Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 59, No. 1, Suppl S, 2012
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.04.046

STATE-OF-THE-ART-PAPER

Left Ventricular Hypoplasia

A Spectrum of Disease Involving the Left Ventricular Outflow Tract, Aortic Valve, and Aorta

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"Hypoplastic left heart syndrome" is an unsatisfactory term describing lethal underdevelopment of the left ventricle (LV). It represents the more severe end of a spectrum of LV hypoplasia, mandating single-ventricle palliation or cardiac transplantation. Less severe "borderline" ventricular hypoplasia may instead allow various biventricular therapeutic strategies and better long-term outcomes. In this review, we consider factors causing and modifying the abnormal development of the LV. LV hypoplasia is typically seen in association with left ventricular outflow tract obstruction, itself part of a spectrum of related defects with common etiologies. Secondary responses to outflow obstruction are complex but involve abnormal flow dynamics and shear stresses that result in compromised and poorly orchestrated ventricular growth and development. Subsequent remodeling is likely influenced by genetic modifiers, including intrinsic myocardial growth signaling pathways, possibly including those of HAND transcription factors. In addition, during the latter stages of gestation, cardiomyocytes undergo a switch in myogenic potential and lose the ability to undergo mitosis. Ventricular hyperplasia can therefore no longer occur; remodeling is instead limited to muscular hypertrophy. Subtle differences in this switch in myogenic potential—and modulators thereof—are likely to be of clinical and therapeutic importance, especially in children with "borderline LVs" being considered for fetal interventions or post-natal biventricular repair strategies. Finally, by more clearly understanding the initiators and propagators of abnormal ventricular development, we can hope to lean away from grouping a heterogeneous group of infants together under the unsatisfactory term "hypoplastic left heart syndrome." (J Am Coll Cardiol 2012;59:S43–S54) © 2012 by the American College of Cardiology Foundation

Left ventricular (LV) hypoplasia describes a lethal congenital heart abnormality that usually occurs in association with obstruction to LV outflow. The degree of hypoplasia is largely proportional to the severity of obstruction except in particular circumstances where an alternative exit for ventricular blood exists (e.g., a ventricular septal defect). When hypoplasia is severe, the LV is not capable of supporting the systemic circulation. In this scenario, the only options for long-term survival include neonatal cardiac transplantation or a sequence of complex open-heart operations in infancy that lead to a univentricular "Fontan" circulation in which the single right ventricle supports the systemic circulation and pulmonary blood flow is entirely passive. When hypoplasia is only mild, the LV may be capable of supporting the systemic circulation once the outflow obstruction is alleviated (biventricular repair). A large number of infants have moderate hypoplasia and therefore fall in a grey zone; clinical decision-making regarding management for these children with "borderline LVs" is a considerable challenge.

Although LV hypoplasia encompasses a spectrum (Fig. 1), the term "hypoplastic left heart syndrome" (HLHS) is frequently used clinically to describe children with severe hypoplasia. The majority of these children have nonpatent outflow tracts (aortic atresia) and a rudimentary LV. For infants with patent, but obstructed outflow, the term HLHS becomes less satisfactory because ventricular hypoplasia may only be mild or borderline. It is for these children with mild or borderline hypoplasia that the pathogenetic mechanisms underpinning LV hypoplasia become especially pertinent; strategies to avert or reduce the development of hypoplasia might allow a greater proportion of children to safely undergo biventricular repair.

The purpose of this review is to: 1) describe important candidate pathogenetic mechanisms that may represent primary triggers leading to LV hypoplasia during embryogenesis; 2) identify processes that may influence the response of the developing LV to the primary triggers; and 3) elaborate on the clinical difficulties in managing the "borderline LV."

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Manuscript received January 31, 2011; revised manuscript received March 28, 2011, accepted May 12, 2011.

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December 27, 2011/January 3, 2012:S43–S54

Abbreviations and Acronyms

HLHS = hypoplastic left heart syndrome

LV = left ventricle/ventricular

LVOT = left ventricular outflow tract

Re = Reynold's number

Aortic Valve Stenosis and the Link With Coarctation

The majority of cases of LV hypoplasia occur in association with downstream obstruction. Except for a small minority of cases, the level of maximal obstruction is at the aortic annular region of the left ventricular outflow tract (LVOT) (1). In fact, in aortic atresia—the most common manifestation of HLHS—the LVOT is nonpatent at the valvar level. Therefore, it has been suggested that LV hypoplasia is predominantly a disease of the aortic valve (2). However, if LV hypoplasia is predominantly a disease of aortic valve development, then one might anticipate a genetic link between HLHS and relatively minor anomalies such as simple bicuspid aortic valve disease.

Evidence for such a link is emerging. Bicuspid aortic valves are the most common cardiac abnormality found in first-degree relatives of children with HLHS (3). In fact, the incidence of bicuspid aortic valves has been reported as high as 11% in otherwise normal first-degree relatives of HLHS probands (2) (vs. 1% to 2% in the wider population). Furthermore, case reports exist of monozygotic twins in which 1 has HLHS (aortic atresia) and the other is otherwise normal aside from a bicuspid aortic valve (4). Lastly, genetic-linkage statistical analysis has very recently provided evidence of shared chromosomal loci (10q22 and 6q23) in the etiology of bicuspid aortic valve disease and a subset of children with HLHS (5).

Cushion defects and NOTCH. The precise mechanisms underlying defective valvar development that result in outflow tract stenosis have not been clearly delineated. The aortic valve is derived from endocardial cushions. A key process in cushion formation is epithelial-to-mesenchymal transformation, a process whereby epithelial cells lose their polarity, detach from basement membrane, delaminate, and migrate into the extracellular matrix with a mesenchymal phenotype. These transformed mesenchymal cells are responsible for 2 key processes in early cushion formation: 1) they remodel the extracellular matrix; and 2) they form the cellular constituents of the endocardial cushions. Therefore, factors regulating endocardial cushion formation seem attractive candidates for abnormal aortic valve and LVOT development.

