Heterotaxy Syndrome: Implications for Anesthesia Management

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HETEROTAXY SYNDROME (HS) results from failure of the developing embryo to establish normal left-right (L-R) asymmetry and is associated with a wide range of major cardiac and extracardiac congenital anomalies. The estimated incidence of HS is 1 in 6,000 to 1 in 20,000 live births.[1] If abortions and stillbirths are included, heterotaxy is found more frequently (0.03%-1.1% of fetuses).[2,3]

Many patients with HS require anesthesia for diagnostic or surgical procedures. Patient outcome previously was poor, but it has improved recently because of a better understanding of the genetic and embryologic aspects of heterotaxy and advances in patient management.[4,5] Consequently, cardiac anesthesiologists are now likely to encounter pediatric and adult patients with HS. Although there are some excellent, current reviews of HS in the genetic, radiology, cardiology, and surgical literature,[5-10] there is very little published to guide the anesthesiologist. The present authors attempt to address this deficiency by summarizing some recent information about HS and discussing the anesthetic challenges presented by the syndrome.

THE DEFINITION OF HETEROTAXY

Heterotaxy is a congenital disorder caused by failed embryonic development of normal L-R asymmetry. The resulting defects are characterized by segmental discordances along the L-R axis. The term "heterotaxy" derives from the Greek word *heteros*, which means other, and *taxis*, which means order or arrangement (ie, other than normal arrangement[5]).

In its broadest sense, heterotaxy encompasses any abnormality of organ situs and some associated disorders of ciliary function. The nomenclature describing the anatomic defects in HS has been complex and controversial (see Table 1 for definitions of commonly used terms).[6,7] A recent article by Jacobs et al[8] on the nomenclature, definition, and classification of cardiac structures in the setting of heterotaxy provides clarity and is recommended. Some authors use heterotaxy interchangeably with situs ambiguus, a more restricted anatomic designation. Situs ambiguus is present when the thoracic and abdominal organs are positioned in such a way with respect to each other as to be not clearly lateralized and thus have neither the usual (situs solitus) nor the mirror-imaged (situs inversus) arrangements.

L-R ASYMMETRY IN EMBRYONIC DEVELOPMENT

Asymmetric positioning of the visceral organs along the L-R axis is visible first on embryonic day 23 when the heart forms a rightward loop. Recent animal studies suggest that endodermally derived ventral node cells play a crucial role in generating correct L-R asymmetry.[11] The ventral node, a transient midline structure that forms during gastrulation (Fig 1), has centrally located, specialized, motile monocilia that contain the motor protein left-right dynein. Unlike conventional cilia, the monocilia rotate clockwise and tilt 40° posterior, such that the rightward sweep is close to the surface and the leftward sweep is away from the surface, thus producing laminar leftward flow of the extraembryonic fluid surrounding the node (Fig 2). Nodal flow initiates a multistep process that concludes when regional, molecular asymmetry is converted into asymmetric organogenesis via differential control of cell proliferation, migration, and/or cell death.[6,12,13]

Experimental data support 2, perhaps complementary, models of how asymmetric gene expression emanates from nodal flow.[7,14-16] The first model proposes that nodal flow produces concentration gradients of secreted morphogens. In the second model, motile cilia in the central portion of the node generate nodal flow. Immotile cilia on the border of the node sense the flow, and the cells harboring them activate the genes in asymmetric fashion (Fig 3).

When the midline barrier separating left from right is disrupted, molecules that are normally asymmetrically distributed in early embryos get mixed together, resulting in abnormal organ sidedness later in development. About 40% of patients with HS have midline-associated defects.[17,18]

GENETIC AND ENVIRONMENTAL FACTORS

Model organism studies have shown that the functions of more than 80 genes are required for normal asymmetric L-R organ development. The true incidence of human L-R patterning defects is not yet known; further definition of the molecular basis may identify a higher incidence than currently has been appreciated.

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Table 1. Terms Commonly Used in the Setting of HS

Situs solitus	The normal arrangement of thoracic and visceral anatomy.
Heterotaxy	Any abnormality in which the internal thoracoabdominal organs show abnormal arrangement across the L-R axis of the body.
Situs inversus totalis	Complete mirror image arrangement of all internal organs.
Situs ambiguus	Situs ambiguus is defined as an abnormality in which there are components of situs solitus and situs inversus in the same person. The thoracic and abdominal organs are not clearly lateralized. Congenital anomalies usually are present.
Isomerism	An isomerism in the context of the congenitally malformed heart is defined as a situation in which some paired structures on opposite sides of the L-R axis of the body are symmetric mirror images of each other.
Left isomerism	A subtype of heterotaxy syndrome characterized by bilateral left-sidedness including 2 left atrial appendages, other cardiovascular malformations, polysplenia, and bilateral bilobed lungs.
Right isomerism	A subtype of heterotaxy syndrome characterized by bilateral right-sidedness including 2 right atrial appendages, other cardiovascular malformations, asplenia, and bilateral trilobed lungs.
Asplenia	No spleen.
Polysplenia	Abnormal formation of splenic tissue including a single spleen with multiple septae or multiple splenules.
Asplenia syndrome	See right isomerism.
Polysplenia syndrome	See left isomerism.
Ivemark syndrome	Initial cases described by Ivemark had asplenia and cardiovascular malformations, subsequently generalized to refer to asplenia or polysplenia cases.
Kartagener syndrome	Ciliary dyskinesia, bronchiectasis, sinusitis, and infertility.
Laterality defect	Any deviation from situs solitus also includes the failure to generate asymmetry (eg, midline liver and persistence of bilateral superior vena cava).
Dextrocardia	Right-sided heart position within the chest rather than in its normal left-sided location; the apex (tip) of the heart points to the right rather than to the left.

