
Left-Right Asymmetry and Human Heterotaxy Syndrome

6

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Abstract

Heterotaxy syndrome is characterized by a wide variety of cardiac and extra-cardiac congenital malformations that are primarily induced by disorders of the left-right axis determination during early embryonic development. Prognosis of the disease remains unsatisfactory because the syndrome is often associated with complicated congenital heart diseases. Long-term follow-up of heterotaxy patients, particularly those who underwent Fontan procedure, is now one of the most important issues in pediatric and adult congenital heart disease clinics. Collaborative studies between pediatric cardiologists and basic scientists are essential for improving the prognosis of heterotaxy syndrome.

Keywords

Heterotaxy • Left-right axis • Signal transduction • Heart surgery

6.1 Introduction

Heterotaxy syndrome is a rare but serious congenital disease that occurs approximately 1 to 5,000–7,000 of live birth [1]. Patients are generally subdivided into “bilateral right sided” (right isomerism) or “bilateral left sided” (left isomerism) according to the characteristic morphology of atrial appendages of the heart. However, there is a wide spectrum of pathology with considerable overlap of the anatomical features.

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6.2 Molecular and Cellular Mechanisms of Left-Right Determination

The left-right axis determination initiates in the primitive node at E7.5 in mice and develops through the following pathways [2, 3]:

1. Breaking of symmetry as a result of leftward “nodal flow”
2. Transmission of asymmetric signals to the lateral plate mesoderm (LPM)
3. Asymmetric expression of nodal and lefty2 in the LPM
4. Situs-specific morphogenesis mediated by asymmetric expression of Pitx2

6.2.1 Node Cell Monocilia Create Leftward “Nodal Flow” and Activate Asymmetry Signaling Around the Node

The determination of the left-right asymmetry starts as leftward nodal flow generated by rotational movement of monocilia in the primitive node [4, 5]. Clockwise rotation of motile cilia creates unidirectional leftward flow because the rotational axes of cilia tilt caudal direction of the embryos [6, 7].

There are two models why nodal flow is perceived by nodal and perinodal cells. One hypothesis (chemosensory model) is that the nodal flow produces a gradient of left determinant particles (node vesicular parcels) containing hedgehog proteins and nodal [8, 9], which activate downstream signaling of nodal in the left-side perinodal cells.

Alternative hypothesis (mechanosensory model) is that the leftward nodal flow provokes an asymmetrical increase influx of Ca^{2+} ion in the sensory cilia cells through PKD2, a causative gene for human polycystic kidney disease [9, 10]. This Ca^{2+} influx is linked to the activation of nodal in the left-side perinodal cells, which is consequently transferred to the left LPM.

6.2.2 Asymmetry Signaling Transmits to the Left Lateral Plate Mesoderm

Transmission of nodal to the left LPM followed by lefty2 and Pitx2 activation [11] and the consequent heart morphogenesis in the normal subjects, right/left isomerism, and situs inversus is summarized in Fig. 6.1a.

6.2.3 Genes Associated with the Human Heterotaxy Syndrome

Recent human and animal model studies have provided insights into the genetic and developmental etiology of the heterotaxy syndrome. In human, genes that are associated with heterotaxy syndrome are ZIC3, NODAL, CFC1, ACVR2B, LEFTY2, CITED2, and GDF1 [12–14].

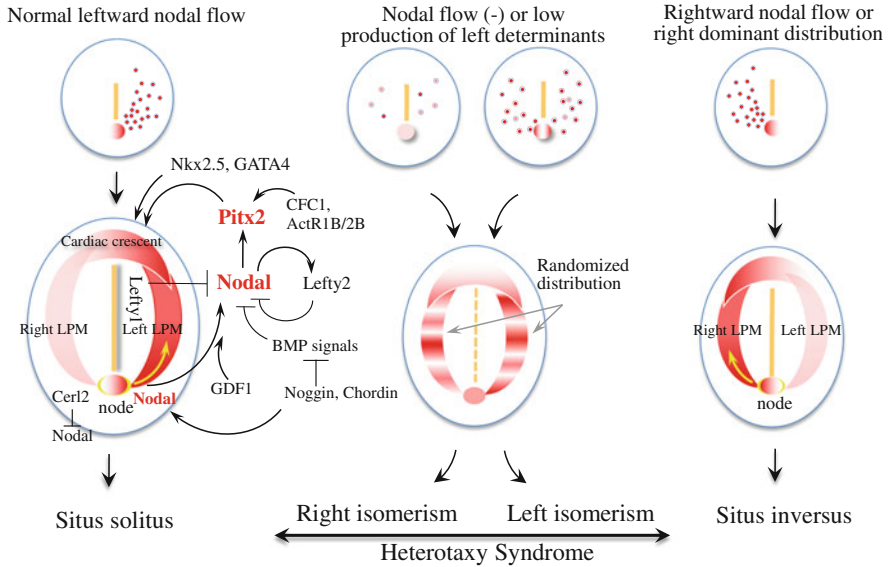


Fig. 6.1 Signal transmission of nodal to the left lateral plate mesoderm followed by *Pitx2* activation and the consequent heart morphogenesis in normal and heterotaxy embryos (Adapted and modified from Ref. [1] with permission)