One such factor that is receiving considerable attention is NOTCH (Fig. 2). NOTCH proteins are a family of 4 single-pass transmembrane proteins with extracellular ligand binding sites characterized by numerous epidermal growth factor (EGF)-like repeats (6). Ligands for the NOTCH receptor (Jagged1, Jagged2, and members of the DSL family) interact with the EGF repeats. The DSL family of ligands are themselves transmembrane proteins (also with EGF repeats), and therefore, the DSL–NOTCH interaction represents a form of close intercellular signaling. Ligand–NOTCH interaction results in cleavage of the NOTCH extracellular portion, close to the membrane. This initial extracellular cleavage then triggers additional cleavage of NOTCH by γ-secretase, at 2 sites within the membrane. Ultimately, therefore, the intracellular portion of NOTCH (NOTCH-ICD) is released and translocates to the nucleus.

Downstream transcriptional effects of NOTCH-ICD include the activation of the transcription factor CSL (6). CSL in the resting state is a transcriptional repressor—partly due to its recruitment of other silencing factors. Interaction with NOTCH-ICD causes CSL to be released from its repressed state and instead activate transcription by directly binding specific promoter sequences. The most thoroughly investigated transcriptional targets for NOTCH1/CSL-mediated signaling are *Hey1* and *Hey2*, which encode basic helix-loop-helix transcription factors. Other transcriptional targets of NOTCH1-mediated signaling include *Cyclin D1*, *nodal*, and *Ephrin-B2*, among others.

Double knockout of *Hey1* and *Hey2* results in severe hypoplasia of major arterial structures (7), and evidence suggests this may be a result of abnormal epithelial-to-mesenchymal transformation within endocardial cushions. Double mutations in *Hey1* and a close functional relative *HeyL* result in both reduced numbers of mesenchymal cushion cells and defective extracellular matrix processing (8)—the 2 key processes obligatory to normal endocardial cushion formation. Double knockout $Hey2^{-/-}$ results in similar deficiencies, and $NOTCH1^{-/-}$ null mutations completely abrogate epithelial-to-mesenchymal transformation in endocardial cushions (8).

The link with aortic coarctation. Interestingly, *Hey1* and *Hey2* are homologues of the zebrafish gene *gridlock* (*grl*). Mutations in *grl* lead to major artery defects—particularly stenosis at the junction of the 2 lateral dorsal aortae (Fig. 3) (9). In the zebrafish, this stenosis leads to absent caudal blood flow. This zebrafish *grl* mutant phenotype bears an eerie resemblance to human aortic coarctation. Aortic coarctation is a stenosis in the thoracic aorta usually occurring immediately after the origin of the left subclavian artery in the region of the ductus arteriosus. Each subclavian artery in the human is an embryologic derivative of the seventh intersegmental artery from the right and left dorsal aortae immediately before the 2 fuse into a single common dorsal aorta. Therefore, the zebrafish *grl* model may represent the "coarctation phenotype" equivalent of human aortic coarctation, thereby suggesting a causal relationship of *Hey1* and *Hey2* to the disease in humans.

The NOTCH1/*Hey* coarctation hypothesis offers a potential mechanism linking the well-known clinical association between bicuspid aortic valve disease and aortic coarctation. In fact, the molecular interplay underlying aortic valve disease and aortic coarctation likely explains the coexistence of HLHS in as many as 7% of neonates

