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Research Article

Sinopulmonary Complications in the Setting of Bodily Isomerism

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Abstract

Introduction: Bronchial isomerism has been demonstrated to be present in the setting of bodily isomerism, or so-called heterotaxy. Bronchial morphology is usually concordant with atrial appendage morphology and has largely been considered to be simply an anatomic finding. This study aimed to investigate the functional implications of bronchial morphology.

Methods: Patients with bodily isomerism who received clinical care since 1998 at our institution were identified. General characteristics, echocardiographic data, surgical data, and data regarding sinopulmonary complications were collected. Sinopulmonary complications investigated included recurrent pneumonias, recurrent upper respiratory tract infections, recurrent ear infections, asthma, chronic lung disease, need for home oxygen and need for pulmonology follow-up. Categorical variables were analyzed using chi-square analysis while continuous variables were analyzed using Mann-Whitney-U test.

Results: A total of 74 patients with bodily isomerism were identified, 13 with left bronchial isomerism and 61 with right bronchial isomerism. Those with right bronchial isomerism tended to have their initial cardiac surgery at a younger age when compared to those with left bronchial isomerism. Those with left bronchial isomerism tended to have higher frequency of recurrent ear infections (23% vs 5%), need for home oxygen (54% vs 16%), and requiring pulmonology follow-up (39% vs 13%).

Conclusion: Bronchial isomerism does appear to have functional implications based on bronchial morphology. Left bronchial isomerism is associated with increased risk of recurrent ear infections, need for home oxygen, and need for pulmonology follow-up.

Keywords: *Sinopulmonary; Bronchial Isomerism; Heterotaxy; Asplenia*

Introduction

Bronchial isomerism is known to mirror bodily isomerism or so-called heterotaxy, and can be assessed by measuring the tracheobronchial angles using standard clinical imaging modalities. Bilateral tracheobronchial angles of less than 135 degrees are consistent with left bronchial isomerism while those greater are consistent with right bronchial isomerism [1,2].

Patients with bronchial isomerism can have abnormalities in multiple organ systems that are best defined by the morphology of the atrial appendices [3-7]. It is now appreciated that segregating patients with isomerism based on splenic anatomy alone is not optimal. In addition to bronchial isomerism, those with right or left appendiceal isomerism may have other congenital malformations. Those with right isomerism, for instance, will often have congenital malformations of the heart requiring univentricular palliation, right bronchial and pulmonary isomerism, intestinal malrotation, and multiple spleens. Those with left atrial isomerism will often have congenital malformations of the heart, will have left bronchial and pulmonary isomerism, and absence of the spleen [3,4,8-10]. These manifestations are more than just anatomic curiosities and will often have functional consequences as well [11-15]. For instance, those with either splenic anatomy, such as those with multiple spleens or even those with a solitary, normally located spleen have been thought to have functional asplenia, increasing the risk of bacteremia and thrombosis [16-19].

Although the immune status of heterotaxy patients was originally thought to be impaired secondary to their splenic status, it is known that these patient may frequently manifest issues related to cellular dyskinesia [20-22]. We hypothesized that those with bronchial isomerism may demonstrate a susceptibility to different sinopulmonary complications depending on whether they had left or right bronchial isomerism.

Methods

Data collection

The medical records of all patients with congenital malformations of the heart and isomerism who were cared for at the Children's Hospital of Wisconsin since 1998 were reviewed. We selected 1998 as this was the year that electronic medical records system was established. Our search included both those patients born in 1998 onwards as well as those born earlier but who continued to receive care at our institution since 1998. Congenital cardiac malformations included both intracardiac lesions as well as abnormalities of the systemic venous return to the heart. We considered isomerism to be present if there was a congenital malformation of the heart and: an abnormal arrangement of the thoracoabdominal organs including the bowel, liver, spleen or lungs. Medical records, medical billing data, and the cardiothoracic surgery database were all used in this search and were queried for "heterotaxy", "asplenia", "polysplenia", "malrotation". In addition, the echocardiography database was queried for "heterotaxy", "interrupted inferior vena cava" and bilateral superior vena cava in association with other structural heart disease.