Data from Zhu et al.[6]

Situs ambiguus comprises approximately 3% of congenital heart-defect cases and has an estimated prevalence of 1 in 10,000 live births.[3] The genetics of situs ambiguus are characterized by locus and allelic heterogeneity, reduced penetrance, variable expression, probable gene-environment interactions, and occurrence in conjunction with chromosomal disorders or multisystem syndromes.[6] Familial clustering of situs ambiguus may be from autosomal dominant, autosomal recessive, or X-linked inheritance. Most cases of situs ambiguus are sporadic. However, careful phenotypic characterization of family members has identified isolated cardiac and noncardiac defects in "unaffected" individuals,[19] and in some cases gene mutations have been implicated.[20] Approximately 10% of infants with HS have a close relative with congenital heart defects. A family history of a congenital heart defect was significantly associated with heterotaxy (odds ratio = 5.1; 95% confidence interval,

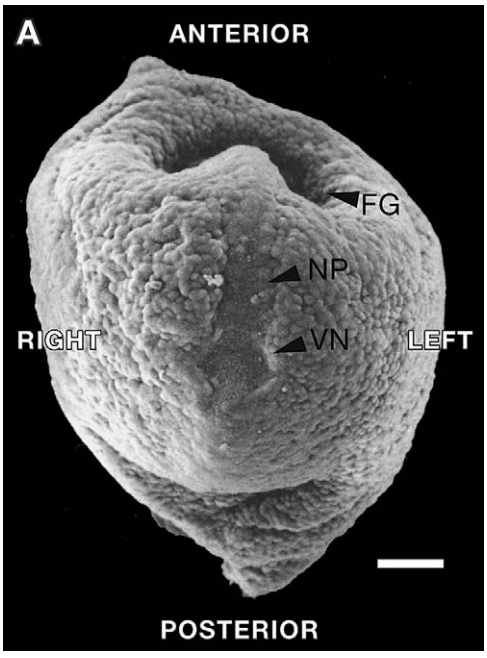

Fig 1. A scanning electron micrograph shows the ventral view of a 7.5-dpc mouse embryo. VN, ventral node; NP, notochordal plate; FG, foregut; Bar, 100 μm. (Reprinted with permission from Hirokawa N, Tanaka Y, Yasushi Okada Y, et al: Nodal flow and the generation of left-right asymmetry. Cell 125:33-45, 2006.)

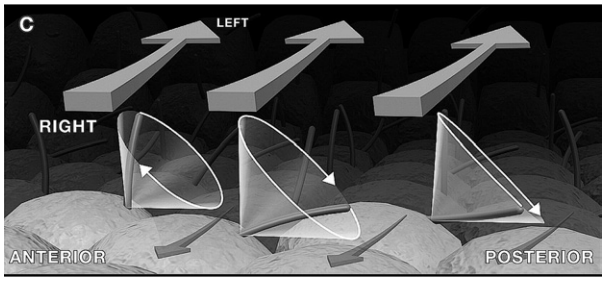

Fig 2. Unlike conventional beating cilia, the monocilia in the node have a clockwise rotational motion. The axis of rotations is tilted 40° ± 10° to the posterior from the vertical angle. As a consequence, the cilia make a leftward swing away from the surface and a rightward sweep near the surface. According to hydrodynamics, a stationary surface retards the movement of fluids by shear resistance. Thus, the rightward sweep is less effective than the leftward swing in generating fluid movement. (Reprinted with permission from Hirokawa N, Tanaka Y, Yasushi Okada Y, et al: Nodal flow and the generation of left-right asymmetry. Cell 125:33-45, 2006.)

