Heterotaxy Syndrome: Implications for Anesthesia Management

Glyn D. Williams, MBChB, FFA(SA), and Angela Feng, MD

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.

From Lucile Packard Children's Hospital, Stanford University, Stanford, CA.

Address reprint requests to Glyn D. Williams, MBChB, FFA(SA), Anesthesia Department, Stanford University Medical Center, 300 Pasteur Drive, H3587, Stanford, CA 94305-5640. E-mail: jumbo@stanford.edu

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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,

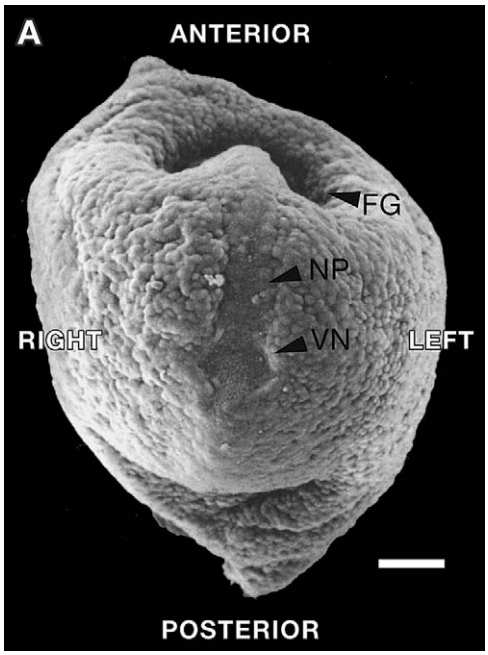

Fig 1. A scanning electron micrograph shows the ventral view of a 7.5-dpc mouse embryo. VN, ventral node; NP, notochordal plate; FG, foregut; Bar, 100 μm. (Reprinted with permission from Hirokawa N, Tanaka Y, Yasushi Okada Y, et al: Nodal flow and the generation of left-right asymmetry. Cell 125:33-45,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

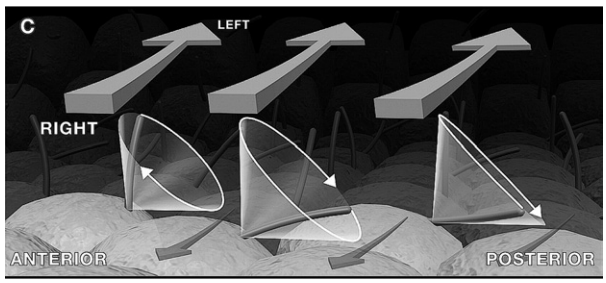

Fig 2. Unlike conventional beating cilia, the monocilia in the node have a clockwise rotational motion. The axis of rotations is tilted 40° ± 10° to the posterior from the vertical angle. As a consequence, the cilia make a leftward swing away from the surface and a rightward sweep near the surface. According 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.)