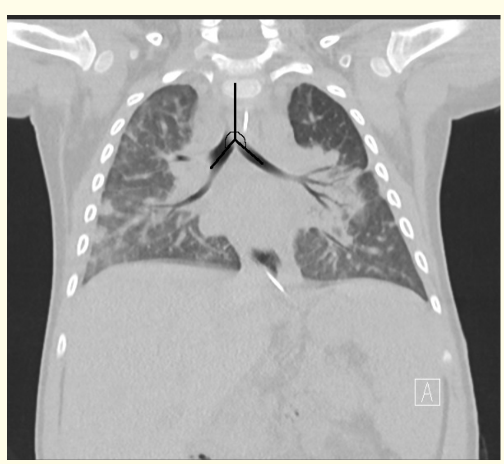
The study was approved by the Institutional Review Board at our institution.

Inferences regarding presence of left or right isomerism

As direct visualization of the atrial appendages at the time of surgical intervention was exceedingly infrequent in our cohort we utilized the intracardiac and extracardiac findings to assign right or left isomerism. Thus, alternative aggregate features employed to segregate patients including the presence and location of a coronary sinus, an interrupted suprarenal inferior caval vein, the presence of multiple spleens, the tracheobronchial angles, and intrapulmonary arterial branching pattern.

Assessment of bronchial angle

Available chest radiography, cardiac angiography, computed tomography, and magnetic resonance images were evaluated for each patient. Tracheobronchial angles were measured as previously described by each imaging modality available [1,2]. The left tracheobronchial angle was measured as the angle between the distal trachea and the proximal end of the left bronchus with the right tracheobronchial angle being measured as the angle between the distal trachea and the proximal end of the right bronchus (Figure 1). The average of the tracheobronchial angles by all available modalities was then used for analysis.



Assessment of outcomes

Recurrent upper respiratory infections were defined as viral or bacterial infections of the upper respiratory tract that from the nasal passages to the trachea with a frequency of at least 3 in 6 months or 4 or in 12 months. Recurrent ear infections were defined as at least 3 viral or bacterial ear infections in 6 months or 4 in 12 months. Recurrent pneumonia was defined as at least 3 viral or bacterial pneumonias in 6 months or 4 in 12 months. These were all assessed using all outpatient and inpatient notes available from our institution. Outside records from primary care physicians or other providers were not available for assessment of these outcomes.

History of chronic lung disease and asthma was assessed by the inpatient and outpatient notes available from our institution as well as the established problem list.

Statistical analysis

Cardiac phenotypic characteristics were compared amongst those with either right or left bronchial isomerism. Descriptive statistics are reported as either median and range or frequency and percentage. Continuous variables were compared using t-tests or Mann-Whitney-U tests where appropriate. Categorical variables were compared using chi-square analysis. P-values were considered statistically significant if less than 0.05. All statistical analysis was done using SPSS Version 20.0 (IBM, Chicago, IL).

Results

Patient characteristics

A total of 74 patients were identified and included in the analysis, 61 (82%) with right bronchial isomerism and 13 (18%) with left bronchial isomerism. Those with left bronchial isomerism were shown to have double inlet left ventricle and interruption of the inferior caval vein more frequently. Characteristically, absence of the spleen was usually associated with right bronchial isomerism and multiple spleens were generally associated with left bronchial isomerism but this finding was not absolute and there were significant variations in anatomic splenic anatomy. Antibiotic prophylaxis was nearly twice as likely to be prescribed for those with right bronchial isomerism. The nature of cardiac repair differed amongst the groups. A majority (61%) of patients with left bronchial isomerism had a biventricular repair while a majority (74%) of patients with right bronchial isomerism had a univentricular repair (Table 1).

