Practice Variation Among Pediatric Cardiologists and Associated Outcomes in the Management of Heterotaxy Syndrome and Malrotation

Study Purpose and Rationale

Heterotaxy syndrome (HS) refers to any anatomical configuration that ranges from, but does not include, complete situs solitus with levocardia and a D-cardiac loop and situs inversus totalis with dextrocardia and an L-cardiac loop. While there is a known association between heterotaxy syndrome and congenital heart disease (CHD), there is no specific type of CHD for which heterotaxy patients have a predisposition. Its severity represents a spectrum from isolated simple lesions, such as atrial septal defects, to more complex defects, including functional single ventricles with variations of systemic and pulmonary venous drainage, including interrupted inferior vena cava, bilateral superior vena cavae, and anomalous pulmonary venous connections. 

This is a unique disorder that occurs in approximately 1 per 10,000 births and involves multiple considerations that could potentially affect the morbidity and mortality of the afflicted child.

In addition to the above association, there has been much data linking heterotaxy syndrome with various gastrointestinal (GI) abnormalities, the most clinically significant being malrotation and midgut volvulus. Malrotation is a term used to describe a failure of normal rotation of any portion of the intestinal tract during embryonic development. This arrest in development can predispose a child to developing a malfixated midgut with a narrow small bowel mesentery, which are risk factors for volvulus. The rate of intestinal malrotation has been reported as approximately 1 in 500 live births overall, but has been found to be present in a large proportion of children and adults with HS. Although a previously undiagnosed patient with malrotation may theoretically present at any juncture of life with an acute volvulus, approximately 66-80% of patients who do present with malrotation will do so in the first month of life and 90% in the first year of life. The incidence of malrotation and other associated digestive tract rotational abnormalities in heterotaxy patients has been shown to be in the range of 32-89%.

Practice variation among pediatric cardiologists in the management of malrotation in heterotaxy syndrome has been a debate in the literature and differs among various institutions. The surgical approach to correction of malrotation involves performance of the Ladd procedure, which consists of detorsing of the bowel, surgical lysis of intra-abdominal adhesive bands, and repositioning of the intestines and mesentery, thus correcting the abnormalities caused by embryologic
The belief by some physicians and institutions is that the benefits of this operation greatly outweigh the risks of “elective” abdominal surgery and the risk of eventually developing midgut volvulus\textsuperscript{1-2,14-16}, with up to 50% mortality experienced as a consequence of short-gut syndrome that can result from midgut volvulus.\textsuperscript{15} Among these physicians, the timing of referral for Ladd procedure depends largely on patient age, cardiac physiology, and personal preference. Several studies have reported the incidence of small bowel obstruction (SBO) post-Ladd procedure ranging from 3% to as high as 30% in HS patients, the most recent of which was reported as 9.7% in 2009 by Yu, et al and 14% in 2007 by Tashjian, et al. Yu, et al (2009) showed that comparing asymptomatic to symptomatic HS patients who had Ladd procedure performed, there was a significantly increase hospital stay in the symptomatic patients who required “emergent” operation, while there was no difference in SBO incidence or mortality between the two groups.

Others believe that prophylactic Ladd procedure is unnecessary in children with heterotaxy syndrome and malrotation due to potential postoperative complications and the otherwise low morbidity and mortality from the natural course of malrotation.\textsuperscript{10-12} Choi, et al (2005) reported from a sample size of 177 patients with HS that only 5 developed symptomatic classic malrotation when managed non-surgically and reported that the 0.6% incidence of volvulus in this population of patients that was treated conservatively is much safer than the SBO risks published in most studies.

With this discrepancy in the literature and lack of consensus seen among pediatric cardiologists who manage patients with heterotaxy syndrome, a larger collection of data across multiple institutions is needed to determine if and when the Ladd procedure is appropriate in these patients.

**Study Design and Statistical Analysis**

This is a retrospective multi-center study investigating the variations in management decisions pertaining to the Ladd procedure in patients with heterotaxy syndrome and to assess the various outcomes related those decisions.