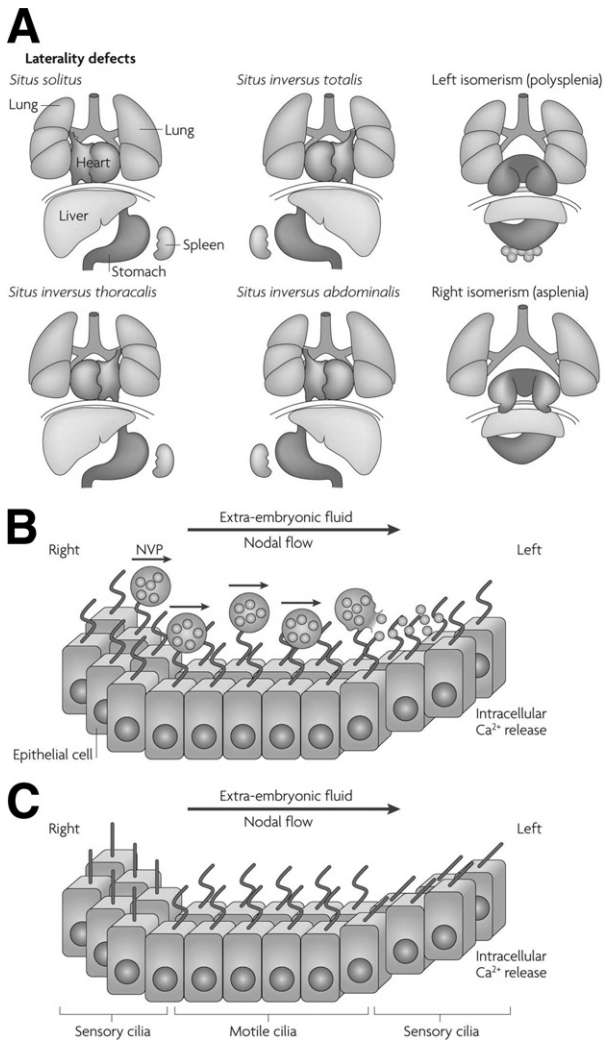

Fig 3. Human laterality disorders and current models for establishing L-R asymmetry. (A) A schematic illustration of normal L-R body asymmetry (situs solitus) and 5 laterality defects that affect the lungs, heart, liver, stomach, and spleen. By their vigorous circular movements, motile monocilia at the embryonic node generate a leftward flow of extraembryonic fluid (nodal flow). (B) The nodal vesicular parcel model predicts that vesicles filled with morphogens (such as sonic hedgehog and retinoic acid) are secreted from the right side of the embryonic node and transported to the left side by nodal flow where they are smashed open by force. The released contents probably bind to specific transmembrane receptors in the axonemal membrane of cilia on the left side. The consequent initiation of left-sided intracellular Ca2+ release induces downstream signaling events that break bilaterality. In this model, the flow of extraembryonic fluid is not detected by cilia-based mechanosensation. (C) In the 2-cilia model, nonsensing motile cilia in the center of the node create a leftward nodal flow that is mechanically sensed through passive bending of nonmotile sensory cilia at the periphery of the node. Bending of the cilia on the left side leads to a left-sided release of Ca^{2+} that initiates the establishment of body asymmetry. (Reprinted with permission from Fliegauf M, Benzing T, Omran H: When cilia go bad: Cilia defects and ciliopathies. Nat Rev Mol Cell Biol 8:880-893, 2007.)

2.0-12.9).[21] Gene mutations associated with heterotaxy are detected increasingly in patients with isolated cardiac malformations, such as transposition of the great arteries.[22-24] Laterality defects also have been associated with environmental exposures,[11] maternal diabetes, and first-trimester cocaine use.[21]

Situs inversus is estimated to occur in 1 in 8,000 to 25,000 individuals.[9] Most cases are caused by ciliary abnormalities (the primary ciliary dyskinesia disorders) and inherited in an autosomal recessive fashion. Situs ambiguus occurs in only a small number of patients with primary ciliary dyskinesia.

CLINICAL PRESENTATION AND DIAGNOSTIC WORKUP

The great majority of patients with HS have complex, congenital heart disease although, in rare instances, the heart may be normal in patients who have visceral heterotaxy.[25-27] Malformations associated with HS are listed in Table 2. In 1955, Ivemark[28] categorized the features of HS into asplenia and polysplenia syndromes (Table 3). Patients with asplenia usually have right isomerism of the atrial appendages, whereas those with polysplenia usually have left isomerism of the atrial appendages.[29] Although certain anatomic features are specific to one or the other syndrome, some features are common to both.[30,31] Malformations in patients with a single, right-sided spleen are similar to those with asplenia.[25] Extracardiac malformations often involve midline structures.[17,32]

Fetal Diagnosis and Fetal Death

Cardiac disease in the fetus generally is first detected echocardiographically at 18 to 20 weeks of gestation. Heterotaxy appears to be one of the easier cardiac lesions to diagnose prenatally,[33] perhaps because major extracardiac anomalies are relatively common.[34] Consistent findings in left atrial isomerism are a large azygos continuation of an interrupted inferior vena cava, atrioventricular block with structural heart disease, and viscerocardiac heterotaxy.[35] Discrepancy between the position of the stomach and the cardiac apex, particularly if associated with a midline liver, is often the first clue of HS. However, Cohen et al[36] found that prenatal diagnosis did not improve outcome even if immediate aggressive care was given after birth. Severe forms of HS are associated with fetal death.[35] Risk factors include complete heart block, atrioventricular septal defect, pulmonary outflow obstruction, totally anomalous pulmonary venous connection, and noncompacted myocardium.[35-38]

Postnatal Diagnosis

Nearly all neonates with the asplenia phenotype present with cyanosis heart disease, and they may have ductal-dependent pulmonary flow.[25] In contrast, the more variable cardiac malformations in polysplenia cause less severe hemodynamic compromise.[25,39] However, patients with left atrial isomerism are more likely to have congenital complete heart block, a factor associated with poor outcome.[40]

Ultrasound can determine the situs of abdominal organs,[41-44] particularly abnormal liver symmetry and presence of the spleen and gallbladder. Magnetic resonance imaging is very

Table 2. Malformations That Can Be Associated With the HS

Organ System	Malformation
Cardiovascular	Atrial isomerism
	Atrioventricular discordance
	Double-outlet right ventricle
	Single ventricle
	Septal defects, including atrioventricular septal defect
	Pulmonary stenosis or atresia
	Left ventricular outflow tract obstruction
	Transposition of the great arteries
	Total/partial anomalous venous return
	Interrupted inferior vena cava
	Bilateral superior vena cava
	Right aortic arch, dextrocardia
	Conduction system abnormalities
	Myocardial noncompaction
Nervous system	Encephalocele
	Holoprosencephaly, hydranencephaly
	Porencephalic, cerebellar or Dandy Walker cysts
	Dysgenesis or agenesis of the corpus callosum
	Atrioventricular malformations of the midbrain
	Hypo- or dysplasia or agenesis of the cerebellum
	Diplo- or hydromyelia
	Myelomeningocele
Skeleton	Hypoplasia or dysostosis of cranial bones
	Pectus carinatum, hypoplasia of the sternum
	Vertebral or rib anomalies, kyphosis/scoliosis
	Caudal regression, bifid sacrum, sacral agenesis
	Short limbs, campomelia, amelia, absence of radii
	Split hand malformation, clubbing of hands, polydactyly
	Equinovarus
Craniofacial	Micro- or anophthalmia, cyclopia, coloboma
	Choanal atresia
	Agnathia/micrognathia
	Cleft lip/palate, high arched palate
Respiratory tract	Laryngeal cleft or hypoplasia
	Tracheoesophageal fistula, tracheal or esophageal atresia
	Pulmonary hypoplasia
Gastrointestinal tract	Omphalocele
	Duplication, hypoplasia or angiodysplasia of the stomach
	Duodenal atresia
	Congenital short bowel
	Anal stenosis or atresia
	Hirschsprung's disease
Pancreas	Hypoplasia, (polycystic) malformations
Liver	Absence of the gallbladder, extrahepatic biliary atresia
	Polycystic liver, ectopic liver tissue in the adrenal glands
Adrenal glands	Horseshoe adrenal
Genitourinary tract	Duplication of the hindgut and genitourinary tract
	Renal agenesis or hypoplasia, cystic malformations, horseshoe kidney
	Testicular hypoplasia
	Penis duplication, hypospadias
	Urethral duplication or urethral valves
	Agenesis of the ovaries
	Duplicated, bi- or unicornuate uterus, vaginal atresia or duplication
Other	Single umbilical artery
	Intrauterine growth retardation
	Cervical lymphocele
	Primary ciliary dyskinesia disorders
	Diaphragmatic hernia

Data from Bartram et al.[5]

helpful for defining extracardiac and cardiac anomalies.[42,44,45] An upper gastrointestinal contrast study screens for abnormalities of intestinal rotation and associated digestive tract disorders whose incidence in HS patients is 40% to 90%.[17,26,42,46-52] Computed tomography imaging will show pancreatic and airway anomalies.[53] A splenic scan can show the presence of one or more small spleens,[25,39] and the presence of Howell-Jolly bodies in a blood smear indicates asplenia or a degree of hyposplenism that represents an increased risk for infections.[54]

Because HS is associated with a wide variety of complex, cardiac malformations, the evaluation of cardiovascular anatomy by echocardiography requires careful evaluation of each cardiovascular segment.[7] A chest x-ray helps assess cardiac situs and size, pulmonary blood flow, bronchial anatomy, liver symmetry, and stomach situs. A lateral chest x-ray that shows widening of the mediastinum (azygous vein enlargement) and absence of an inferior vena cava shadow suggests an interrupted inferior vena cava.[42] An electrocardiogram may help assess atrial situs and conduction abnormalities. Initial Q waves in the right-sided leads are a sign of ventricular inversion (L-loop).[25] Cardiac catheterization, computed tomography scans, and magnetic resonance imaging may be necessary in some patients to completely delineate cardiac anatomy; assess cardiac function, fibrosis, and ventricular mass; and thereby guide clinical management.

Primary Ciliary Dyskinesia Disorders

Primary ciliary dyskinesia (PCD) is a genetically heterogenous disorder usually inherited as an autosomal recessive trait. Estimated incidence is 1 in 30,000. New diagnostic tests include the measurement of nasal nitric oxide production and systematic analysis for mutations in genes encoding ciliary proteins.[55]

The clinical manifestations reflect ciliary dysfunction (Table 4).[9,56] Patients with PCD develop lung disease because mucociliary clearance is impaired. The disease typically progresses to overt bronchiectasis during late childhood, and it can ultimately cause chronic respiratory failure.[57] Most (95%) PCD patients have recurrent otitis media and sinusitis. Almost all male PCD patients are infertile because of sperm dysmotility. In female PCD patients, ciliary dysfunction in the fallopian tubes may contribute to subfertility.

Dysfunction of the embryonic node monocilia is associated with the complete mirror image of the usual arrangement of thoracic and abdominal organs (situs inversus totalis) in ap-