	Left bronchial isomerism (n=13)	**Right bronchial isomerism (n=61)**	**p-value**
Atrioventricular septal defect	7 (54)	41 (67)	0.610
Double outlet right ventricle	2 (15)	25 (41)	0.082
Double inlet left ventricle	1 (8)	0 (0)	0.029
Bilateral superior caval vein	9 (69)	28 (46)	0.127
Left superior caval vein	9 (69)	31 (51)	0.227
Interrupted inferior caval vein	8 (62)	15 (25)	0.009
Discordant atrioventricular connection	1 (8)	13 (21)	0.255
Discordant ventriculoarterial connection	2 (15)	15 (25)	0.474
Genetic syndrome	0 (0)	11 (18)	0.097
Prenatal diagnosis	8 (62)	47 (77)	0.245
Age at postnatal heterotaxy diagnosis (days)	7.5 (0.0 to 92.0)	15.0 (1.00 to 825.0)	0.330
Death	1 (8)	13 (21)	0.255
Age at death (years)	3.9	0.5 (0.1 to 23.3)	0.928

Splenic anatomy *Absence of a spleen* *Solitary, normally located spleen* *Multiple spleens*	4 (31) 1 (8) 8 (61)	43 (70) 9 (15) 9 (15)	0.001
Antibiotic prophylaxis at any point	5 (39)	46 (75)	0.009
Age prophylaxis started (days)	3 (0 to 173)	7.5 (1 to 850)	0.755
Intestinal malrotation	8 (62)	26 (43)	0.214
Need for gastrointestinal tube	5 (39)	14 (23)	0.245
Arrangement of the abdominal organs *Midline liver with right or left sided stomach* *Left sided liver with right sided stomach* *Right sided liver with left sided stomach*	4 (31) 7 (54) 2 (15)	15 (25) 24 (39) 22 (36)	0.348
Chronic arrhythmia (not postoperative)	8 (62)	31 (51)	0.482
Need for pacemaker	4 (31)	8 (13)	0.117
Age at pacemaker placement (years)	13.8 (3.0 to 24.6)	0.1 (0.1 to 18.3)	0.544
Need for extracorporeal membrane oxygenation	2 (15)	7 (12)	0.695
Bacteremia	4 (31)	11 (18)	0.300
Repair status at most recent follow-up *Univentricular* *Biventricular* *Transplant*	5 (39) 8 (61) 0 (0)	45 (74) 13 (21) 3 (5)	0.013
Age at most recent follow-up (years)	6.6 (0.5 to 27.8)	3.8 (0.1 to 33.6)	0.423

Table 1: *patient characteristics.*

Cardiac surgery and respiratory support

Nearly all (92%) of those with left bronchial isomerism and all (100%) of those with right bronchial isomerism required cardiac surgery. Patients with right bronchial isomerism underwent initial cardiac surgery at an earlier age and required mechanical ventilation for a greater number of days postoperatively. Median age at initial cardiac surgery was 12 (0 to 871) and 86 (4 to 558) days in those with right and left bronchial isomerism, respectively (p = 0.046). Median number of postoperative ventilator days after the initial cardiac surgery was 0.5 (0.0 to 8.0) and 3.5 (0.0 to 114.0) days in those with right and left bronchial isomerism, respectively (p = 0.035). After the initial intervention, there were no other significant differences in the frequency subsequent cardiac surgeries, age at the time of these cardiac surgeries, or ventilatory support required after these surgeries (Table 2).

	Left bronchial isomerism (n=13)	Right bronchial isomerism (n=61)	p-value
Need for initial cardiac surgery	12 (92)	61 (100)	0.882
Age at initial cardiac surgery (days)	86.0 (4.0 to 558.0)	12.0 (0.0 to 871.0)	0.046
Need for mechanical ventilation before initial cardiac surgery	2 (15)	13 (21)	0.879
Extubated in the operating room after initial cardiac surgery	5 (39)	10 (16)	0.162
Need for reintubation after initial cardiac surgery	0 (0)	6 (10)	0.481
Total number of ventilator days after initial cardiac surgery	0.5 (0.0 to 8.0)	3.5 (0.0 to 114.0)	0.035
Length of hospital stay for initial cardiac surgery (days)	32.0 (4.0 to 134.0)	25.0 (3.0 to 235.0)	0.538