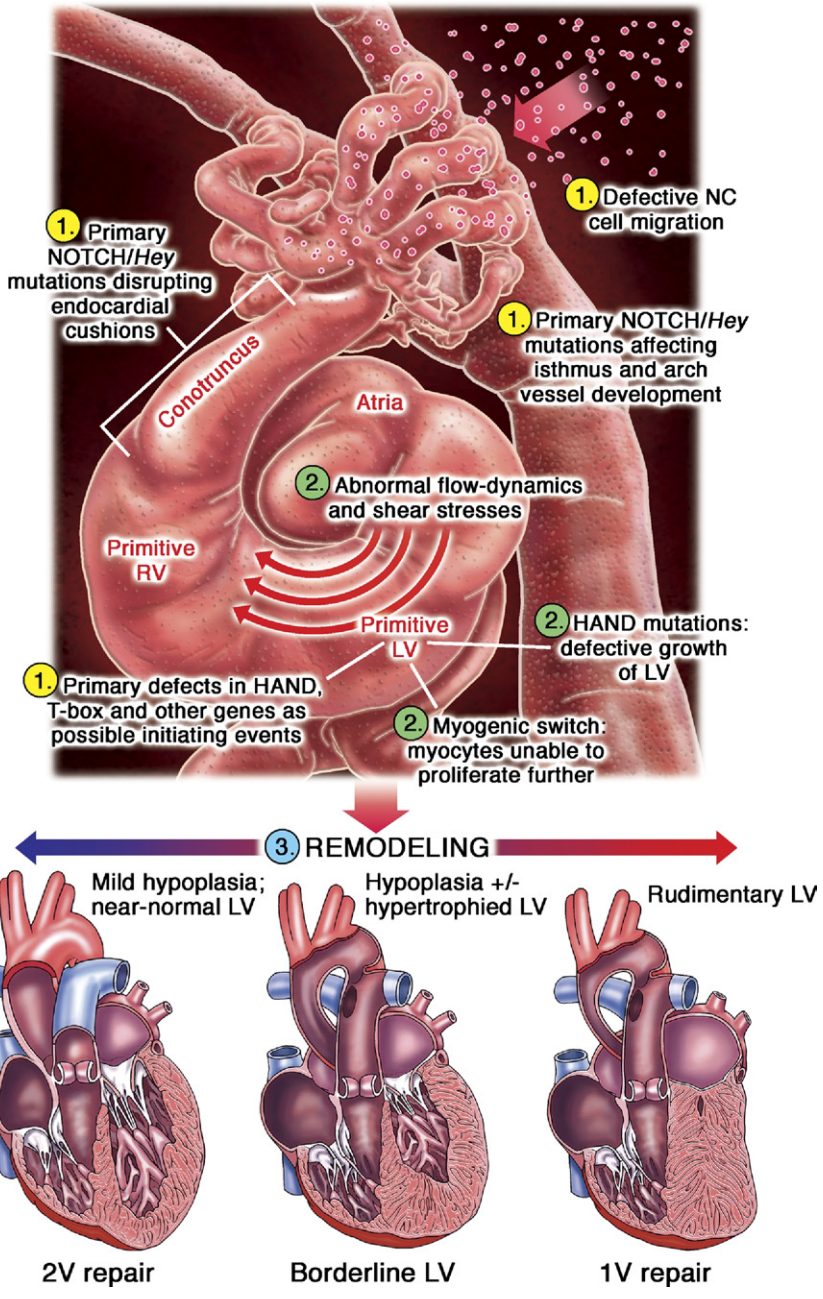

Figure 1 **The Hypoplastic Left Ventricle Model**

(1) A primary initiating event occurs that disrupts normal development of the outflow tract endocardial cushions. Cushion formation is coordinated by the influx of neural crest (NC) cells. The NOTCH/*Hey* signaling axis appears to be important in epithelial-to-mesenchymal transformation within endocardial cushions and also plays important roles in arch vessel development and the pathogenesis of coarctation. Finally, defects in genes involved in ventricular growth and differentiation (e.g., HAND and T-box genes) might occasionally be primary initiators of left ventricular hypoplasia. **(2)** Abnormal left ventricular outflow tract (LVOT) development leads secondarily to abnormal flow-dynamics and shear-stresses within the downstream developing ventricle. Ventricular growth is likely intricately related to signal transduction from such mechanical forces. The secondary response of the developing ventricle to abnormal outflow tract development may also be modulated by variations in genes orchestrating ventricular growth (such as HAND proteins). Finally, the nature and timing of the "myogenic switch"—when myocytes lose their ability to proliferate—likely has important implications for growth and remodeling of the left ventricle (LV) in the face of outflow tract obstruction. **(3)** Overall, it is the extent and nature of ventricular growth and remodeling that will determine the function and morphology of the formed ventricle and where it sits on the spectrum of left ventricular hypoplasia. 1V = univentricular; 2V = biventricular; AV = aortic valve; RV = right ventricle.

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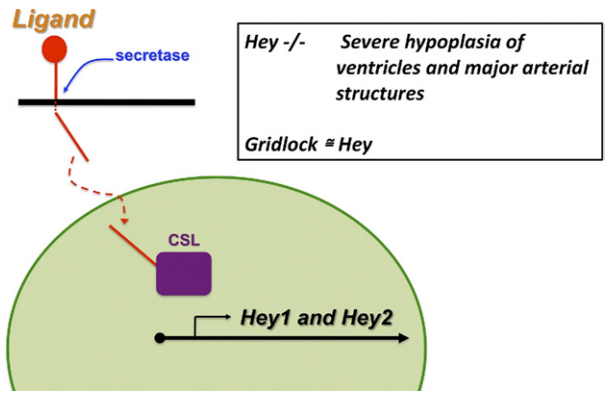

Figure 2 Schematic Representation of NOTCH-Mediated Signaling

NOTCH proteins are a family of transmembrane receptors. Once bound to their ligands (members of the Jagged family and DSL ligands), the intracellular portion (NOTCH-ICD) is cleaved by secretase and translocates to the nucleus. Within the nucleus, NOTCH-ICD binds transcription factors, for example, CSL leading to activation of promoters for genes including especially *Hey1* and *Hey2*, which themselves encode basic helix-loop-helix transcription factors. $Hey^{-/-}$ knockout animals exhibit severe hypoplasia of the ventricles and defects in major vascular structures.

presenting primarily with coarctation of the aorta (10). The combination of mild, diffuse hypoplasia of the entire LVOT and ventricle, with aortic coarctation—an entity recently coined "hypoplastic left heart complex" (11)—could similarly be explained by a NOTCH/*Hey* signaling aberration. Finally, Shone complex (12)—an occasional manifestation of HLHS due to multilevel stenoses involving the mitral valve, aortic valve, supravalvular aorta, and coarctation—could also be attributed to *Hey* family mutations disrupting epithelial-to-mesenchymal transformation, endocardial cushion formation, and large vessel stenoses analogous to those seen in *grl* zebrafish mutants (13). Additionally, NOTCH1 in particular has been implicated in bicuspid aortic valve disease and premature calcification of bicuspid valves in adults (14).

Link with other gene and chromosomal defects. The NOTCH signaling axis presented in the preceding text is not the only candidate linking the interplay between LVOT development and ventricular hypoplasia. Turner syndrome (45,X0) is associated with bicuspid aortic valve disease, coarctation, and aortic stenosis (15), suggesting a role for chromosome X. In a large North American series of infants who all underwent Norwood (univentricular) operation for HLHS, Turner syndrome was the most common coexisting genetic syndrome, and its presence was also associated with significant decrements in survival (16). Such survival decrements might conceivably relate to the strong link (17) between cardiovascular defects and fetal lymphedema in Turner syndrome. The association between Turner syndrome, aortic valve disease, LV hypoplasia, and lymphedema is an intriguing one that warrants further attention.

Recently, genetic linkage studies have revealed other chromosomal loci to be associated with left-sided outflow tract lesions, including ventricular hypoplasia (18) (see Grossfeld et al. [19] for a useful summary). Microsatellite genotyping among families harboring a spectrum of lesions has now revealed linkage peaks corresponding to loci 16p12, 2p23, and 10q21 in general, 10q22 and 6q23 linking bicuspid aortic valve and LV hypoplasia, and 2p15 specifically for HLHS (5,18).

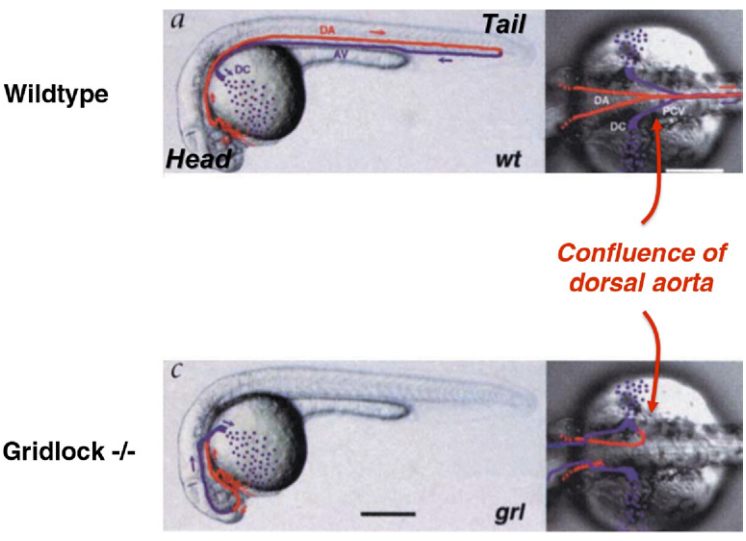

Figure 3 Impact of *gridlock*$^{-/-}$ on Arterial Development in the Zebrafish

Mutants display atresia at the point of fusion of the 2 dorsal aortae. In humans, the point of fusion of the dorsal aortae occurs immediately beyond the seventh segmental artery (later subclavian arteries), the site of aortic coarctation. wt = wild type. Reproduced, with permission, from Weinstein et al. (9).