Table 3. Asplenia and Polysplenia Syndromes

Feature	Asplenia (Bilateral Right-Sidedness)	Polysplenia (Bilateral Left-Sidedness)
No malformations	Asplenia rarely is reported to occur without other severe malformations in individuals with situs solitus or complete situs inversus.	Asymptomatic polysplenia with heterotaxia occurs without severe or complex cardiac or visceral malformation.
Extracardiac malformations	Common in such systems as gastrointestinal, genitourinary, bronchopulmonary, axial skeletal, and central nervous systems.	Common in such systems as gastrointestinal, genitourinary, bronchopulmonary, axial skeletal, and central nervous systems. Extrahepatic biliary atresia (EHBA) is uniquely associated with polysplenia, and it has been estimated that 10% ± 20% of patients with EHBA have associated polysplenia malformations.
Sex	Male >female.	Male = female.
Liver	Bilaterally symmetrical (76%-91%).	Bilaterally symmetrical (50%-67%).
Lung lobation	Bilaterally trilobed (81%-93%).	Bilaterally bilobed (72%-88%).
Bronchial position*	Bilaterally eparterial (95%).	Bilaterally hyparterial (68%-88%).
Cardiac malformations	Often functionally univentricular heart. Outcome poor.	Often functionally biventricular heart. Outcome better than right isomerism.
Congenital heart malformations	99%	90%
Superior vena cava	Bilateral (46%-71%) to ipsilateral atria.	Bilateral (33%-50%) to the ipsilateral atria or 1 coronary sinus.
Coronary sinus	Absent.	Present or absent.
Inferior vena cava	The inferior vena cava and the abdominal aorta usually have an anomalous relationship, both lying on the same side of the spine, regardless of the side occupied by the vena cava. A separate and contralateral hepatic vein is present 28% of the time.	Interrupted with azygos continuation and separate hepatic drainage to atria (58%-100%).
Pulmonary veins	Total anomalous connection, either to a superior vena cava or to an infradiaphragmatic connection (64%-72%).	Partial anomalous pulmonary connection (usually 2 veins to each atrium), infrequently total anomalous venous connection (37%-50%).
Coronary sinus	Absent (80%-85%)	Absent (26%-42%)
Atrial septum	Secundum atrial septal defect and primum atrial septal defect. Common atrium (57%).	Secundum atrial septal defect or primum atrial septal defect. Common atrium (25%-30%).
Atrioventricular junction	Atrioventricular septal defects (84%-92%).	Atrioventricular septal defects (80%).
Ventricles	Ventricular component of atrioventricular septal defect. Often unbalanced with hypoplasia/absence of 1 ventricle (44%-55%), 42% have either left ventricular hypoplasia or an absent left ventricle, and 13% have right ventricular hypoplasia or an absent right ventricle. Two well-developed ventricles (45%).	Ventricular septal defect or ventricular component of an atrioventricular septal defect or single ventricle. Hypoplasia/absence of 1 ventricle (37%), left ventricular hypoplasia in 24%, and right ventricular hypoplasia in 13% of cases. Two well-developed ventricles (63%). Ventricular noncompaction (rare association).
Position of the heart	Dextrocardia (36%-41%).	Dextrocardia (33%-42%).
Obstruction to blood flow	Subvalvar and valvar pulmonary stenosis or atresia (88%-96%).	Subvalvar and valvar pulmonary stenosis or atresia (42%-43%). Mitral, subaortic, aortic stenosis or atresia (17%-22%). Coarctation of aorta.
Ventriculoarterial relationship	Double-outlet right ventricle (82%). Transposition of great arteries (9%).	Double-outlet right ventricle (17%-37%). Transposition of great arteries (2%).
Coronary arteries	Single coronary artery (19%).	Two coronary arteries.
Conduction: Sinoatrial node	Usually bilateral sinus nodes, located in venoatrial grooves.	Usually absent or hypoplastic, located close to atrioventricular junction.
Conduction: Atrioventricular node	Variable number and location. Depends on ventricular topology and morphology (see text).	Variable number and location. Depends on ventricular topology and morphology (see text).

Data from:

Van Praagh S, Santini F, Sanders SP: Cardiac malpositions with special emphasis on visceral heterotaxy (asplenia and polysplenia syndromes), in Fyler DC (ed): Nadas' Pediatric Cardiology. Philadelphia, PA, Hanley & Belfus/Mosby, 1992, pp 589-608

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Rose et al.[39]

Applegate et al.[42]

Phoon CK, Neill CA: Asplenia syndrome: Insight into embryology through an analysis of cardiac and extracardiac anomalies. Am J Cardiol 73:581-587, 1994

*An eparterial bronchus branches superior to the first lobar division of the pulmonary artery. A hyparterial bronchus branches inferior to the first lobar division of the pulmonary artery.

Table 4. Clinical Manifestations of Primary Ciliary Dyskinesia

Organ	Clinical Manifestation
Lung	Respiratory distress in term neonates
	Bronchitis/recurrent infections
	Bronchiectasis
Ears	Otitis media
	Hearing loss
	Cholesteatoma (after tympanostomy)
Nares/sinus	Chronic sinusitis
	Polyposis
Genitourinary tract	Male infertility
Organ laterality	Situs inversus totalis
	Situs ambiguous with cardiac and extracardiac anomalies
Central nervous system	Hydrocephalus (rare)

Reprinted with permission from Morillas et al.[9]

proximately half of the PCD patients due to randomization of L-R body asymmetry.[15] The presence of PCD with chronic sinus and airway infections, coupled to situs inversus, also is referred to as "Kartagener" syndrome. Some (6%) PCD patients have situs ambiguus.[58] Patients with situs inversus or situs ambiguus should be evaluated for PCD, and PCD patients should have a cardiac evaluation.[9]

ANESTHESIA FOR PATIENTS WITH HETEROTAXY

There is a dearth of information about HS in the anesthetic literature. Kinney et al[59] described an anesthetic protocol for children undergoing cardiac magnetic resonance imaging. Leung et al[60] reported an infant with asplenia who developed intraoperative hyperthermia on 3 occasions. The suggested mechanism was a fentanyl-induced alteration in thermoregulation with activation of nonshivering thermogenesis.[60]

The wide diversity of the heterotaxy phenotype precludes full consideration of all anesthetic implications of each anomaly. The authors' intention is to list those aspects of the HS that may be pertinent to anesthesia management (Table 5) and to discuss some in greater detail.

Cardiac Anomalies

Most patients with HS have congenital heart anomalies. The perioperative challenges encountered when managing these children can be grouped simplistically as (1) abnormal vasculature, (2) single-ventricle concerns, (3) complex cardiac anomalies, and (4) conduction abnormalities.

Abnormal Vasculature

The abnormal situs and relationship of thoracic structures may prompt the cardiac surgeon to modify the surgical approach. Examples of abnormal vasculature include (1) the vascular anatomy hinders optimal surgical exposure, thereby necessitating cardiopulmonary bypass (CPB) for a procedure usually performed off-pump; (2) bilateral superior vena cavae may influence CPB cannulation strategies; and (3) a right aortic arch will influence placement of an aortopulmonary surgical shunt. Surgical trauma to the phrenic or recurrent laryngeal nerves is perhaps more likely with HS.