Pediatric cardiologists at approximately 50 major medical centers in the United States will receive an e-mail announcing the study, accompanied by a link to a brief online questionnaire. The data submitted through this questionnaire will be accessed only by the Principle Investigator, Dr. Wyman Lai, and collaborating investigator Dr. Arash Salavitabar. The questionnaire will consist of questions asking about the size of the participant’s institution and the approach of the given physician to referral of patients with heterotaxy syndrome for gastrointestinal imaging and the Ladd procedure. The questionnaire should take approximately 5-10 minutes to complete. Participating physicians will be provided a contact e-mail address and phone number for the above investigator in case of any questions or concerns regarding the questionnaire prior to submission.
Two national, multi-center databases, the Society of Thoracic Surgeons (STS) and the Pediatric Health Information System (PHIS), will be linking their data in a HIPAA-compliant manner in the next two months. Data is submitted to these databases by participating U.S. medical centers. From this data will be retrieved patient diagnoses, demographic information, surgical procedures, and outcomes in patients with heterotaxy syndrome.

The first group of subjects to be analyzed is the physician group who responds to the aforementioned survey. The second group will consist of patients with heterotaxy syndrome who received the following management approaches: prophylactic Ladd procedure, no Ladd procedure in the absence of symptoms, and emergent Ladd procedure.

Outcomes will include overall mortality, hospital mortality, length of hospital stay, and incidence of volvulus, small bowel obstruction, cardiovascular arrest, respiratory arrest, and infection.

On review of the literature, there were a total of 575 patients reported in 8 different institutional studies on patients with heterotaxy syndrome with respect to the Ladd procedure and outcomes.\(^1\)\(^-\)\(^9\)\(^,\)\(^11\)\(^-)\(^15\)\(^-,\)\(^17\) The duration of these studies ranged from 4 years to 32 years. When the sample size for each institution is extrapolated to a 10-year projection, the mean number of patients with heterotaxy syndrome per institution per 10-year period is approximately 56. Based on this data, it can be conservatively assumed that each institution will have data on 50 patients over 10 years. Also assuming that at least a 50% survey response rate is achieved, it can be estimated that a patient sample size of 1250 will be attained. Using the most recently reported rates of SBO post-Ladd procedure in patients with HS, an estimate of 12% incidence will be used, vs. the 0.6% rate of volvulus in patients with HS who are conservatively watched for symptoms. Since the majority of institutional studies in the literature report the recommendation of prophylactic Ladd procedure, a ratio of 2 to 1 will be estimated as the proportion of patients who have undergone prophylactic Ladd procedure to those were managed by the conservative approach. Using a chi-square test and with power of 0.8 and alpha of 0.05, an effect size of less than 7.1% will need to be observed in the conservatively managed group in order to show a significant decrease in complications.

We hypothesize that 1.) there will be an overall superior mortality and morbidity rate in the conservatively treated group who did not receive the prophylactic Ladd procedure as compared to the group which was treated more aggressively with the prophylactic Ladd procedure, specifically when looking at SBO vs. volvulus rates, and 2.) there will be a large variety in the distribution of approaches to patients with heterotaxy syndrome with respect to evaluation and treatment of malrotation, but with a majority of physicians preferring the more aggressive approach.
**Study Procedure**
Not applicable.

**Study Drugs**
There will be no study drugs used in this study.

**Medical Device**
There will be no medical devices used in this study.

**Study Questionnaire**
Please see the attached questionnaire.

**Study Subjects**

Board-certified pediatric cardiologists at U.S. academic medical centers will be sent a brief survey and will be invited to participate, and thus will constitute the first group of study subjects. All pediatric cardiologists affiliated with major medical centers in the U.S. that perform pediatric and congenital heart surgery are eligible, with approximately 50 medical centers to be chosen.

The second group of study subjects will consist of children diagnosed with heterotaxy syndrome whose health information have been entered into the following national multi-center databases: the Society of Thoracic Surgeons (STS) and the Pediatric Health Information System (PHIS), and subsequently linked together. Data will only be used for patients seen in the last 10 years of reported data and who have complete data for the 1st year of life.

Exclusion criteria will include 1.) incomplete records, 2.) comcomitant abdominal conditions predisposing the patient to malrotation, or 3.) the operation represented a second Ladd procedure.

**Recruitment of Subjects**

Pediatric cardiologists will receive an e-mail announcing the study and providing a link to a short online questionnaire. Completion and submission of the questionnaire will imply consent to participate in the study, as explicitly stated in the e-mail communication provided to them.