Finally, specific genes other than *NOTCH* have been identified as associated with a subset of patients with HLHS. These include genes encoding the cardiac gap junction Connexin43 (*GJA1*) (20), an EGFR family tyrosine kinase receptor (*ERBB4*) (21), the cardiac transcription factor NKX2.5 (*NKX2.5/CSX*) (22,23), and the HAND proteins (24) (discussed in later text).

In summary, obstruction to left ventricular outflow at the aortic valvar level is the predominant lesion found in infants with hypoplastic LVs. Chromosomal linkage analyses are now suggesting familial links to exist between even mild aortic valve and outflow tract anomalies and HLHS, supporting a causal relationship. Recently, molecular signaling pathways common to endocardial cushion development, large artery vasculogenesis, and ventricular hypoplasia have been identified. NOTCH- and Hey-mediated signaling defects likely compromise epithelial-to-mesenchymal transformation in endocardial cushions thereby precipitating aortic valve defects, including severe stenosis in some. Similar mechanisms may underlie more diffuse stenotic phenotypes, multilevel stenoses (Shone complex), and aortic coarctation. Additional gene products—including Connexin43, tyrosine kinase receptors, and NKX2.5, among others—are involved in a subset of patients, implying pathogenetic heterogeneity.

Primary Hypoplastic Signals

Although LV hypoplasia is often considered to be secondary to outflow obstruction, the discovery of 2 basic helix-loop-helix transcription factors—HAND-1 and HAND-2—that appear central to early ventricular development raises the possibility that in a minority of cases, the primary defect is in the ventricle itself. Certainly, it is likely that they play some role in modulating the ventricular response to outflow obstruction. Both *HAND-1* and *HAND-2* are coexpressed uniformly in the cardiac crescent of the primary heart field (25). During initial development of the heart tube, their expression is again fairly uniform, but marked differences in expression are then seen in the craniocaudal axis in a ventricle-specific fashion (25) (leading to left–right asymmetry after looping) (Fig. 4). *HAND-1* transcripts are detected particularly in the conus arteriosus, truncus arteriosus, primitive atrium, and primitive ventricle, but expression is notably deficient in the bulbus cordis (the future right ventricle). Instead, *HAND-2* is predominantly expressed in the bulbus cordis. Experimental loss-of-function mutations of *HAND-2* are not compatible with life because of inadequate right ventricular development (26). The corollary was therefore hypothesized that mutations in *HAND-1* are associated with LV hypoplasia and abnormalities in LVOT development. Indeed, early attempts to develop *HAND-1*–null mutant mice resulted in embryos that exhibited no attempt at rightward looping or development of a primitive ventricle. In addition, early embryonic death resulted from lack of placental trophoblastic development (27). Elegant mammalian studies involving mutations in *HAND-1* and *HAND-2* have since demonstrated that mutations in either lead to a variety of serious defects in ventricular morphogenesis and that the impact of mutations among these *2* proteins are cumulative (Fig. 5) (28).

Recently, gene-sequencing studies have investigated the role of *HAND* mutations in human cardiac development (24). Among the Leipzig collection of human hearts with

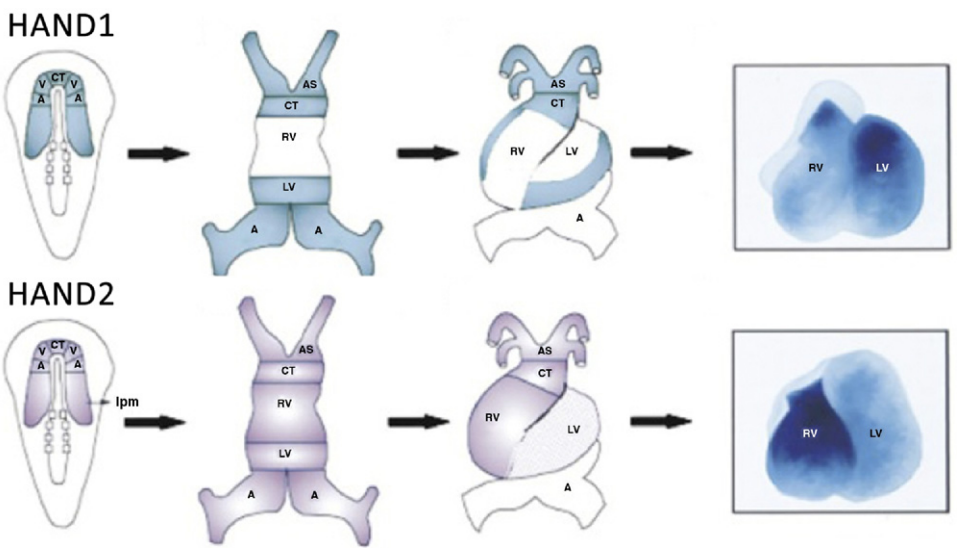

Figure 4 **HAND-1 and HAND-2 Are Both Expressed in the Primary Heart Field**

Subsequently, expression becomes asymmetric in both the left–right axis and craniocaudal axis. HAND-1 is expressed especially in the outflow tract and primitive ventricle. HAND-2 is instead located particularly in the bulbus cordis (developing right ventricle). A = primitive atrium; AS = aortic sac; CT = conotruncus; V = ventricles; other abbreviations as in Figure 1. Reproduced, with permission, from Srivastava (25).