Likewise, anesthetic management might have to be modified because of abnormal vascular anatomy. For example, patients with a right aortic arch could have an aberrant course of the subclavian artery that might influence the choice of the site for arterial blood pressure monitoring. The aorta or other arteries may impinge on the esophagus, pulmonary veins, trachea, or bronchi. Transesophageal echocardiographic probe compression of structures can compromise ventilation and hemodynamics.

A totally anomalous return to an extracardiac site (often with obstruction of blood flow) is seen commonly in those with isomeric right atrial appendages but rarely is seen in the setting of isomerism of the left appendages. In contrast, those with isomerism of the left atrial appendages usually have abnormal drainage of all or some of the pulmonary veins to the right side of the atrial mass, with displacement of the primary atrial septum to the left side of the common atrial chamber.[61] Total anomalous pulmonary venous return is associated with poor outcome not only at initial presentation but also later because recurrent pulmonary vein stenosis with resultant pulmonary hypertension is not tolerated, especially in patients with single-ventricle physiology.[62]

Patients with a single ventricle and an interrupted inferior vena cava have separate hepatic drainage to the atria. Therefore, hepatic blood flows to the systemic and not the pulmonary circulation. This anatomy is associated with the development of acquired arteriovenous and venovenous collaterals that may result in a pulmonary right-to-left shunt and cyanosis. Also, in patients who have undergone a Fontan procedure, a right-to-left shunt with "steal" of pulmonary artery flow can occur via the azygous system.[7]

Single-Ventricle Management

Many HS patients with heart anomalies have single-ventricle physiology. Management challenges include (1) neonatal issues, (2) optimizing the balance between pulmonary and systemic blood flow, (2) cardiac surgery (often complex repairs such as Norwood variant procedures), (4) repeat surgery (eg, staged single-ventricle palliation), and (5) bidirectional Glenn (cavopulmonary anastomosis) and Fontan physiology and complications. Heterotaxy patients are more likely to have risk factors associated with poor Fontan outcome, including abnormal heart rhythm,[36] atrioventricular valve regurgitation, a morphologically dominant right ventricle, pulmonary vein stenosis, increased pulmonary vascular resistance, obstruction of ventricular outflow tract or aorta, and significant noncardiac anomalies.[63] Myocardial function may be compromised by fibrosis, ischemia, volume overload, increased afterload, CPB, noncompaction,[38] and other factors.

Complex Cardiac Anomalies

Many of the anomalies include atrioventricular discordance, an unbalanced atrioventricular canal defect, double-outlet right ventricle, right and/or left ventricular outflow tract obstruction, anomalous drainage of the pulmonary veins, and ventricular-arterial discordance. These lesions are associated with a higher surgical risk and an increased incidence of neurologic deficits both before and after surgery.[64] Perioperative management requires a good understanding of the physiology of each patient's specific cardiac lesion.

Table 5. HS and Anesthesia

Anesthetic Concern	Heterotaxy Characteristic
Cardiac	
Single-ventricle physiology	Right or left ventricular hypoplasia, unbalanced atrioventricular septal defect
Intracardiac shunt	Atrial septal defect, ventricular septal defect, patent ductus arteriosus
Atrioventricular valve regurgitation/stenosis	Atrioventricular septal defect, single ventricle
Subvalvular and valvular aortic stenosis	Polysplenia syndrome
Subvalvular and valvular pulmonary stenosis	Polysplenia and asplenia syndromes
Qp:Qs* balance	Double-outlet right ventricle, single ventricle, atrioventricular septal defect, ventricular septal defects, anomalous pulmonary venous return.
Cyanosis	Cardiac shunt with Qp:Qs <1*
Heart failure	Cardiac shunt or regurgitant valve resulting in volume overload. Obstructive cardiac anomaly causing increased ventricular afterload. Cyanotic heart disease, arrhythmia, myocardial noncompaction, cardiopulmonary bypass.
Pulmonary venous hypertension	Total/partial anomalous pulmonary venous return
Pulmonary arterial hypertension	Recurrent pulmonary vein stenosis, cardiac shunt with Qp:Qs >1*
Site for arterial monitoring	Dextrocardia, situs inversus, right aortic arch, aberrant subclavian artery
Tracheal or bronchial compression by vascular structures	Dextrocardia, situs inversus, right aortic arch
TEE: compression of airway or vessels	Dextrocardia, situs inversus, right aortic arch
TEE: no gastric images because stomach lies distant from heart	Situs ambiguuus
TEE: contraindicated	Tracheoesophageal fistula repair
Venovenous collaterals creating SVC-to-IVC shunt	Kawashima Glenn physiology
Cardiopulmonary bypass venous cannulation	Bilateral superior vena cavae
Small right internal jugular vein: difficult access	Bilateral superior vena cavae
Femoral venous access, catheter course	Abnormal inferior vena cava location and connections (interrupted)
Persistent chylothorax postoperatively	Abnormal lymphatic drainage
Aortopulmonary collaterals	Usually single ventricle and pulmonary atresia
Myocardial ischemia	Single coronary artery: at risk for compression, emboli
Congenital heart block	Left atrial isomerism
Acquired heart block	Surgery: especially if complex cardiac lesion
Arrhythmias	L-looped ventricles, left isomerism
Venous anatomy influences site of transvenous pacing	Left superior vena cava, Fontan palliation
Reoperation	Single-ventricle palliation, recurrent outflow tract obstruction, regurgitant valves
Recurrent laryngeal and phrenic nerve injury	Right aortic arch
Emergency neonatal procedure	Total anomalous pulmonary venous return, single ventricle with restrictive intra-atrial communication
Extracardiac	
Neural	
Raised intracranial pressure	Neural tube defects
Neurologic deficits	
Meningitis	
Skeleton	
Abnormal airway	Hypoplasia of cranial bones
Restrictive lung disease	Kyphoscoliosis, pectus carinatum
Difficult intravenous access	Limb deformities
Craniofacial	
Obligate mouth breather	Choanal atresia
Abnormal airway	Micrognathia
Aspiration of food	Cleft lip/palate
Otitis media, sinusitis	Primary ciliary dyskinesia
Respiratory tract	
Aspiration pneumonia	Laryngeal cleft, esophageal atresia
Difficulty with mechanical ventilation	Tracheoesophageal fistula, tracheal
Chronic pulmonary disease	bronchus
Respiratory failure, pulmonary hypertension	Pulmonary hypoplasia, primary ciliary dyskinesia
	Diaphragmatic hernia

Table 5. Cont'd

Anesthetic Concern	Heterotaxy Characteristic
Gastrointestinal tract	
Infection, bowel rupture, or obstruction	Omphalocele
Bowel obstruction, bowel ischemia	Duodenal atresia, midgut volvulus, anal atresia
Short-gut syndrome	Congenital or acquired short bowel
Gastroesophageal reflux disease	Esophageal atresia, microgastria
Pancreas	
Pancreatic dysfunction and infection	Hypoplasia
Liver	
Liver dysfunction	Extrahepatic biliary atresia
Adrenals	
Consider if abdominal mass detected	Horseshoe adrenal
Genitourinary tract	
Renal dysfunction and urinary infections	Duplications, renal agenesis, urethral valves
Problems with urinary catheter	Hypospadias
Male and female infertility	Anomalies of reproductive organs, primary ciliary dyskinesia
Emergency neonatal procedure	Diaphragmatic hernia, intestinal abnormality
Other	
Increased perinatal risk	Intrauterine growth retardation
Immunocompromised	Asplenia syndrome

Abbreviations: SVC, superior vena cava; IVC, inferior vena; TEE, transesophageal echocardiography.
*Qp:Qs ratio of pulmonary blood flow to systemic blood flow.

Conduction Abnormalities

The arrangements of the sinoatrial nodes are exclusively dependent on the type of isomerism. In a right isomerism, there are bilateral sinus nodes, and multiple P-wave morphologies may be seen in the surface electrocardiogram. In a left isomerism, the sinus nodes are hypoplastic or absent. The nodes in a right isomerism are located in the venoatrial grooves bilaterally, even in the presence of only 1 superior caval vein. The surgeon should avoid these areas when performing cavopulmonary anastomoses or the Fontan operation. In a left isomerism, the sinoatrial nodes, when present, are closer to the atrioventricular junction. Sinus nodal dysfunction in those with isomeric left atrial appendages may manifest as sinus bradycardia, junctional rhythm, or conduction abnormalities ranging from first-degree to complete atrioventricular block.[65] Complete atrioventricular block has been reported in up to one-third of patients with isomeric left atrial appendages.[65-67] In addition, abnormal automaticity of the atrioventricular node may explain the relatively high incidence of junctional ectopic tachycardia occurring after congenital heart surgery.[65]

The location of atrioventricular conduction pathways is influenced by both the atrioventricular connection and the ventricular topology. When there are biventricular atrioventricular connections, the dominant feature is ventricular topology, whereas for univentricular connections the dominant feature is ventricular morphology.[29,68] In a left isomerism, usually the ventricular loop determines the atrioventricular conduction axis. With right-hand topology, there is typically a solitary atrioventricular node located posteroinferiorly at the meeting point of the ventricular septum and the atrioventricular junction. With left-hand topology, in contrast, usually there are 2 atrioventricular nodes situated posteroinferiorly and anterolaterally. Supraventricular tachycardia is more common in these patients.[65,69] The tachycardia is presumed to be caused by nodal re-entry, with antegrade conduction through a posteriorly located node, and retrograde via the other node. Treatment with catheter ablation usually is successful. Atrioventricular conduction can be damaged during biventricular repair but usually is not at risk during cavopulmonary anastomosis or the Fontan operation. In patients requiring implantation of a pacemaker, it is necessary to have a thorough understanding of the patient's anatomy and previous operative procedures before embarking on the delivery of a transvenous pacing system.[7]

Extracardiac Anomalies

The extracardiac anomalies that most frequently challenge the anesthesiologist are gastrointestinal abnormalities, hepatic dysfunction, splenic dysfunction, respiratory abnormalities, and associated midline defects.

Gastrointestinal Anomalies

Malrotation of the gut is very common in both subtypes of HS,[70] and many centers use contrast studies to screen all individuals with HS.[42-71] Once malrotation is diagnosed, a prophylactic Ladd procedure generally is recommended to prevent volvulus of the midgut,[52] although some dispute this approach.[72,73] Other gastrointestinal anomalies that may require surgery include duodenal atresia, microgastria, hiatal hernia, and omphalocele. Anal atresia occurs in those with isomeric right atrial appendages. Anesthetic concerns for intestinal volvulus could include emergency surgery, aspiration risk, electrolyte imbalances, hypovolemia, septicemia, shock, respiratory distress from a distended abdomen, and acute renal failure. The prognosis is poor.

Hepatic Dysfunction

About 10% of children with isomeric left-atrial appendages have biliary atresia with progressive obliteration of the

intra- and extrahepatic bile ducts.[17,48] Approximately 70% of these patients will require liver transplantation. In addition to the anesthetic challenges of hepatic dysfunction, anesthesia and surgical planning for transplantation will require accurate delineation of the patient's venous and arterial anatomy.

