomical Abnormalities in CHD Biventricular Repairs. The three groups describe individuals either having a complex case with two properly sized ventricles, a case in which an individual has a small right ventricle, and a case in which an individual has a small left ventricle. Aortic Stenosis (AS), Atrioventricular Canal (AVC), Double Outlet Right Ventricle (DORV), Hypoplastic Left Heart Syndrome (HLHS), Patent Foramen Ovale (PFO), Pulmonary Atresia/Intact Ventricular Septum (PAIVS). Figure taken from Davies et al., 2023.

As described by BCH, conditions that can be treated through the use of biventricular repairs include HLHS, unbalanced AV canal, DORV,

double inlet right or left ventricle, and PA with intact ventricular septum. This is not a comprehensive list but highlights a few congenital heart defects present in patients within this study. Again, not every individual with these heart defects can be treated by biventricular repair but they can be potential candidates. A specially trained medical professional will evaluate each case and determine whether or not this repair mechanism is an option (Davies et al., 2023).

CHD and Abdominal Pathology

The main focus of this study was to look at the association between congenital heart defects and abdominal pathology requiring emergent surgical intervention. Literature, although limited, is available regarding the topic and states that there are many factors that play a role in the connection between the two. It seems that abdominal problems arise either due to the congenital heart defect itself and the clinical implications of it or because of ischemia that can occur when being treated for the cardiac defect (Güney et al., 2015).

One study reported that over a span of seven years 105 neonates that were dealing with congenital gastrointestinal (GI) pathology were explored for CHD. The results showed that 38% of the

subjects were found with both an abdominal pathology and congenital heart defect. Of this 38%, majority of the subjects were reported to be male. (Chéhab et al., 2007).

Another study from 2015 also investigated whether or not an association could be made between the two (abdominal pathology and CHD). This retrospective analysis reviewed cases involving congenital heart anomalies in which the patients underwent cardiac angiographical examinations or surgical procedures. These patients were then screened for abdominal pathology. Of the 76 patients analyzed, 14 had a congenital heart anomaly and had been operated on due to abdominal issues. 6 of the 14 patients received some type of cardiac surgical intervention (Güney et al., 2015).

Between these two cases, the most common abdominal pathologies found were necrotizing enterocolitis (NEC), intestinal perforation, esophageal atresia, esotracheal fistulas, and anal atresia (Chéhab et al., 2007; Güney et al., 2015). Aside from these GI abnormalities, it has also been described that intestinal rotation, omphalocele, and, though not as commonly, gastroschisis are often found in patients with congenital heart defects (Ferdman et al., 2007; Gibbin et al., 2003).

Although it is known that restriction or the improper flow of blood throughout the heart and systemic organs will quickly lead to organ necrosis, which is seen in patients with NEC, the exact cause of the association between CHD and certain abdominal pathologies is unknown, and literature on the matter is not abundant. It is clear that patients with congenital heart defects should be evaluated for abdominal/GI pathology but, in order to further progress the knowledge of the medical field in this area of study further investigation is needed. Mortality rates for certain isolated GI abnormalities, such as NEC, omphalocele, and gastroschisis, just to name a few, can range from 5.9% to near 100% depending on the etiology of the case (Brebner et al., 2020; Fogelström et al., 2021; Ginglen & Butki, 2024). These percentages may be even greater when the abdominal pathology is seen as an addition to some congenital heart defects, but further analysis is needed.

Experimental Goals

Major predictor variables that were investigated within this study were prematurity, birth or admission weight if <2.5kg, prostaglandin E1 (PGE1) exposure, chromosomal/genetic anomalies, and the presence of a single congenital heart defect. The primary outcome of

this study was time to return to bowel function with the secondary outcomes being survival to discharge, total length of stay in the intensive care unit (ICU), and total hospital length of stay.

The specific aims of this retrospective study were to determine the types of abdominal pathology that require urgent and emergent surgical intervention in neonates and infants with CHD, to evaluate risk factors associated with the development of acute abdominal pathology in neonates and infants with CHD, and to determine the outcomes of neonates and infants with CHD that require surgery for acute abdominal pathology. Though this was the case, it will later be mentioned that due to limitations within this study, such as cohort size, the conclusions that can be made about our population are purely descriptive rather than statistically significant.

METHODS

This was a retrospective study of all neonates and infants with congenital heart defects and an abdominal diagnosis of interest that underwent cardiac surgical intervention at Boston Children's Hospital (BCH) between January 1st, 2010 and July 31st, 2023. This study received approval from the Institutional Review Board of Boston Children's Hospital (IRB- P00038328) on May 11th, 2021.

Once the date range and initial inclusion criteria were decided on, relevant current procedural terminology (CPT) abdominal codes were selected for this study. CPT codes, developed by the American Medical Association, are a uniform list of codes used to specifically describe healthcare procedures and services. These codes are used by healthcare professionals and insurance providers (*CPT® Overview and Code Approval*, 2024; Dotson, 2013). The specifically selected abdominal CPT codes were then entered into Boston Children's Hospital internal database, known as BCH360, to pull a relevant list of patient medical record numbers (MRNs). BCH360 returned a list of patients who had a congenital heart defect, and a corresponding cardiac procedure between the desired date range, along with a relevant abdominal CPT code.

This list of MRNs was then imported into CSANDS, which is Boston Children's Hospital cardiac surgery electronic database, and HC360, being Boston Children's hospital heart center electronic database. CSANDS is used to document cardiac surgical procedures carried out at BCH whereas HC360 is used to document cardiac catheterization procedures performed at BCH. After the MRNs were entered into each database, CSANDS returned a relevant list of patients that had a cardiac procedure and abdominal diagnosis. This

list included 936 individual cases. This was the population of patients that would be focused on and used for any future operations within the study.

Each patient in this list who had postoperative abdominal diagnosis and abdominal procedure performed was then entered into a spreadsheet. Eleonore Valencia, M.D., an attending physician in the cardiac intensive care unit (CICU) at BCH and myself, proceeded to individually review each diagnosis and procedure performed. Since we were specifically interested in abdominal diagnoses requiring urgent and emergent surgical intervention, Dr. Valencia was selecting these cases from the list of 936 patients. Once this process was complete, 16 individual patients that had undergone a cardiac procedure, due to the presence of a congenital heart defect, and had an urgent and emergent abdominal pathology were selected. This was the cohort of patients used in the data analysis within this study. Figure 6 included below illustrates a generalized flowchart that was created for this study depicting how the finalized list was created and how these patients were selected.