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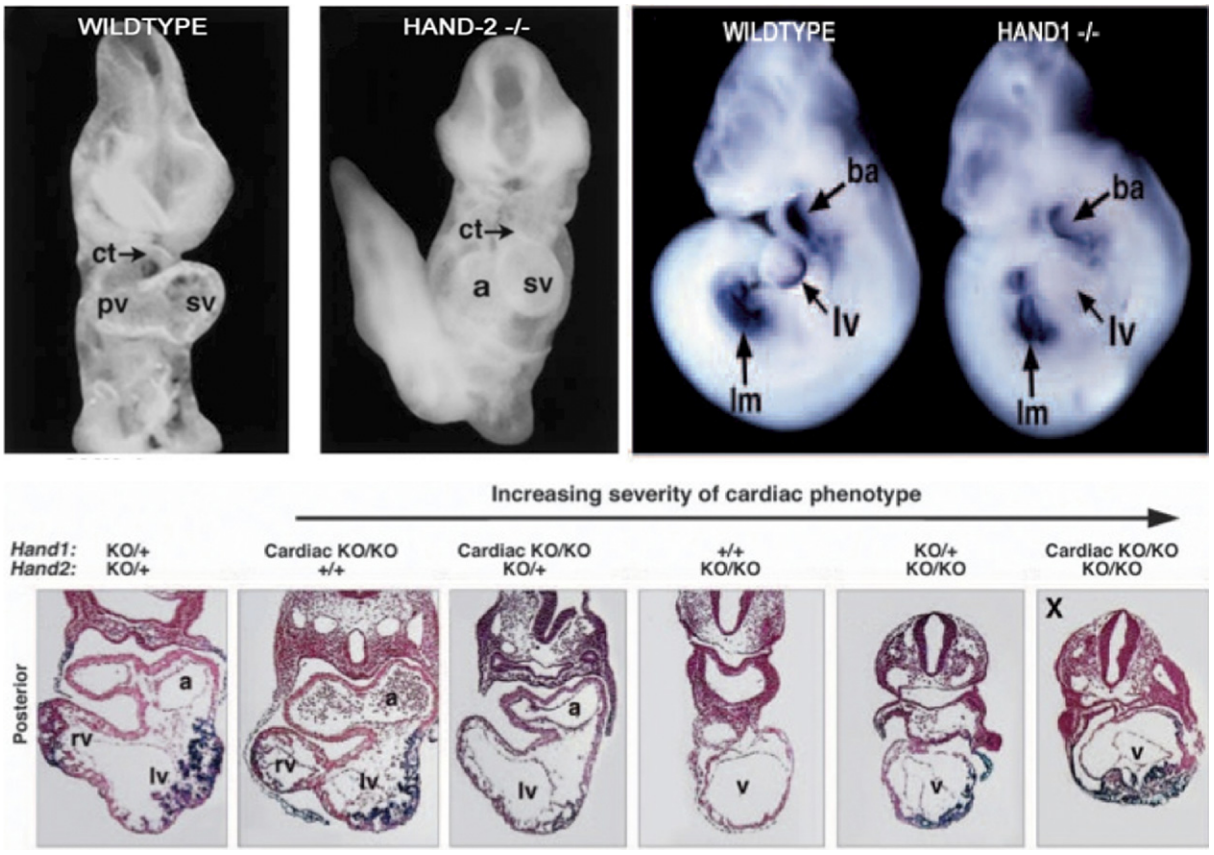

Figure 5 **HAND-1 Null Mutants Exhibit Absence or Severely Hypoplastia of the Developing Left Ventricle (In Addition to Fatal Trophoblastic Defects)**

HAND-2 null mutants exhibit severe hypoplasia of the developing right ventricle. The impact of mutations is cumulative. In the **lower panel**, the severity of abnormal cardiac morphogenesis increased left to right. ba = branchial arch; KO = knockout; lm = lateral mesoderm; lv = left ventricle; pv = pulmonic (right) ventricle; sv = systemic (left) ventricle; other abbreviations as in Figures 1 and 5. Reproduced, with permission, from McFadden et al. (28).

congenital defects, 31 had ventricular hypoplasia (24 left and 7 right) in addition to a multitude of other coexisting lesions. The *HAND-1* gene sequence was amplified from myocardial tissue from the hypoplastic ventricle from each of these specimens and compared with the *HAND-1* gene sequence amplified from a normal human heart. In addition, *HAND-1* gene sequences were amplified from myocardial tissue from the nonhypoplastic normal ventricle of the 31 experimental hearts. In 24 (77%) of the hypoplastic tissue specimens, a common frame-shift mutation (A126fs) was identified (24).

The A126fs mutation resulted in both an ~9-kDa fragment of the HAND-1 protein product and also a 2.5-fold reduction in mutant protein expression (perhaps due to mRNA instability). The truncated mutant protein is predicted to have only very sparse α-helical content. In functional experiments using luciferase reporter assays, the A126fs mutant HAND-1 product was incapable of modulating reporters containing D- and E-box transcriptional control elements (24). These latter 2 elements are sequences known to be regulated by the HAND-1 protein (29). No specimen was homozygous for the A126fs mutation; consistent with the observation in mice that homozygous *HAND-1*$^{-/-}$ null mutants died early in utero as a result of placental insufficiency.

Interestingly, *HAND-1* A126fs mutations were not restricted to the hypoplastic ventricle. In 8 specimens, the A126fs mutation was identified in the nonhypoplastic ventricle in addition to the hypoplastic ventricle. This observation is consistent with the notion that myocardial progenitors within the primary heart field contribute to all cardiac chambers and structures, whereas those from the secondary heart field are more specific to particular regions such as the outflow tract (30). If the origin of the A126fs mutation occurred during proliferation of the primary heart field, then the defect would be detected in all subsequent primary heart field derivatives.

In summary, evidence is accumulating that suggests defects in HAND-1 and -2 expression or function may play important roles in left and right ventricular hypoplasia, respectively. First, the 2 HAND proteins demonstrate differential expression in a ventricle-specific fashion during the critical stages of heart tube

development and cardiac looping. Second, loss-of-function mutations result in nonviability due in part to lack of development of the left and right ventricular precursors, respectively. Third, gene-sequencing studies of human hearts affected by LV hypoplasia have recently demonstrated loss-of-function mutations in HAND-1 in a large proportion.