Splenic Dysfunction

In the polysplenia syndrome, there are multiple, small, poorly functioning spleens, whereas in asplenia the spleen is usually absent.[25] The assessment of splenic function is important, and antibiotic prophylaxis for bacterial infections and vaccination against pneumococcus may be required. Malaria, babesiosis, and certain viral infections also may be more severe in individuals with asplenia.

Respiratory Abnormalities

Congenital respiratory anomalies of relevance include choanal atresia, micrognathia, cleft lip and palate, tracheoesophageal fistula, tracheal bronchus,[74] and lung hypoplasia. Many anesthesiologists are familiar with the management of these lesions. However, PCD is less well known. There are currently no treatments to correct ciliary dysfunction. Clinicians typically follow the general guidelines for the treatment of bronchiectasis, including enhancing mucociliary clearance with physiotherapy, postural drainage, exercise, mechanical oscillatory vest percussion, and hypertonic saline. Cough suppressants should be avoided because cough is the only intact mechanism for mucociliary clearance in these patients.[75] Acute infectious exacerbations should be managed with appropriate oral, intravenous, or inhaled antibiotics.[58,75] Patients should receive routine immunizations for respiratory pathogens, avoid exposure to pathogens, and avoid smoking and other irritants that may increase mucus production. Localized bronchiectasis previously has been managed by lobectomy, but its benefit is limited. Surgical interventions may be required for specific complications of chronic suppurative otitis media and sinusitis such as tympanostomy, nasal polypectomy, and surgical sinus drainage. Lung transplant may be an option for patients with end-stage lung disease.[9]

Midline Defects

Midline defects that may require surgical interventions include neural, craniofacial, renal, and skeletal abnormalities (Table 2). Ultimately, the infant with HS requires a complete and thorough multisystem assessment in order to plan appropriate perioperative care.

OUTCOME

The natural history of HS with cardiac involvement is poor. Half of those patients who undergo initial palliation do not survive.[69,76] Many children with a right isomerism have univentricular hearts and obstructed pulmonary veins; their outcome is worse than those with a left isomerism[10,77] (Fig 4). A 10-year survival of 93% is reported for patients with HS

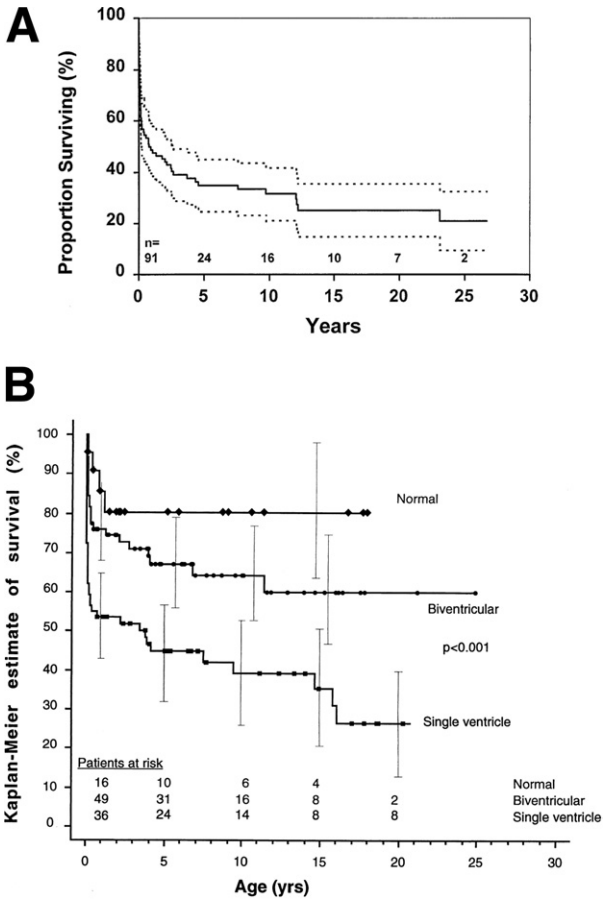

Fig 4. (A) The Kaplan-Meier survival curve for 91 patients with right isomerism. Only 4 patients underwent biventricular repair. The dashed lines represent 95% confidence limits. (Reprinted with permission from Hashmi A, Abu-Sulaiman R, McCrindle BW, et al: Management and outcomes of right atrial isomerism: A 26-year experience. J Am Coll Cardiol 31:1120-1126, 1998.) (B) The Kaplan-Meier survival curve for 163 patients with left isomerism. Twenty-two patients had a structurally normal heart, 71 had a heart suitable for biventricular repair, and 70 were suitable for univentricular palliation. Vertical bars represent 95% confidence limits. (Reprinted with permission.[77])

(mostly those with a left atrial isomerism) undergoing biventricular repair; however, reintervention and arrhythmia were common.[78] Although many HS candidates for the Fontan procedure have risk factors associated with poor outcome, recent studies suggest improved survival.[4,79-82]

Transplantation of the heart or heart and lungs is offered when there are no other surgical options. Perioperative challenges include pulmonary hypertension, abnormal systemic and hepatic venous anatomy and allograft presensitization. Acceptable short- and longer-term survival after heart transplantation have been reported.[83]

CONCLUSIONS

Better elucidation of the basic mechanisms governing L-R axis asymmetry has improved the understanding of heterotaxy. The

syndrome can result from genetic and environmental factors, and it is associated with an extremely wide range of congenital anomalies. Congenital heart defects, present in many patients with HS, are a major determinant of patient outcome. Extracardiac anomalies further complicate patient management. Satisfactory anesthesia care of these high-risk patients requires knowledge of the patient's anatomy and physiology and recognition that HS can cause multiorgan dysfunction.

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