Need for second cardiac surgery	10 (77)	47 (77)	0.992
Age at second cardiac surgery (years)	0.4 (0.1 to 10.1)	0.6 (0.1 to 5.8)	0.703
Need for mechanical ventilation before second cardiac surgery	1 (8)	4 (7)	0.980
Extubated in the operating room after second cardiac surgery	4 (31)	15 (25)	0.860
Need for reintubation after second cardiac surgery	0 (0)	3 (5)	0.273
Total number of ventilator days after second cardiac surgery (days)	2.0 (0.0 to 15.0)	1.0 (0.0 to 95.0)	0.676
Length of hospital stay for second cardiac surgery (days)	29.0 (5.0 to 197.0)	15.5 (0.0 to 235.0)	0.668
Need for third cardiac surgery	4 (31)	21 (34)	0.760
Age at third cardiac surgery (years)	4.2 (0.4 to 17.1)	4.1 (0.5 to 18.3)	0.744
Need for mechanical ventilation before third cardiac surgery	0 (0)	1 (2)	0.884
Extubated in the operating room after third cardiac surgery	2 (15)	11 (18)	0.938
Need for reintubation after third cardiac surgery	0 (0)	1 (2)	0.897
Total number of ventilator days after third cardiac surgery	0.0 (0.0 to 6.0)	0.0 (0.0 to 6.0)	0.524
Length of hospital stay for third cardiac surgery (days)	15.0 (6.0 to 197.0)	8.0 (0.0 to 44.0)	0.035
Recurrent upper respiratory infections	4 (31)	8 (13)	0.117
Recurrent ear infections	3 (23)	3 (5)	0.029
Recurrent pneumonia	0 (0)	3 (5)	0.414
Chronic lung disease	2 (15)	6 (10)	0.559
Asthma	3 (23)	6 (10)	0.185
Requiring pulmonology follow-up	5 (39)	8 (13)	0.029
Need for home oxygen at any point (non-tracheostomy)	7 (54)	10 (16)	0.004

Table 2: *Outcomes.*

Sinopulmonary symptoms

The frequency of sinopulmonary diagnoses was significantly different in those with right and left bronchial isomerism. Those with left bronchial isomerism were significantly more likely to have recurrent ear infections, need for pulmonology follow-up, and need for home oxygen. Recurrent ear infections were present in 5% and 23% of those with right and left bronchial isomerism, respectively ($p = 0.029$). Need for pulmonology follow-up was required 13% and 39% of those with right and left bronchial isomerism, respectively ($p = 0.029$). There was a need for home oxygen was present in 15% and 54% of those with right and left bronchial isomerism, respectively ($p = 0.004$). No statistically significant differences were noted in the frequency of recurrent upper respiratory infections, recurrent pneumonia, chronic lung disease, or asthma.

Discussion

Bronchial isomerism identified is the imaging feature most likely to reflect isomeric status. It was Van Mierop and colleagues who initially demonstrated and corroborated this by necroscopy findings with subsequent confirmation by Landing and colleagues [23]. Shortly thereafter, Partridge and colleagues were able to demonstrate the role of chest radiography in making this determination. This study noted that a ratio of less than 1.5 between the lengths of the right and left-sided bronchi from the carina to the first branching was consistent with bronchial isomerism, a ratio of 1.5 and 2.0 was suggestive, while a ratio of greater than 2.0 was consistent with asymmetric bronchi. Tracheobronchial angles of less than 135 degrees were also found to be consistent with left isomerism while tracheobronchial angles of greater than 135 degrees were found to be consistent with right isomerism. Right and left bronchial isomerism was also found to be distinguishable by means of the ratio between the bronchial length and tracheal width [1]. These findings have now all been confirmed by modern day clinical imaging such as computed tomography, and magnetic resonance imaging.

The clinical implication of bronchial isomerism has not been well studied. Our current study demonstrates that there are significant clinical differences between those with right and left bronchial isomerism with those with left bronchial isomerism with regard to requirement for earlier initial cardiac surgery, days required of postoperative mechanical ventilation after initial cardiac surgery, the greater risk of recurrent ear infections, need for pulmonology follow-up, and need for home oxygen therapy.

While it is intuitive that those with absence of a spleen will have splenic dysfunction and increased infection risk, those with bodily isomerism and multiple spleens or even a normally located, solitary spleen may have splenic dysfunction which has been associated with increased risk of bacteremia and thrombosis [16,17]. The mechanism of this increased risk is unknown.