Flow Dynamics

Flow-streaming. The advent of fetal echocardiography has allowed prenatal diagnosis and assessment of HLHS. Its use has demonstrated LV hypoplasia to evolve in severity with gestation (31,32). This clinical finding reflects the fact that normal cardiac morphogenesis requires blood flow–directed remodeling in addition to intrinsic patterning. Blood flow remodeling describes the secondary development and differentiation of structures as a direct result of shear stress and flow dynamics of blood flow within them. This is not a new concept; over 3 decades ago, the first model of hypoplastic left heart was described and was achieved by temporarily obliterating blood flow through the LV in 5-day-old chick embryos (33). Twenty percent of the experimental group survived, all displaying varying degrees of left-sided structural hypoplasia. The experiment led the authors to accurately hypothesize that their model of "flow-volume hypoplasia" was a result of abnormal "flow-volume streaming" (33).

Several experimental models have been developed to investigate the impact of alterations in hemodynamic physiology on cardiac development, including causing outflow obstruction. Conotruncal banding causes mild-to-moderate increases in ventricular afterload and precipitates cardiomyocyte hyperplasia and hypertrophy, altered myosin chain gene transcription profiles, increased contraction, and altered myofiber orientation. However, the changes precipitated by this model are all triggered predominantly by increases in intraventricular pressure, which exerts a radial force perpendicular to the flow of blood (34).

Shear stress. Shear stress instead describes a frictional force acting along the endothelial surface parallel to the flow of blood. Laminar blood flow begins to pass through the human heart on day 24 of gestation, a couple of days after early myocardial cell contraction (34). Flow characteristics are frequently described by the Reynold's number (Re): for values ≈1, inertia forces within the fluid match those of the fluid viscosity itself, and flow is therefore laminar. With progressively higher Re values, inertia becomes increasingly dominant, leading initially to localized laminar vortices within the flow and subsequently—for Re ≥2,100—inertia becomes so great that turbulent flow then occurs. In the developing embryo, the Re of blood is very low, and flow is predominantly laminar. The inner curvature of structures therefore experiences the higher velocity of blood. Later in gestation, the Re increases, and the outer curvatures experience the highest velocities of blood (or even turbulent flow). However, despite laminar flow properties within early embryonic cardiovascular structures, modern optical microparticle velocimetry estimates the blood velocity in the LVOT to be in the region of 26 mm/s—which corresponds to wall shear stress comparable to that found in adult aortic tissue (≈5 to 7 Pa).

In addition, shear stress is not uniform within developing cardiac structures. According to Hagen-Poiseuille's law of volumetric flow, shear stress is inversely proportional to luminal radius. Therefore, within the developing heart tube, early sulci and expansions—followed by looping—result in a complex and dynamic pattern of flow dynamics and shear stresses. These forces act via various transmembrane signal transduction proteins to affect intracellular mechanisms. Candidate mechanoreceptors acting in this fashion include integrins, tyrosine kinase, and G-protein–coupled receptors and ion channels (34). Surface glycoprotein probably acts to assist in shear stress sensing.

Signal transduction. Especially important in shear stress signal transduction are believed to be ultrastructural membrane cilia. For example, the prevailing hypothesis explaining visceral handedness is that leftward flow of fluid across the primitive node during the trilaminar disc stage causes asymmetric (right-to-left) bending of motile cilia leading to a polarized membrane with high left-sided calcium flux (35). The left-sided calcium flux then leads to increased local expression of the *nodal* gene; genetic asymmetry is established and sidedness determined. In vascular structures, endothelial membrane cilia are an important interface through which shear sensing is transduced. Downstream gene expression is mediated via protein kinases and second messenger systems. Important candidates for specific gene targets include endothelin-1, nitric oxide synthase, and Krüppel-like factor-2 (36). Endothelin-1 acts as a vascular and cardiomyocyte growth factor (in addition to sustained vasoconstrictor), and its modulation in response to shear stress is complex (34). However, endothelin-1 knockout vertebrates display a range of complex cardiac malformations (37). The importance of Krüppel-like factor-2 (a zinc finger transcription factor) is implied by direct induction in response to elevated shear stress, particularly in large arterial walls. Its loss of function leads to high-output cardiac failure independent of anemia or structural defects (38). A role of nitric oxide synthase is appealing because nitric oxide physiologically antagonizes the effects of endothelin-1 and Krüppel-like factor-2 and has been shown to be induced by shear stress in chick embryos (34).

In summary, signal transduction and gene modulation are directly affected by shear stresses mediated via cardiovascular endothelium. The precise regional and temporal patterns of these phenomena are undoubtedly complex, and the details of interplay among candidate downstream transcription control elements and gene products have not been fully elucidated. However, experimental manipulation of flow through developing left-sided cardiac structures is known to exert profound effects on left atrial, LV, and left atrioventricular valve development. In the clinical setting, phasic flow patterns are now known to be abnormal in the

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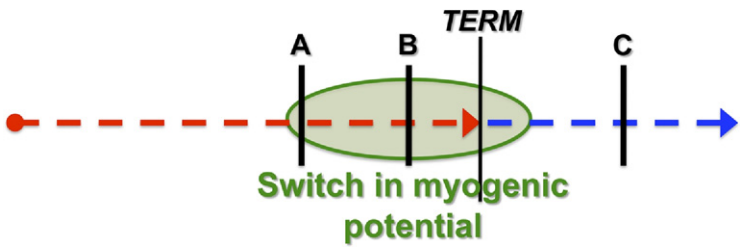

Figure 6 **Schematic Representation of the Switch in Myogenic Potential Late in Gestation From Hyperplasia to Hypertrophy**

Post-natal mammalian cardiomyocytes **(C)** are generally unable to replicate and therefore cardiac muscle can only undergo hypertrophy in response to load or injury. Conceivably, a fetus who receives therapeutic relief of outflow obstruction before the switch in myogenic potential **(A)** might continue on to grow a left ventricle of adequate size and function to support a systemic circulation. Fetal interventions later in gestation **(B)** when hyperplastic potential is less may not permit adequate ventricular growth.

pulmonary veins and left atrium of infants with HLHS (39). In fact, even in the absence of other cardiac anomalies, early closure of the foramen ovale in the first trimester (and therefore markedly reduced left-sided blood flow) is believed to be an occasional cause of mitral atresia, aortic atresia, and HLHS (40).