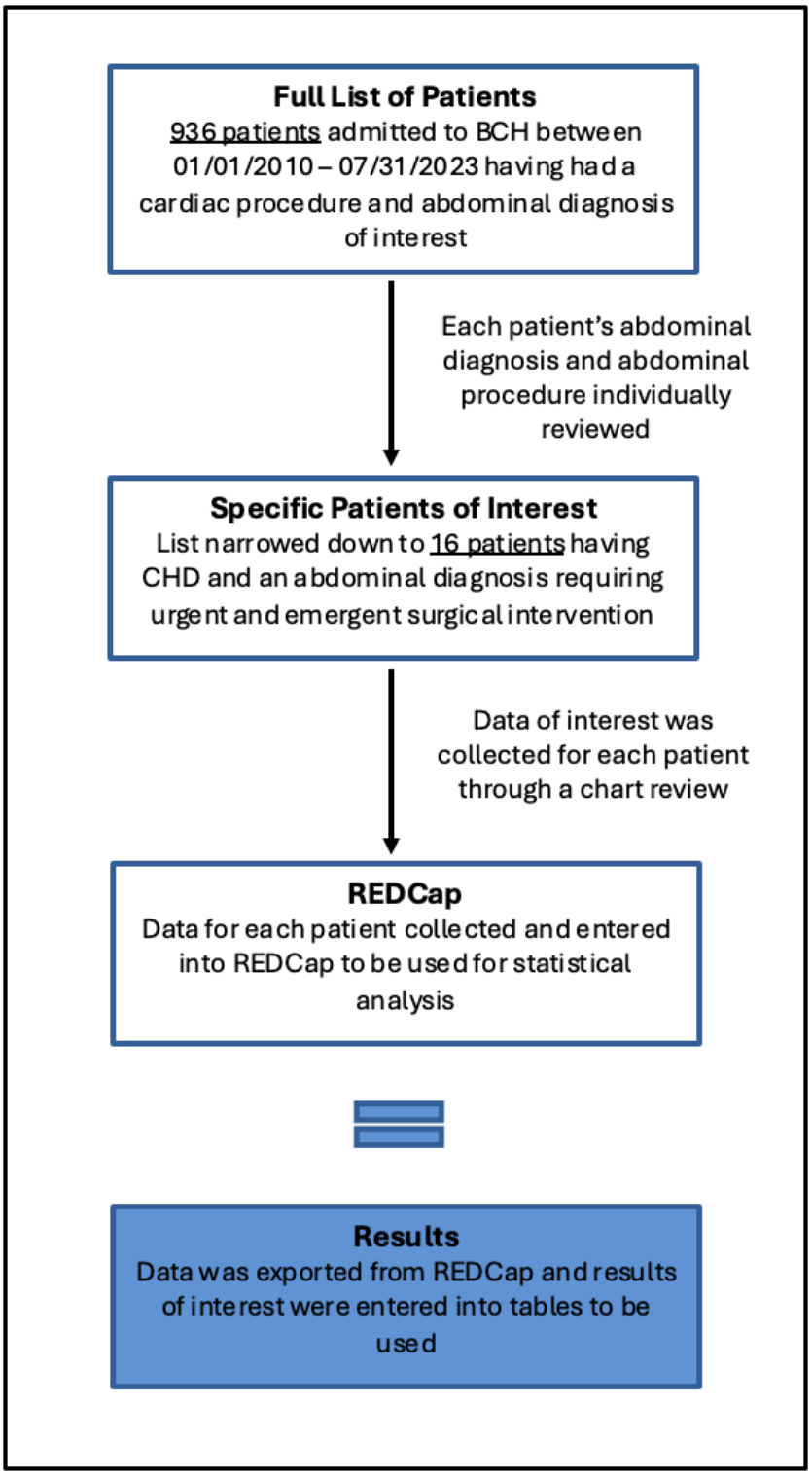

Figure 7. Patient Inclusion Flowchart.

The data included in this study, pertaining to the 16 patients of interest, was handled using the Research Electronic Database Capture (REDCap) system at BCH. REDCap is a data capture software, developed in 2004 at Vanderbilt University, which was created as a clinical support tool for translational research (Harris et al., 2009, 2019). REDCap provides its users with the ability to import external data but to also export data that the user has entered into different file types such as a comma-separated value (CSV) file and a Microsoft Excel file. The information included in each individuals REDCap profile was broken down into eleven different sections including demographic data, covariates, cardiac procedure, echocardiogram, hospital course, abdominal procedure, nutritional management, ventilation, vasoactive-inotropic score (VIS), pediatric logistic organ dysfunction (PELOD) score, and outcomes. Table 1 below diagrams the data that was entered into each REDCap section for each individual patient.

Demographic Data	**Covariates**
Date of Birth	Birth weight (lbs.)
Sex	Birth weight (oz.)
Ethnicity	Gestational age (GA)
Race	Non-cardiac congenital abnormalities
Cardiac Procedure	**Echocardiogram**
Segmental anatomy	Echo date

Heterotaxy	Echo timeframe
Single vs. biventricular CHD	Ventricles
Cardiac diagnosis	Gradient across arch
Cardiac procedure type	Z-score of isthmus
Date of cardiac procedure	Z-score of transverse arch
Cardiac procedure	AV regurgitation
Timing of CHD repair	Right Ventricle Function
Weight at time of surgery (kg)	Left Ventricle Function
Regional perfusion time (min.)	Ejection Fraction
Fibrillation time (min.)	Z-score of Ejection Fraction
Pump time (min.)	
Cross clamp time (min.)	
Arrest time (min.)	
ECMO	
Cardiac complications	
STAT value	
Hospital Course	**Abdominal Procedure**
Date admitted to hospital	Abdominal diagnosis
Date admitted to ICU	Location at time of abdominal diagnosis
Date discharged from ICU	Prostaglandin exposure
Date of readmit to ICU	Date of abdominal procedure
Date of 2nd discharge from ICU	Days between CHD and abdominal surgery
Date of discharge from hospital	Abdominal procedure in relation to CHD repair
Total hospital length of stay	Abdominal procedure occur in admit of CHD repair
Length of readmission to ICU	Abdominal procedure
Total ICU length of stay	Abdominal procedure complications
Nutritional Management	**Ventilation**
Enteral feeding prior to abdominal event	Invasive ventilation
Route of enteral feeds	Invasive ventilation start date
Type of enteral feeds	invasive ventilation stop date
Concentration of enteral feeds	Duration of invasive ventilation
Volume of enteral feeds per day prior to abdominal event	Non-invasive ventilation
Parenteral nutrition prior to abdominal event	Non-invasive ventilation start date

