Outcomes of multistage palliation of infants with functional single ventricle and heterotaxy syndrome

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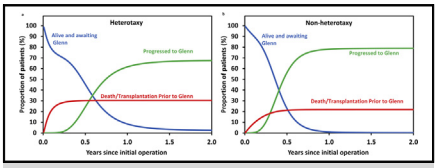
ABSTRACT

Background: Management of infants with heterotaxy syndrome and functional single ventricle is complicated due to associated cardiac and extracardiac anomalies. We report current era palliation results.

Methods: Between 2002 and 2012, 67 infants with heterotaxy syndrome underwent multistage palliation. Competing risks analyses modeled events after surgery (death vs Glenn procedure) and examined factors associated with survival. In addition, early and late outcomes following first-stage palliation surgery were compared with a matched contemporaneous control group of patients with nonheterotaxy single ventricle anomalies.

Results: Fifty-eight patients (87%) required neonatal palliation, including a modified Blalock-Taussig shunt (n = 34; 51%), Norwood operation (n = 12; 18%) or pulmonary artery band (n = 12; 18%), whereas 9 patients (13%) underwent a primary Glenn procedure. Competing risks analysis showed that at 1 year after first-stage palliation surgery, 29% of the patients had died or undergone transplantation and 63% had undergone a Glenn procedure. By 5 years after the Glenn procedure, 64% of patients had undergone a Fontan procedure. The overall 8-year survival rate was 66%. On multivariable analysis, factors associated with mortality were unplanned reoperation (hazard ratio [HR], 2.9; 95% confidence interval [CI], 1.1-7.3; $P = .005$) and total anomalous pulmonary venous connection repair (HR, 2.3; 95% CI, 1.0-5.6; $P = .056$). Comparison with the contemporaneous matched patients with nonheterotaxy single ventricle anomalies showed that first-stage palliation in the patients with heterotaxy was associated with a higher rate of in-hospital death (27% vs 10%; $P = .022$), and significantly longer durations of ventilation and intensive care unit stay. Interstage mortality, survival after the Glenn procedure, and progression to the Fontan procedure were comparable in the 2 groups.

Conclusions: The management of infants with heterotaxy and a functional single ventricle remains challenging. First-stage palliation is associated with high operative mortality and increased resource utilization owing to surgical morbidity. Nonetheless, outcomes beyond hospital discharge are comparable to those for patients with other single ventricle anomalies. Efforts to improve survival in those patients should focus on perioperative care. (J Thorac Cardiovasc Surg 2016;151:1369-77)



Competing events following palliation for heterotaxy syndrome versus nonheterotaxy syndrome single ventricle.

Central Message

Single ventricle palliation for heterotaxy syndrome is associated with higher morbidity and mortality than other single ventricle anomalies.

Perspective

First-stage palliation of infants with heterotaxy syndrome and functional single ventricle anomalies is associated with high operative mortality and increased resource utilization owing to surgical morbidity. Nonetheless, outcomes beyond hospital discharge are comparable to those in infants with other nonheterotaxy single ventricle anomalies.

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Visceral heterotaxy syndrome is defined as an abnormality in which the internal thoracoabdominal organs demonstrate

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CONG

Abbreviations and Acronyms

BTS = modified Blalock-Taussig shunt
CI = confidence interval
ECMO = extracorporeal membrane oxygenation
HR = hazard ratio
IQR = interquartile range
LAI = left atrial isomerism
OR = odds ratio
PAB = pulmonary artery band
RAI = right atrial isomerism
TAPVC = total anomalous pulmonary venous connection

an abnormal arrangement across the body's left–right axis.[1] Children born with heterotaxy syndrome often have complex congenital cardiac anomalies that require surgical intervention. Although some of these children have cardiac anomalies that are amenable to biventricular repair, many others have a functional single ventricle that requires multistage palliation, with the initial surgery dictated by the anatomy and the degree of systemic or pulmonary outflow obstruction.[1-8]

Surgical management of children with heterotaxy syndrome and a functional single ventricle is challenging, owing to the presence of complex morphological features, such as total anomalous pulmonary venous connection (TAPVC), atrioventricular valve dysfunction, pulmonary atresia, arrhythmias, and heart block, all of which are established risk factors for increased morbidity and mortality following single ventricle palliation.[2-13] Additional extracardiac anomalies associated with heterotaxy syndrome, such as ciliary dysfunction, intestinal malrotation, and asplenia, can contribute to increased early operative morbidity and complexity of postdischarge management, further adversely affecting late outcomes in those challenging patients.[7,11,12,14-17]