Restrictive atrial septum. Flow dynamics not only influence growth of left-sided cardiac structures, but may also be important determinants of maturation of the pulmonary vasculature. A small proportion of infants with HLHS have an intact or restrictive atrial septum thereby impeding left atrial and pulmonary venous egress. Their neonatal mortality is particularly high, even after successful atrial decompression (41). Doppler studies reveal significant differences in pulmonary venous phasic flow patterns in such infants (39,42). These differences—in addition to pulmonary venous hypertension and profound postnatal cyanosis—may be responsible for abnormalities in pulmonary maturation that persist even after relief of atrial septal obstruction by septostomy (43). Abnormalities in pulmonary maturation might include venous "arterialization," impaired vasoreactivity, parenchymal abnormalities, and dilated lymphatics. Interestingly, maternal hyperoxygenation has recently been used to successfully identify infants with restrictive atrial septa though impaired vasoreactivity (44). Pre-emptive identification of such infants may in the future allow for early noninvasive atrial septal defect enlargement through novel techniques such as ultrasound histotripsy (45).

In summary, circumstantial evidence is strong to support the notion that reduced or abnormal flow dynamics within the developing LV (as a result of primary defects in the outflow tract) contribute exigently to LV hypoplasia. The lesser degrees of LV hypoplasia encountered in aortic atresia with ventricular septal defect offer some proof of concept to the role of flow dynamics in LV hypoplasia: the septal defect offers an outflow to the LV cavity, thereby allowing through-flow and promoting ventricular growth. Finally, altered flow dynamics and left atrial egress probably modulate the maturation of pulmonary vasculature, thereby impacting the risk profile of neonatal treatment strategies.

Remodeling: Hypoplasia Versus Hypertrophy

The developed human heart is capable of cardiomyocyte hypertrophy, but not hyperplasia. In contrast, during embryogenesis, cellular proliferation (hyperplasia) is an obligatory requirement. Therefore, at some point during development, ventricular muscle undergoes a switch in potential from hyperplasia to hypertrophy. This switch in myogenic potential may have important implications for ventricular remodeling in neonates with left ventricular outflow obstruction. For example, the inability of a hypertrophied, hypoplastic LV to undergo hyperplastic remodeling once outflow obstruction is alleviated greatly compromises the success of biventricular repair strategies in infants with a borderline LV (Fig. 6).

In contrast to the typical hypertrophic response that accompanies post-natal ventricular outflow obstruction, aortic banding in fetal sheep mid-gestation leads to initial cardiomyocyte hypertrophy, which is followed by a hyperplastic phase (46). Experimental right atrial clipping in first trimester chick embryos leads to increased left-sided flow and a hyperplastic ventricular growth response (47). Details behind the switch from hyperplastic potential that occurs later in gestation are unclear. In rats and sheep, it occurs around—or shortly after—the time of birth (48), although it may be earlier in humans (49). It is heralded in rats by a final nuclear division without cytokinesis, therefore leading to binucleation. However, the signal prompting this final division is not known. Confusingly, identical cardiomyocyte stimuli have been shown to trigger either cellular hypertrophy or hyperplasia in a time-dependent fashion. Angiotensin II, for example, is known to directly stimulate hypertrophy of post-natal hearts via the ERK mitogen–activated protein kinase pathway. However, in late gestation, angiotensin II triggers hyperplasia—but not hypertrophy—via the same ERK-signaling pathway (50). Presumably, therefore, different downstream steps, or additional modulators, are responsible and have yet to be identified.

Interestingly, in normal individuals, subtle differences in the switch in myogenic potential from hyperplasia to hy-

pertrophy may have important implications for adult cardiovascular health. Gestational weight (even within the normal range) is one of the strongest independent predictors of mortality from coronary atherosclerosis in later life (51). Many "conventional" risk factors for atherosclerosis themselves appear to be strongly linked to gestational weight and the environment in utero (52). One postulated mechanism underlying this phenomenon is that exposure to intrauterine stress and/or an earlier switch from hyperplasia leads to a reduced absolute number of cardiomyocytes (52). An otherwise normal ventricle with fewer cardiomyocytes will exhibit cellular hypertrophy, and intercapillary distances must be larger. The safety margin during times of myocardial ischemia may therefore be less (52).

In summary, differences in cardiac remodeling may influence the relative extent of hypertrophy and hyperplasia resulting from other primary cardiovascular defects. After the switch from hyperplastic potential, ventricular remodeling is hampered by its ability to only undergo hypertrophy, rather than growth. It is likely that the total number of cardiomyocytes present at the time of the switch from hyperplasia to hypertrophy will have implications for late function and survival of infants subjected to biventricular repairs. With the advent of fetal diagnosis of congenital heart lesions, pharmacologic strategies to promote or prolong the period of hyperplastic potential would be of real therapeutic value. *Finally, knowledge of the timing of loss of hyperplastic potential will likely have important implications for the success and durability of fetal interventional strategies aimed at alleviating outflow obstruction.*

Fetal Intervention

After initial reports in the early 1990s (53), transcatheter fetal aortic valve dilation has become a viable therapeutic option in certain centers (54). The aim of such intervention is to avoid single-ventricle palliation by improving the dimensions and performance of left-sided structures during the latter stages of pregnancy. Balloon dilation of fetal aortic stenosis has now been shown to result in enhanced aortic (and mitral) valvular growth and improved LV function (55). These favorable consequences appear to increase the chances of successful post-natal biventricular physiology (55), although comparisons to "controls" can be difficult. Disappointingly, intervention for aortic stenosis even in the second trimester has not been shown to improve growth and development of LV dimensions (55). The reasons for this are not obvious, but it may be that the window for hyperplastic remodeling in humans is earlier than currently feasible by conventional transcatheter techniques.

Irrespective of the lack of LV growth after fetal aortic valvotomy, it appears that a certain group of fetuses within the "grey zone" may be salvaged from univentricular physiology. However, it is important to be able to more clearly identify candidates likely to benefit from this risky technology. Severe LV hypoplasia is unlikely to be salvaged. Therefore, potential candidates for fetal aortic valvotomy include those with severe aortic stenosis in conjunction with LV length within 80% of normal (z-score ≥ 2), aortic valvular z-score diameters between -3.5 and -2 and flow reversal in the transverse aortic arch (54). Future efforts to more clearly define the timing and signals involved in loss of hyperplastic remodeling may translate to fetal interventions that lead to growth of LV dimensions that cross percentiles towards normal.

The Management Conundrum

A challenging group of children with LVOT obstruction are born with a LV that is neither rudimentary nor "near normal." These "borderline ventricles" of moderate hypoplasia represent a clinical decision-management problem, because the decision to pursue biventricular repair or univentricular repair must frequently be made in the first few days of life. This decision is difficult to reverse and may prove fatal if incorrect.

Intuitively, biventricular physiology is considered superior to univentricular physiology. This notion has led to a clinical bias favoring biventricular repairs in infants with borderline LV hypoplasia (1,56). However, preferentially pursuing biventricular repairs in infants with borderline hypoplasia compromises aggregated survival, because many such infants would actually have better predicted survival if instead a Norwood (univentricular) repair had been pursued (1). Reasons for this include the considerable complexity of certain biventricular repair approaches (57), higher rates of reintervention associated with biventricular repair (58), and judgment error.

Long-term survival in the face of an inadequate systemic pumping chamber seems incongruous. However, it has been made a reality through 5 decades of research and surgical evolution in areas of cardiopulmonary support, deep hypothermic circulatory arrest, cardiac reconstruction, systemic-pulmonary shunt physiology, cavopulmonary shunt and single-ventricle physiology, and neonatal intensive care medicine. Consequently, since the first successful repairs of HLHS by Dr. William Norwood in the early 1980s (59), late survival for the (otherwise lethal) lesion are now in the region of 70% (1,60) and as high as 90% in certain centers (61).

However, not everything is rosy. Univentricular repair of infants with hypoplastic LVs involves multiple-staged, open-heart operations, and families can expect the first few years to be punctuated with numerous lengthy admissions to tertiary hospitals. The highest-risk initial "Norwood" operation is typically undertaken in the first couple of weeks of life, at an average patient weight of only $\approx$3 kg (1). It involves a lengthy duration on cardiopulmonary support, usually necessitating deep hypothermia and circulatory arrest and therefore the potential for cerebral injury. Perioperative complications are common, and include emergent repeat cardiac catheterizations and interventions (62), or even need for salvage cardiac transplantation (1). Even late after initial successes, right ventricular and tricuspid valve

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dysfunction may ensue, requiring further open-heart operations (63). Superimposed on cardiac morbidity is a high incidence of neurological dysfunction: 20% of infants have magnetic resonance imaging–detectable white matter lesions at birth (64), which increases to ≈50% after Norwood operation. Gross spastic disabilities may be present in 5% to 10%, and subnormal intelligence quotients, behavioral problems, and delayed schooling are the norm in older children (65). Recent efforts to limit exposure to cardiopulmonary bypass and circulatory arrest during the neonatal period through "hybrid" approaches are encouraging but—at present—are associated with equally high mortality (66).

The paradox. The high morbidity associated with univentricular repair (despite improving trends in overall mortality) leads to a clinical paradox. The paradox is that although the majority of physicians advise parents with prenatally diagnosed HLHS to continue pregnancy and then undergo univentricular repair, the majority of the same physicians would recommend termination of pregnancy if *one* of the couple were a member of their own family (67)*. A cynic would suggest that this paradox is driven by medical self-fulfillment. The medical profession relishes challenges, enjoys developing and experimenting novel therapies—and they keep us in business: as much as a third of the entire service of large pediatric cardiovascular divisions in North America is related to treating LVOT obstruction, performing the multiple-staged, univentricular operations and dealing with their complications. A more comfortable reason behind the apparent discrepancy may be a greater understanding by physicians of the huge burden that all the various aspects of treating a child with LV hypoplasia imparts on the family unit (68). The discord between the data we use to advise patients (mortality data) and our own experiences of the morbidity suffered by patients and their families that lead to discordant advice illustrates an important gap in clinical understanding. As such, aggressive efforts to lessen morbidity experienced by survivors and improve their neurologic and functional performance should be the next major objective for our specialty.

Summary

LV hypoplasia is a continuum of severity dependent on numerous modifying factors (Fig. 1). It is typically seen in association with LVOT obstruction, which is itself part of a spectrum of related defects with common etiologies. The secondary responses to outflow obstruction are complex but involve abnormal flow dynamics and shear stresses, which result in compromised and poorly orchestrated ventricular growth and development. The remodeling process is the crucial determinant of the morphological picture encountered at term gestation. Remodeling is likely influenced by genetic modifiers, including intrinsic myocardial growth signaling pathways, possibly including those of HAND transcription factors. In addition, during the latter stages of gestation, cardiomyocytes undergo a switch in myogenic potential and lose the ability to undergo mitosis. Ventricular hyperplasia can therefore no longer occur, and remodeling is limited to muscular hypertrophy. Subtle differences in this switch in myogenic potential—and modulators thereof—are likely to be of clinical and therapeutic importance, especially in children with "borderline LVs" (Fig. 1) being considered for fetal interventions or post-natal biventricular repair strategies. Finally, by more clearly understanding the initiators and propagators of abnormal ventricular development, we can hope to lean away from grouping a heterogeneous group of infants together under the unsatisfactory term "hypoplastic left heart syndrome."

*At the Congenital Heart Surgeons' Society annual meeting, Montreal 2004, an audience of ≈ 100 congenital heart surgeons and cardiologists from North America and Western Europe responded anonymously to the following question: what do you advise a young couple receiving a diagnosis of HLHS at 14 weeks gestation during their first pregnancy? Answer: termination of pregnancy 21%, compassionate care 6%, Norwood operation 73%. The next question was: *your daughter* is the pregnant lady in question; what do you advise? Answer: termination of pregnancy 67%, compassionate care 5%, Norwood operation 26%, transplantation 1%.

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Key Words: borderline left ventricle ■ embryology ■ fetal ■ hypoplastic left heart syndrome ■ left ventricular hypoplasia.