6.3 Clinical Manifestation of the Heterotaxy Syndrome

Factors that deteriorate prognosis of the heterotaxy syndrome are complications with pulmonary venous obstruction, pulmonary arterial distortion, regurgitation of atrioventricular valve, elevated pulmonary vascular resistance, and impaired ventricular function [15].

6.3.1 Right Isomerism

Neonates with right isomerism typically show single atrium, single right ventricle, and univentricular atrioventricular connection often associated with atrioventricular valve regurgitation. First-stage palliation (2–4 weeks after birth) is a control of pulmonary blood flow with pulmonary banding or systemic-pulmonary shunt. Pulmonary venous obstruction due to total anomalous pulmonary venous drainage should be precisely diagnosed and repaired by surgical operation.

The second-stage palliation is the bidirectional Glenn shunt, where the right and/or left superior vena cava is isolated and is connected to the pulmonary artery. This operation is, in general, performed around 6 months after birth.

The third-stage palliation is Fontan procedure. Recently, a modification using extra-cardiac artificial conduit-type total cavo-pulmonary connection (TCPC) is

most often employed, because the long-term prognosis of the conventional atrio-pulmonary connection is proved to be unsatisfactory characterized by enlargement of the atrium, intractable atrial tachyarrhythmias, and thromboembolisms.

After successful completion of the TCPC, cyanosis disappears and the general conditions of the patients improve. However, number of patients who underwent successful Fontan procedure is approximately 50 % because right isomerism often accompanied with combination of severe and complicated congenital heart diseases [16].

6.3.2 Left Isomerism

Left isomerism is typically associated with atrioventricular septal defect, persistent left superior vena cava, interrupted hepatic portion of the inferior vena cava, and atrioventricular conduction disturbance. In left isomerism, sinus node and atrioventricular nodes are usually hypoplastic, and sinus bradycardia or complete atrioventricular block is frequently accompanied.

6.4 Long-Term Prognosis of Heterotaxy Patients

Although the medical and surgical treatments of the heterotaxy syndrome have remarkably advanced, long-term prognosis of the patients remains unsatisfactory. Right isomerism has been recognized as one of the worst forms of CHD with overall 5-year survival ranging from 30 to 74 %. The results are better in left isomerism with 5-year survival rates ranging between 65 and 84 %, which is still considerably lower than survival for most other forms of CHD [17]. The main reason is that the nature of the Fontan single ventricle physiology is fundamentally imperfect. Representative long-term complications of the Fontan operation are illustrated in Fig. 6.2.

6.4.1 Protein-Losing Enteropathy

Protein-losing enteropathy (PLE), one of the most severe manifestations of the failing Fontan circulation, occurs in 5–10 % of the total postoperative cases [15]. Chronic loss of serum proteins into the gastrointestinal tracts results in systemic edema, ascites, pleural effusion, diarrhea, gastrointestinal bleeding, susceptibility to infections, and ultimately cachexia. The underlying mechanism of PLE remains uncertain. Elevated inflammatory reactions such as TNF- α or IFN- α , dilatation of intestinal lymphatic vessels, and widening between intestinal epithelial cells may be involved in the protein and fluid losses [18]. Steroids, high molecular weight heparin, sildenafil, surgical interventions, for instance, fenestration of atrial-level communications or conversion of the Fontan circuit, are effective. To date,

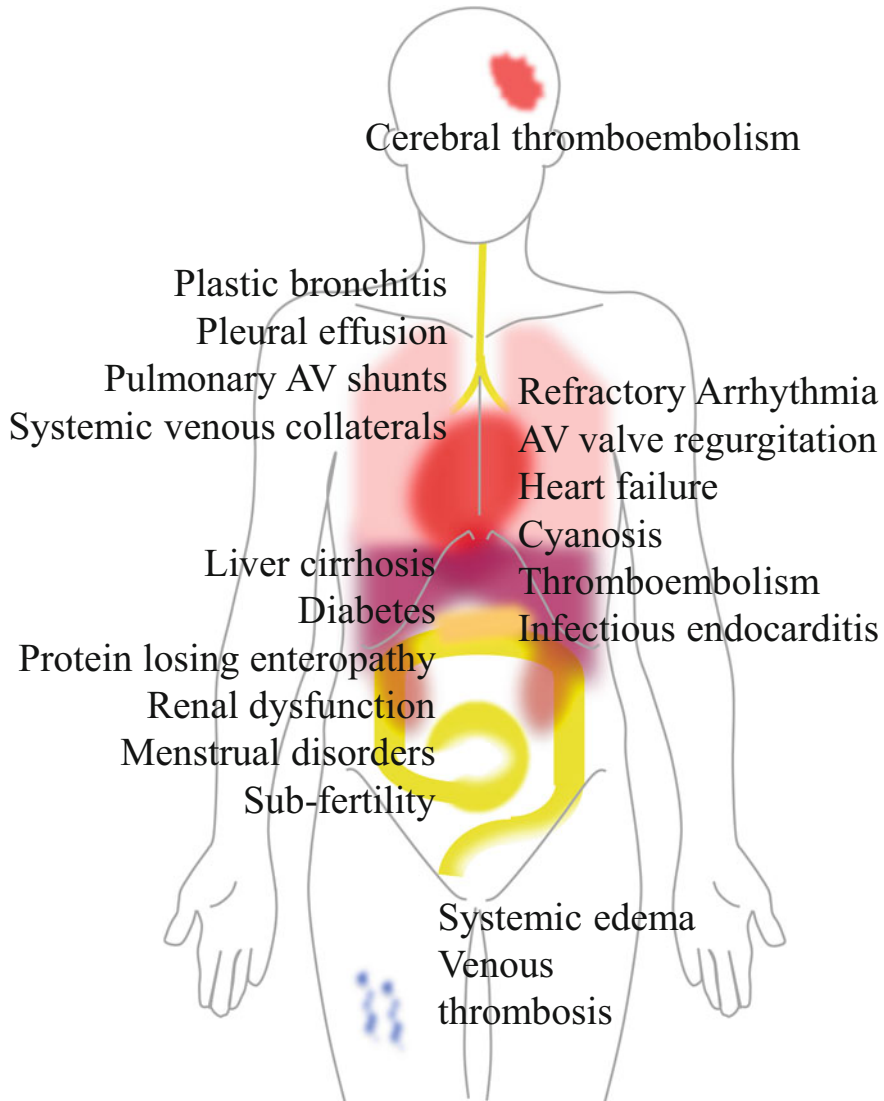


Fig. 6.2 Possible complications of mid- to long term after completion of Fontan procedure for heterotaxy patients (Adapted and modified from Ref. [1] with permission)

cardiac transplantation is considered as the only and complete resolution of PLE pathophysiology.

6.4.2 Arrhythmias

Reentrant atrial tachyarrhythmias are the commonest in patients after Fontan procedure and are often associated with deterioration of hemodynamics, either causally or as a result [15]. Hemodynamic abnormalities such as valve regurgitation or outflow obstruction, if present, should be aggressively treated by surgery.

6.4.3 Heart Failure

Initial feature of heart failure long after the Fontan procedure is characterized by worsening of ventricular relaxation and compliance [15]. These abnormalities may be caused by exposure of hypoxia and volume/pressure overload preceding the Fontan procedure, repetitive surgical operations, and hemodynamic disadvantages of the Fontan circuit. These changes are primarily progressive and consequently lead to failure of the Fontan circuit. Late after the Fontan procedure, systolic dysfunction becomes apparent. Administration of angiotensin converting enzyme inhibitors or β -blockades may be beneficial for particular patients, although the clinical evidence and cellular mechanisms remain to be elucidated.

6.4.4 Hepatic Dysfunction

Hepatic dysfunction, liver fibrosis, and cirrhosis are common complication of patients long after Fontan operation. Recently, cases with hepatocellular carcinoma after Fontan operation have been reported [19, 20]. Careful observation should be necessary to detect the hepatic changes long after Fontan operation.

6.4.5 Management of Failing Fontan Patients

Patients who underwent atrio-pulmonary connection or lateral tunnel procedure are likely to be complicated with thromboembolism or intractable arrhythmias due to enlargement of the right atrium [14]. Surgical intervention with conversion to TCPC is required before such complications become irreversible. Cardiac transplantation may be the only option for patients with severe heart failure, intractable arrhythmias, or recurrent PLE.

6.5 Future Direction and Clinical Implications

In the basic science field, embryonic development of left-right asymmetry has been uncovered by means of mouse genetic engineering. In addition, advanced human genetics have uncovered many responsible genes for heterotaxy syndrome. By means of innovative technologies such as whole genome sequencing or patient-

based human inducible pluripotent stem cells, novel genes will be clarified and analyzed. In the clinical field, anatomical and physiological diagnosis from the fetal period, better clinical managements after birth, and tailor-made surgical operations will improve the prognosis. Cell- or tissue-based regeneration therapies and a new ventricular assist device could improve cardiac function of failing Fontan patients. Multiple approaches including basic and clinical science are necessary to improve the prognosis and quality of life of heterotaxy patients.

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