We hypothesized that results of multistage palliation of neonates born with heterotaxy syndrome and functional single ventricle have improved in the current era, owing to advances in perioperative care and outpatient management, and that their palliation outcomes are comparable to those in neonates born with other nonheterotaxy single ventricle anomalies. To test this hypothesis, we examined early and late results following single ventricle palliation in infants with heterotaxy syndrome and compared them with those recorded in a matched group of contemporaneous infants with nonheterotaxy single ventricle anomalies at our institution.

PATIENTS AND METHODS

Between 2002 and 2012, 67 consecutive infants with heterotaxy syndrome underwent their first palliative surgery at Children's Healthcare of Atlanta, Emory University. Patients were identified using our institutional surgical database. Demographic, morphologic, clinical, operative, and hospital details were abstracted from the medical records for analysis. This study was approved by the hospital's Institutional Review Board, and the requirement for individual consent was waived for this observational study.

Echocardiographic Data Collection and Classification

All preoperative echocardiograms were reviewed retrospectively by a single echocardiographer (B.S.). Our morphological inclusion criteria were based on the most recent nomenclature review and classification scheme reported by Jacobs and colleagues in 2007.[1] In that report, heterotaxy syndrome is defined as an abnormality in which the internal thoracoabdominal organs demonstrate a abnormal arrangement across the body's left–right axis. By convention, heterotaxy syndrome does not include patients with either the expected usual or normal arrangement of the internal organs along the left–right axis, also known as "situs solitus," or patients with complete mirror-imaged arrangement of the internal organs along the left–right axis, also known as "situs inversus."[1] Left atrial isomerism (LAI) is defined as a subset of heterotaxy syndrome in which some paired structures on opposite sides of the body's left–right axis are symmetrical mirror images of each other, and have the morphology of the normal left-sided structures. This condition is commonly associated with polysplenia. Right atrial isomerism (RAI) is a subset of heterotaxy syndrome in which some paired structures on opposite sides of the body's left–right axis are symmetrical mirror images of each other, and have the morphology of the normal right-sided structures. This is commonly associated with asplenia.[1] All patients were considered to have a functional single ventricle, although some had 2 well-formed ventricles that were not considered amenable to septation owing to the presence of a noncommitted ventricular septal defect, multiple ventricular septal defects, or straddling of the atrioventricular valves.

Follow-up

Time-related outcomes were determined from recent office visits documented in the electronic chart of the Children's Healthcare of Atlanta system or from direct correspondence with pediatric cardiologists outside of the system. The mean duration of follow-up was 5.5 ± 4.2 years and was 94% complete.

Statistical Analysis

Data are presented as mean with standard deviation, median with interquartile range (IQR), or frequency and percentage, as appropriate. Time-dependent outcomes after first- stage palliation surgery and after the Glenn operation were modeled parametrically. Parametric probability estimates for time-dependent outcomes uses models based on multiple overlapping phases of risk using PROC HAZARD (available for use with the SAS system at http://www.clevelandclinic.org/heartcenter/hazard). The HAZARD procedure uses maximum likelihood estimates to resolve risk distribution of time to event in up to 3 phases of risk (early decreasing or peaking hazard, constant hazard, and late increasing hazard). Maximum likelihood estimates are calculated iteratively using nonlinear optimization-based algorithms. Smoothed survival curves were generated using the HAZPRED procedure in SAS. PROC HAZPRED computes predictions for the survivorship and hazard functions along with their confidence limits.

Competing risks analysis was performed to model the probability over time of each of 2 mutually exclusive endpoints after first-stage palliation surgery: death/transplantation and survival to the Glenn procedure. After the Glenn procedure, competing risks models were not used, owing to the small number of death/transplantation events following this procedure.

For the outcome of hospital death following first-stage palliation, logistic regression was used to identify risk factors associated with hospital death. The following variables were tested: sex, age, weight, prematurity, extracardiac anomalies, heterotaxy syndrome type (RAI vs LAI), dominant ventricle morphology (left, right, or both), morphology of the atrioventricular valve (common atrioventricular valve, tricuspid valve, mitral valve, or all), antegrade pulmonary blood flow (absent, restricted, or unrestricted),