Formal requests will be sent to the leaders of the STS and PHIS databases in order to gain access to the data submitted by U.S. medical centers.
Confidentiality of Study Data

Efforts to maintain confidentiality will be utilized. Questionnaires will not contain any identifying information of the patients whom they have managed and from whom they report their practices. Questionnaire data and scores will likewise be kept in a database linked to the physician name provided by the physician completing the questionnaire, but will not be reported with any identifying information in any publications. This data will be stored in a secure location, accessible only to the investigators.

Potential Conflict of Interest
There is no conflict of interest to report.

Location of Study
All data will be acquired electronically.

Potential Risks
There are no risks to patient safety or comfort since this is a retrospective study.

Potential Benefits
This study will make pediatric cardiologists aware of the practice variation in managing patients with heterotaxy syndrome and the outcomes related to those decisions in hopes of potentially creating a standardized protocol for the management of such patients.

Alternative Therapies
There are no experimental therapies being used in this study.

Compensation to subjects
No compensation will be provided to subjects.

Costs to subjects
There will be costs to the subjects.

Minors as Research Subjects
This is a retrospective observational study involving data from the hospitalizations of minors.

Radiation or Radioactive Substances
No radiation or radioactive substances are involved in this study.
References:


Heterotaxy Syndrome and Ladd Procedure Pilot Survey

1. Physician & Institution Names:

2. Does your institution have a standardized protocol in evaluating for and treating malrotation when approaching patients with heterotaxy syndrome?
   a.) Yes
   b.) No

2a. If you answered “Yes” to Question #9, does your personal approach to these patients agree with that of your institution? (Please skip if not applicable)
   a.) Yes
   b.) No

• If you answered “No” to Question #2, please answer the following questions based on your own practices.
• If you answered “Yes” to Question #2, please answer the following questions based on the approach of your institution.

3. What is the total number of pediatric and congenital heart surgery cases seen by your institution per year?
   a.) Less than 150
   b.) 150-249
   c.) 250-349
   d.) Greater than or equal to 350

4. For patients with suspected heterotaxy syndrome, at what point do you typically perform GI imaging to evaluate for intestinal malrotation?
   a.) Electively, even in absence of GI symptoms
   b.) In presence of GI symptoms, such as feeding intolerance, abdominal distension, and bilious or non-bilious vomiting

5. For patients with heterotaxy syndrome, what is the first imaging modality you typically use when evaluating for intestinal malrotation?
   a.) Upper Gastrointestinal (GI) contrast study
   b.) Abdominal ultrasound
   c.) Do not routinely evaluate for malrotation
6. When heterotaxy syndrome is suspected, at what point do you refer patients for possible Ladd procedure?
   a.) When clinical GI symptoms occur but only in the presence of imaging either consistent with malrotation or of unclear anatomy
   b.) When clinical GI symptoms occur, regardless of imaging results
   c.) In the presence of imaging consistent with abnormalities of intestinal rotation, even in the absence of GI symptoms

7. If it is your practice to refer asymptomatic patients with heterotaxy syndrome for a prophylactic Ladd procedure when imaging is consistent with intestinal malrotation, at what point do you refer patients for this procedure?
   a.) During the initial hospitalization in the newborn period, as soon as possible after recovery from heart surgery, if necessary
   b.) During the initial hospitalization, in the newborn period, near the time of discharge
   c.) Electively after discharge from initial hospitalization

Comment:

8. If you chose answer (c) for Question #7, please specify at what age ranges you would typically refer these patients for an elective operation:
   a.) In the neonatal period (Less than 4 weeks of age)
   b.) 1-2 months of age
   c.) 3-6 months of age
   d.) 7-12 months of age
   e.) Greater than 12 months of age

9. If applicable to your practice, what is your main reason for deferring prophylactic Ladd procedure in your asymptomatic heterotaxy syndrome patients? (Please choose more than one answer, if applicable)
   a.) Risks of bowel resection or adhesive small bowel obstruction as potential postoperative complications.
   b.) Suboptimal hemodynamics related to associated congenital heart disease causing increased risks of perioperative complications
   c.) Additional medical conditions, aside from related cardiac defects, causing increased risks of perioperative complications
   d.) Not applicable; would not defer referral due to concerns for future volvulus requiring emergent operation

Comments: