Increased postoperative respiratory complications in heterotaxy congenital heart disease patients with respiratory ciliary dysfunction

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Objective(s): Congenital heart disease (CHD) and heterotaxy patients have increased postoperative and respiratory complications. We recently showed CHD-heterotaxy patients can have respiratory ciliary dysfunction (CD) similar to that associated with primary ciliary dyskinesia, including low nasal nitric oxide and abnormal ciliary motion. In this study, we investigated whether CHD-heterotaxy patients with CD may have worse postsurgical outcomes.

Methods: We examined postsurgical outcome in 13 heterotaxy-CHD patients with CD (25 surgeries), compared with 14 heterotaxy-CHD patients without CD (27 surgeries). Outcome data were collected for each surgery, including respiratory complications, tracheostomy, use of inhaled β-agonists or nitric oxide, length of hospital stay, days on ventilator, and death.

Results: The CD versus the no-CD CHD cohorts had similar Risk Adjustment in Congenital Heart Surgery-1 risk categories, repair track, age at surgery, and follow-up evaluation times. Respiratory complications (76% vs 37%; $P = .006$), need for tracheostomy (16% vs 0%; $P = .047$), and use of inhaled β-agonists (64% vs 11%; $P = .0001$) all were increased significantly in heterotaxy-CHD patients with CD. No significant differences were detected in postoperative hospital stay, days on mechanical ventilation, or surgical mortality. A trend toward increased mortality for the CD group beyond the postoperative period was observed (33% vs 0%; $P = .055$) in patients younger than age 10 years.

Conclusions: Our findings showed that heterotaxy-CHD patients with CD may have increased risks for respiratory deficiencies. Overall, there was a trend toward increased mortality in CD patients with intermediate follow-up evaluation. Because β-agonists are known to increase ciliary beat frequency, presurgical screening for CD and perioperative treatment of CD patients with inhaled β-agonists may improve postoperative outcomes and survival. (J Thorac Cardiovasc Surg 2014;147:1291-8)

CHD

Supplemental material is available online.

Heterotaxy constitutes a wide spectrum of defects involving abnormal left-right patterning of organ situs in the abdominal and thoracic cavities. The aberrant left-right asymmetry can range from milder forms involving a single organ system to more complex disease involving indeterminate patterning of multiple thoracoabdominal organs. Heterotaxy occurs in approximately 1 in 10,000 live births and is associated with 3% of cases of congenital heart disease (CHD).[1-3] Despite significant advances in medical and surgical management of CHD over the past few decades, short- and long-term morbidity and mortality remain high for CHD patients with heterotaxy.[4-6]

One study evaluating surgical outcomes after the Fontan surgery showed a 2-fold higher postoperative mortality rate for CHD patients with heterotaxy compared with CHD patients without heterotaxy.[7] We previously showed in a retrospective study that 87 heterotaxy-CHD patients had more postoperative complications, higher postoperative mortality rates, and increased respiratory complications compared with 634 CHD patients without laterality defects with similar Risk Adjustment in Congenital Heart Surgery-1

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Abbreviations and Acronyms

CD = ciliary dysfunction
CHD = congenital heart disease
ECMO = extracorporeal membrane oxygenation
PCD = primary ciliary dyskinesia
PLE = protein-losing enteropathy
PVR = pulmonary vascular resistance
RACHS-1 = Risk Adjustment in Congenital Heart Surgery-1

(RACHS-1) risk categories.[8] Relevant to these findings are observations from a *Dnahc5* mutant mouse model of primary ciliary dyskinesia (PCD), which showed that PCD is associated with a 40% incidence of CHD associated with heterotaxy. This observation reflects the known requirement for motile cilia function at the embryonic node for left-right patterning, and the essential role of motile cilia function in the respiratory epithelia for airway clearance.[9] Together, these findings suggest a common etiology involving ciliary dysfunction in PCD and heterotaxy, and the respiratory complications in these patients. Consistent with this, a retrospective study of 337 PCD patients showed a 6% incidence of heterotaxy, with 67% of the heterotaxy patients showing CHD.[10]

To further investigate whether airway cilia dysfunction may be linked with CHD associated with heterotaxy, we conducted a study of CHD-heterotaxy patients to assess the prevalence of airway ciliary dysfunction (CD). Patients were evaluated with 2 tests normally used to diagnose PCD. This included measurement of nasal nitric oxide, which is typically low in PCD patients, and video microscopy of nasal airway epithelia to examine possible abnormal airway cilia motility. From these studies, we determined 42% of patients with heterotaxy-CHD have CD similar to patients with PCD, including low or borderline-low nasal nitric oxide and abnormal airway ciliary motion.[11] Furthermore, sequencing analysis showed these patients were enriched for mutations in 10 known PCD genes, and analysis of respiratory symptoms suggested CHD-heterotaxy patients with CD older than 6 years of age have more respiratory symptoms.

In this study, we prospectively examined this same heterotaxy-CHD patient cohort, evaluating surgical outcomes in the subset of patients who underwent cardiac surgery. This included 52 surgical encounters in a total of 13 heterotaxy-CHD patients with CD (25 surgeries) and 14 heterotaxy-CHD patients without CD (27 surgeries). We hypothesized that CHD-heterotaxy patients with CD may have a higher morbidity/mortality rate and increased postoperative complications compared with CHD-heterotaxy patients without CD.

METHODS

Case Selection

This study was approved and conducted in accordance with the Children's National Medical Center Institutional Review Board. Patients with heterotaxy and CHD undergoing cardiac surgery at the Children's National Medical Center between 2005 and 2010 were enrolled prospectively in the study based on the inclusion and exclusion criteria as previously described.[11] Nasal nitric oxide measurements and videomicroscopy of airway epithelia were obtained during the preoperative evaluation or just before discharge.[11] Patient care team members were blinded to ciliary function status throughout study. Briefly, heterotaxy in this study was broadly defined as deviation from normal left-right asymmetry in any thoracoabdominal organ differing from situs solitus and situs inversus totalis.[12] Therefore, our case cohort comprised patients with congenital heart defects associated with laterality disorders, such as pulmonary, cardiovascular, gastrointestinal, splenic, and/or hepatobiliary systems. CHD patients are considered to have abnormal cardiovascular situs if they have dextrocardia/mesocardia, interrupted inferior vena cava, atrial-isomerism/ambiguous/inversus, atrioventricular discordance, superior/inferior ventricles, and ventricular-arterial discordance. Phenotype can be solely cardiovascular in nature without atrial isomerism. Isolated CHD comprising a double-outlet right ventricle with no other situs defects was excluded.

Outcome Data Collection

Relevant medical history and preoperative data including age at surgical intervention, preoperative weight, and history of neonatal respiratory distress were obtained from the medical records. Detailed surgical data and postoperative outcome data were recorded from progress notes, respiratory care data sheets, surgical reports, and discharge summaries. Postoperative length of stay; surgical procedures performed, particularly single-ventricle versus biventricular surgical tracks; and their RACHS-1 risk categories were detailed for each surgical encounter.[13] RACHS-1 risk categories have been shown to correlate well with in-hospital mortality and length of postoperative hospital stay, which allows for relevant comparisons between different groups undergoing surgery for CHD.[14]

Postoperative mortality, defined by death within 30 postoperative days or within the postoperative hospital stay, and mortality beyond the postoperative period were collected via the cardiothoracic surgical database or death certificates in electronic medical records. Extracorporeal membrane oxygenation (ECMO) support and use of inotropic and pulmonary vasodilator medications during the postoperative period were determined. Postoperative respiratory outcome measures including length of mechanical ventilation, placement of new tracheostomy, continued need for existing tracheostomy for ventilation, use of inhaled β-agonists, duration of initial postoperative chest tube, prolonged ventilatory course, and respiratory complications were gathered for each surgical encounter. Patients with existing tracheostomies preoperatively were evaluated thoroughly by the Department of Pulmonology to determine whether the tracheostomy was needed for ventilation. Respiratory complications were broadly defined to include failed extubations, respiratory failure, culture or polymerase chain reaction–positive respiratory infection, stridor, and radiographic evidence of pleural effusions, atelectasis, pneumothorax, and pulmonary edema.

A prolonged ventilatory course was defined as postoperative mechanical ventilation for longer than 10 days based on analyzing the distribution of postoperative mechanical ventilatory duration seen in our retrospective study at this institution, which represented the upper 10% of cases.[8] This definition of a prolonged ventilatory course was used previously in a pediatric cardiac surgical population.[15] Preoperative pulmonary vascular resistance (PVR) was obtained from cardiac catheterization reports for all patients who underwent hemodynamic evaluation before surgical intervention, with an increased PVR defined as 3 or more Woods unit $\times$ m^2. Medical records were reviewed extensively for a diagnosis or clinical suspicion of protein-losing enteropathy (PLE) including perioperative albumin levels. Length of follow-up evaluation was available for all patients and