Volume of parenteral feeds per day prior to abdominal event	Non-invasive ventilation stop date
Preoperative lipids given	
Preoperative type of lipids	
Postoperative enteral feeds start date and time	
Postoperative type of enteral feeds	
Postoperative starting concentration of enteral feeds	
Postoperative date and time when enteral feeds = 100mL/kg	
Postoperative type of enteral feeds when feeds = 100mL/kg	
Postoperative concentration of enteral feeds when feeds = 100mL/kg	
Postoperative time to tolerance of full enteral feeds	
Postoperative parenteral nutrition start date and time	
Postoperative parenteral nutrition end date and time	
Postoperative nutrition duration	
Postoperative lipids start date and time	
Postoperative lipids end date and time	
Postoperative lipids duration	
Time to return to bowel function	
VIS	**PELOD Score**
Dopamine	Mean arterial blood pressure (lowest value)
Dobutamine	Lactate (highest value)
Epinephrine	Glasgow coma score (lowest value)
Norepinephrine	Pupillary reaction
Milrinone	PaO2 (lowest value)
Vasopressin	Corresponding FiO2
Levosimendan	PaO2 (highest value)
VIS score	Mechanical ventilation
	Leukocyte count (lowest value)
	Platelet count (lowest value)
	Creatinine (highest value)

	PELOD Score
Outcomes	
Alive or deceased	
Readmissions	
Readmission for cardiac	
Cardiac readmission notes	
Readmission for abdominal	
Abdominal readmission notes	

Table 1. Data Collected and Entered into REDCap.

This data above that was entered into REDCap for each individual patient was collected using Cerner. Cerner is an electronic medical record (EMR) platform used at BCH. After all the data was entered from Cerner, a Microsoft Excel file was exported from REDCap containing all the data within these eleven different sections for the 16 total patients of interest.

Lastly, result tables were created including the data of interest in regard to this study. These tables can be seen below in the results section (refer to Table 2., Table 3., and Table 4.). Data was then handed off to Steven Staffa, a biostatistician employed by BCH in the Anesthesiology department. Since the population of patients (16) being analyzed for this specific study was small, the analysis was focused on describing the data rather than looking for statistical

significance between variables. Results were calculated and can be seen below.

RESULTS

The goal of this section is to thoroughly describe the patient population. The patient population was not large enough to conduct a full statistical analysis to draw conclusions about relationships between predictor variables, covariates, and overall outcomes of this study. Table 2, table 3, and table 4 were created to describe our patient population.

Demographics and Patient Characteristics

In regard to the demographics of the patient population used for this study, 16 total patients' data was evaluated in order to calculate this data. Of these 16 patients, 6 were females (37.5%) while 10 were males (62.5%). Prematurity, described as a newborn being <37 weeks gestational age (GA), was an imperative covariate to include within this study since prematurity is known to be an important factor in the determinant of overall health of an individual. 8 patients (50%) were born prematurely with 3 of the 16 total patients (18.8%) having a chromosomal anomaly or genetic syndrome. 10 patients (62.5%), a

majority, were born with a non-cardiac congenital anomaly which raises the question of whether or not individuals with one congenital anomaly are more likely to develop another congenital anomaly. Although a conclusion about this relationship cannot be made in this study, an abundance of literature seems to be available regarding this topic.

Undoubtably one of the biggest predictor variables focused on within this study was whether or not the patients congenital heart defect was single or double ventricle (biventricular) defect. As described previously in this article, it has been shown to be an important predictor variable when searching for a relationship between congenital heart defects and associated abdominal pathology. 3 of the 16 patients (18.8%) had a single ventricle congenital heart defect meaning that the majority of patients (81.2%) had a biventricular congenital heart defect. This is most certainly a variable of interest and could possibly have a direct association with the development of abdominal pathology though no conclusions about this can be drawn from this study. All of this demographic data discussed can be found in Table 2.

Variable	**N (%) or Median (IQR)**

Number of Patients	16
Age (days) (a)	57 (3, 79)
Sex	
Female	6 (37.5%)
Male	10 (62.5%)
Premature (b)	8 (50%)
Chromosomal anomaly/ Genetic syndrome	3 (18.8%)
Non-cardiac congenital anomaly	10 (62.5%)
Single Ventricle	3 (18.8%)
STAT Category	
1	0/5 (0%)
2	2/5 (40%)
3	1/5 (20%)
4	1/5 (20%)
5	1/5 (20%)

Table 2. Patient Characteristics.

Abdominal Procedures and Surgical Characteristics

Table 3 includes all intra-abdominal diagnostic and surgical characteristics. There were nine different abdominal diagnoses across the cohort of patients. NEC, known to have a relationship with the perfusion of oxygenated blood to the GI system, was the most common intra-abdominal diagnosis with 5 patients (31.3%) experiencing this condition. Immediately following NEC in order of most prevalent to least prevalent was bowel obstruction occurring in 4 patients (25%), intestinal malrotation and perforation tied at 3 patients (18.8%) each (6 total), ileostomy along with gastrointestinal

disorder and duodenal atresia each being seen in 2 patients (12.5%) (6 total), and finally jejunostomy was present in 1 patient (6.3%).

Ventricular function was a covariate that was closely looked at by examining the echocardiogram report closest in date to the abdominal procedure of interest in each patient. In almost all instances, except for a select few, left and right ventricular function was normal. This was the case because each patient's abdominal procedure occurred after their cardiac procedure. The conclusion that can be drawn from this data is that almost all cardiac procedures were able to repair ventricular function back to normal in 15 out of the 16 patients within this population.

The preoperative and postoperative nutrition was also evaluated during within this study. 13 out of 16 patients (81.3%) received either enteral, parenteral, or both enteral and parenteral nutrition 72 hours prior to the index abdominal event. 6 total patients (37.5%) received enteral nutrition either through a nasogastric tube (NGT) or nasojejunal tube (NJT). 5 of the 6 patients (83.3%) receiving enteral feeding received it through an NGT whereas only 1 of the 6 patients (16.7%) received it through an NJT. The type of feeding each patient received was either breast milk or formula. Only 1 patient of 6 total (16.7%) received breast milk as their type of feeding. The other 5

patients (83.3%) received their nutrition through formula. No patient within this population received both breast milk and formula. A majority of patients experiencing enteral feeds either received nutrition with a caloric density of 24 kcal or 26 kcal. 2 out of the 5 patients (40%) received enteral feeds with a caloric density of 24 kcal whereas 2 out of the 5 patients (40%) received enteral feeds with a caloric density of 26 kcal. 1 patient (20%) received enteral feeds with an unknown caloric density.

There were six different abdominal procedures that were performed on the 16 patients included in the patient population. Some patients underwent multiple abdominal procedures listed. The most common abdominal procedure performed was a gastrostomy, open; without constriction of gastric tube (eg, Stamm procedure) (separate procedure) with 12 patients (75%) undergoing this procedure. The other five procedures performed from most commonly performed to least commonly performed were Gastrorrhaphy, suture of perforated duodenal or gastric ulcer, wound or injury with 3 patients (18.8%) undergoing this procedure, Laparoscopy; surgical jejunostomy being performed in 2 cases (12.5%), and finally change of gastrostomy tube, percutaneous, without imaging or endoscopic guidance as well as Enterotomy, small intestine, other than duodenum; for decompression

(eg, Baker tube) and Enterotomy, small intestine, other than duodenum; for exploration, biopsy(s), or foreign body removal each being performed 1 time (6.3%).

Variable	**N (%)**
Intra-abdominal diagnosis	16 (100%)
Bowel Obstruction	4 (25%)
Duodenal Atresia	2 (12.5%)
Gastrointestinal Disorder	2 (12.5%)
Gastrointestinal Problem Acquired	0 (0%)
Ileostomy	2 (12.5%)
Intestinal Malrotation	3 (18.8%)
Intestinal perforation	3 (18.8%)
Jejunostomy	1 (6.3%)
Necrotizing Enterocolitis (NEC)	5 (31.3%)
Cardiac surgery status at time of intra-abdominal diagnosis	
Pre	
Post	0/15 (0%)
PGE1 at time of intra-abdominal diagnosis	0/14 (0%)
Ventricular function (a)	
Left Ventricle Normal	12/15 (80%)
Left Ventricle Mild dysfunction	2/15 (13.3%)
Left Ventricle Moderate dysfunction	0/15 (0%)
Left Ventricle Severe dysfunction	1/15 (6.7%)
Right Ventricle Normal	14/15 (93.3%)
Right Ventricle Mild dysfunction	1/15 (6.7%)
Right Ventricle Moderate dysfunction	0/15 (0%)
Right Ventricle Severe dysfunction	0/15 (0%)
Nutrition mode 72 hours prior to index abdominal event	
Enteral - Nasogastric (NGT) or nasojejunal tube (NJT)	
NGT	5/6 (83.3%)
NJT	1/6 (16.7%)
Enteral or parenteral nutrition	11 (68.8%)
Enteral and parenteral nutrition	2 (12.5%)
Enteral nutrition	6 (37.5%)

Parenteral nutrition	7 (43.8%)
Nutrition type 72 hours prior to index abdominal event	
Breast milk	1/6 (16.7%)
Formula	5/6 (83.3%)
Breast milk + formula	0/6 (0%)
Nutrition caloric density (kcal) 72 hours prior to index abdominal event	
20	0/5 (0%)
22	0/5 (0%)
24	2/5 (40%)
26	2/5 (40%)
28	0/5 (0%)
30	0/5 (0%)
Unknown	1/5 (20%)
Abdominal procedure	
Change of gastrostomy tube, percutaneous, w/o imaging	1 (6.3%)
Enterot sm int oth/thn duo decomp	1 (6.3%)
Enterot sm int oth/thn duo explore bx/fb rmvl	1 (6.3%)
Gastrorrhaphy suture prf8 duol/gstr ulcr wnd/inj	3 (18.8%)
Gastrost opn w/o constrct gstr tube spx	12 (75%)
Laparoscpy surg jejunost	2 (12.5%)

Table 3. Intra-abdominal Diagnostic and Surgical Characteristics. Change of gastrostomy tube, percutaneous, w/o imaging = Change of gastrostomy tube, percutaneous, without imaging or endoscopic guidance; Enterot sm int oth/thn duo decomp = Enterotomy, small intestine, other than duodenum; for decompression (eg, Baker tube); Enterot sm int oth/thn duo decomp explore bx/fb rmvl = Enterotomy, small intestine, other than duodenum; for exploration, biopsy(s), or foreign body removal; Gastrorrhaphy suture prf8 duol/gstr ulcr wnd/inj = Gastrorrhaphy, suture of perforated duodenal or gastric ulcer, wound or injury; Gastrost opn w/o constrct

gstr tube spx = Gastrostomy, open; without constriction of gastric tube (eg, Stamm procedure) (separate procedure); Laparoscopy surg jejunost = Laparoscopy; surgical jejunostomy.

Outcomes

The primary outcome investigated in this study was time to return of bowel function. This value was calculated by calculating the number of days passed between the date of the abdominal procedure of interest and the date when postoperative enteral feeds were started. The postoperative enteral feeds need to have been tolerated for a 24-hour period in order to meet the criteria of being the start date. 14 of the 16 patients (87.5%) had data available in order to calculate the time to return of bowel function. The median values was used to best represent the patient population, since there were outliers present in the data, rather than the mean value. The median number of days it took the cohort to return to bowel function was 11.7 days with the minimum number of days being 5.1 and the maximum number of days being 19.7.

The secondary outcomes evaluated in this study were the ICU length of stay, total hospital length of stay, and survival to discharge. The ICU length of stay was calculated by calculating the number of

days passed between the date admitted to the ICU and the date discharged from the ICU. If a patient experienced a readmission to the ICU, the length of stay was calculated the same way as it was for the first admit to the ICU. If a readmission did in fact occur, the total number of days spent in the ICU during the readmission was added to the total number of days spent in the ICU for the first admission thus leaving us with the total ICU length of stay. The total length of stay was calculated by calculating the number of days passed between the admit date and the discharge date for the index abdominal event.

The median value was used to best represent the patient population for ICU length of stay and total hospital length of stay. The median number of days spent in the ICU for 4 patients with enough data available to carry out this calculation was 45 with the minimum being 20 and the maximum being 60. The median number of days spent in the hospital in total was 101 with the minimum being 57 and the maximum being 119. Of the 16 patients included in the patient population, 14 (87.5%) survived to discharge.

Variable	**N (%) or Median (IQR)**
Time to return of bowel function (days) (a)	11.7 (5.1, 19.7) n=14

ICU length of stay (days)	45 (25, 60) n=4
Total hospital length of stay (days)	101 (57, 119)
Survival to discharge	14 (87.5%)

Table 4. Post-Abdominal Surgery Outcomes.

Discussion

Key predictor variables and covariates evaluated within this study were the presence of single ventricle congenital heart defects, whether a patient was born prematurely or not, birth or admission weight, the presence of non-cardiac congenital anomalies, and nutritional management 72 hours prior to the relevant abdominal event. Important findings of this study include median time to return of bowel function, median ICU length of stay, median total hospital length of stay, and the number of patients that survived to discharge. It is difficult to draw conclusions from this data since the patient population was very small so statistically significant claims cannot be made.

The major limitation in this study was the population size. As discussed, this mainly had an impact on what analysis can be completed using the data and what statistically significant claims can be made.

Covariates that were not included in the data analysis include cross-clamp time, regional perfusion time, and circulatory arrest time that occurred during each patients CHD cardiac procedure. Each of these covariates has an effect on perfusion of blood around the body. The perfusion of blood throughout the body is an important predictor variable that should be investigated in cases where heart defects are being surgically corrected and an abdominal pathology is present. As previously mentioned, when blood does not perfuse organ systems properly for an extended period of time then proper amounts of oxygen cannot be delivered to organ systems thus organ necrosis can occur. In cases of NEC, this has been described to be the underlying mechanism causing necrosis, though each case is different.

Each patient's medical records were extensively reviewed and served as the source of data collected. Though thorough chart reviews were performed, some data could not be collected and analyzed due to its lack of presence. Data missing for some patients, not all, included timeframe of abdominal diagnosis, patient location at time of abdominal diagnosis, z-score of isthmus and transverse arch in regard to patient's echocardiograms, and lowest and highest partial pressure of oxygen in the arterial blood 24 hours prior to the abdominal procedure of interest. Some data may have been present and simply

overlooked, indicating human error, but extensive patient chart reviews were conducted.

In a retrospective study like this where a total of 936 individual postoperative abdominal diagnoses and abdominal procedures performed needed to be sorted through in a timely manner, time is certainly of the essence. If all eleven sections of data (refer to table 1.) needed to be collected for 936 individual patients, rather than just for the 16 urgent and emergent abdominal cases, it would take an exceptional amount of time to complete the study. It is possible to conduct a study of this matter with large quantities of data and it would be extremely informational but proper time should be allotted for its completion so that the study is not rushed and so that no mistakes are made.

An extensive literature review conducted before, during, and after this studies completion provided a very strong foundation of background information imperative for its full understanding. Being aware of the literature that is currently present regarding the matter is important in determining what future studies should focus on.

Future studies of this kind should focus on the effect that congenital heart defects and correctional cardiac surgery have on perfusion of blood flow throughout the abdomen and how that

perfusion affects abdominal pathology. Other areas of importance are nutritional management at the time of abdominal diagnosis and single ventricle defects causing cyanosis and hypotension and their relevant effects. It is known that abdominal pathology is often seen in neonates and infants with CHD, and although each case is different, the exact cause of this relationship is not fully understood. With congenital heart defects being the most common congenital abnormality in the world, the connection between the two is certainly a pressing issue and a full understanding of the relationship and its predictor variables can positively impact the lives of many babies, children, and adults globally.

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