Similarly, to splenic anatomy and function, the mechanism behind the functional differences between isomeric right and left bronchi is unclear. Both bronchial and lung morphology coincided with one another and thus either could mediate these differences.

Significant differences exist between the morphologic right and left lungs. Studies have demonstrated differences in lung volumes between the normal morphologic right and left lungs with the right lung demonstrating greater volumes [24-26]. Regional distribution of ventilation also differs between the morphologic right and left lungs and may be altered by positional changes [27,28]. The differences in ventilation are not clearly understood and to date, no studies have been able to provide definitive mechanisms accounting for these differences.

It is increasingly recognized that ciliary dyskinesia, abnormalities in ciliary motion, play a role in the developing of congenital malformations of the heart. This must be differentiated from primary ciliary dyskinesia which is attributable to an altered ultrastructural abnormality. Ciliary dyskinesia can be demonstrated in approximately half of patients with isomerism and has been demonstrated to impact the need for postoperative respiratory support and in development sinopulmonary disease [20-22]. To date, no studies have demonstrated significant differences in the degree or presence of ciliary dyskinesia between right and left isomerism. It may be possible that the degree of ciliary dyskinesia may differ between those with right and left isomerism which may account for the differences found in our study. A combination of both lower lung volumes in those with left bronchial isomerism and the presence of ciliary dyskinesia may potentially mediate some of these differences as well.

Increasing understanding of isomerism has demonstrated additional functional consequences. The functional consequences of isomerism were first noted in respect to the spleen and the understanding that not only was absence of a spleen associated with functional asplenia but also presence of multiple spleens or even a solitary, normally located spleen This study has raised concerns about the increased frequency of sinopulmonary complications in this population which appears to validate concerns of ciliary dyskinesia, which may also be the underlying factor mediating functional asplenia in those with various splenic anatomy. It, thus, is vital for isomerism to be identified in patients. This can be done when there is an intracardiac lesion or a systemic venous abnormality in addition with one of the following: bronchial isomerism, abnormal arrangement of the stomach and liver, abnormal splenic anatomy, or intestinal malrotation. Isomerism can then be segregated into right or left based on direct visualization of the atrial appendages at the time of cardiac surgery, evaluation of the atrial appendages at the time of cardiac computed tomography studies, or by inference using an aggregate of intracardiac and extracardiac findings [29].

The use of the terms isomerism, asplenia, or polysplenia in isolation do not identify the more practical aspects of living with these conditions. Venous abnormalities, ciliary dyskinesia, cardiac conduction abnormalities, intestinal malrotation, and the risk of bacteremia are not conveyed by use of these terms in isolation. Use of the splenic syndromes to classifieds isomerism is also not optimal as it now understood that morphology of the atrial appendages is what better correlates with isomerism and not splenic anatomy [4,5]. Thus, use of right or left isomerism conveys the most information.

The current study is not without its limitations. Firstly, the retrospective nature of this study leaves it vulnerable to deficiencies in documentation from which the clinical data was extracted. Our study also relies on clinical derived inferences as opposed to autopsy or surgical inspection for assignment of right and left isomerism. This does however represent the current clinically employed methods of diagnosis in these conditions. This may be inadequate to identify some patients. The small number of patients also limits this current analysis.

Prospective studies and improved data reporting may further delineate the significance of problems inherent with isomerism and provide the substrate for defining the mechanisms involved in increased postoperative support requirements as well as increased sino-pulmonary infections. These efforts may assure improving the care of patients with isomerism and improve survival. An emphasis on direct visualization of both atrial appendages at the time of cardiac surgery or evaluation of appendage morphology at the time of cardiac computed tomography will help segregate patients accurately into right or left isomerism and improve future academic endeavors.

Conclusion

Bronchial isomerism, in the setting of bodily isomerism, has functional implications. Those with left bronchial isomerism are more likely to undergo initial cardiac surgery at an earlier age, require more days of mechanical ventilation after initial cardiac surgery, have recurrent ear infections, require home oxygen, and require pulmonology follow-up.

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