Hypoplastic Left Heart Syndrome
New Insights
Paul Grossfeld

Hypoplastic left heart syndrome (HLHS) is one of the most severe congenital heart defects, accounting for 20% to 25% of mortality in infants born with congenital heart disease. In the United States, ∼2000 infants are born each year with HLHS.1 To date, there is a paucity of studies that define the underlying genetic, molecular and cellular mechanisms of HLHS.2–4

Most cases of HLHS are thought to arise secondarily because of decreased flow into the developing embryonic left ventricle, although in some cases, abnormal left ventricular growth could be the primary defect. There is strong evidence for a genetic etiology for HLHS, although very little is understood about the genetic mechanisms underlying HLHS. Nineteen percent of first degree relatives of infants with HLHS have a congenital heart defect.5 In addition, there are several chromosomal disorders that are associated with HLHS. For example, 10% of all infants born with a terminal 11q deletion (Jacobsen syndrome) have HLHS.6 Mutations in at least one gene, the cardiac transcription factor NKX2.5, have been identified in patients with HLHS.7,8

Similar to many of the most severe congenital heart defects, treatment strategies for HLHS have evolved and are still changing. The two current surgical strategies include the three-stage Norwood/Fontan procedure, or, alternatively, cardiac transplantation. The Norwood procedure, which is performed optimally in the neonatal period to avoid the development of pulmonary vascular disease, entails reconstructing the aortic arch, transsecting the pulmonary artery, anastomosing the pulmonary artery root to the reconstructed aorta, and placing a systemic to pulmonary artery shunt (either from aorta or more recently, from the right ventricle). Although there has been significant progress in outcomes, neither surgical approach is curative and long-term outcomes are uncertain. Consequently, there has been an ongoing effort to develop alternative strategies for the treatment of HLHS. Ideally, a two-ventricle repair, in which only the hypoplastic arch is repaired, would be preferable to preserve the left ventricle as the systemic ventricle.

Although the dogma has been that hypoplasia of the left-sided structures of the heart is irreversible, (thereby making a two-ventricle approach not feasible for most patients) there is evidence that hypoplastic left-sided structures may be capable of growth under certain physiologic conditions. For example, infants with HLHS waiting for a transplant can exhibit significant postnatal growth of the left-sided structures of the heart.9 However, the mechanisms underlying postnatal growth of an HLHS heart are unknown.

Currently, only a small subset of HLHS patients, those with patency (ie, not atresia) of the mitral and aortic valves and with only mild hypoplasia of the left ventricle, may be amenable to a two-ventricle repair. Even among this subset of patients, one of the ongoing challenges in the management of patients with hypoplasia of the left sided structures is to determine which patients have a left ventricle that will be capable of supporting the systemic circulation. Although there are some computer-generated models that can assist to decide between a one versus two-ventricle repair, they are far from exact and have limitations. For example, in some patients with mild hypoplasia of the left sided structures at birth, there may be insufficient postnatal growth of the left ventricle, ultimately resulting in a left ventricle that cannot sustain normal systemic cardiac output. Consequently, it may not be possible to determine, at the outset, if a hypoplastic left ventricle can grow postnataally. Thus, most clinicians opt for the “safer” (albeit tenuous) single ventricle repair when in doubt. Ideally, early identification of patients that are capable of postnatal growth of the left-sided structures would optimize the selection process of those patients that are best suited for a two-ventricle repair.

In this issue of Circulation Research, deAlmeida et al.10 describe a series of experiments that begin to give possible insights into the mechanisms of HLHS. Using a chick hemodynamic model, they surgically ligated the embryonic left atrium (thereby restricting prograde blood flow into the left ventricle) which gave rise to left ventricular hypoplasia. Next, they demonstrated that the hypoplastic left ventricle can be “rescued” by subsequent clipping of the right atrium (thereby forcing more blood flow across an atrial communication, and away from the tricuspid valve, to what was destined to be a hypoplastic left ventricle). The left ventricular growth was physiologic and not a pathologic response of a failing ventricle to volume overload. Furthermore, this “hemodynamic rescue” was associated with cardiac myocyte hyperplasia.

These results have important potential clinical implications. First, these studies demonstrate that at least under some
circumstances, an embryonic hypoplastic left ventricle can be salvaged, and that myocyte proliferation can be induced under the appropriate physiologic stimulus. Second, these studies raise the interesting possibility that at least in some cases, HLHS may be the consequence of abnormal myocyte proliferation, despite normal prograde flow to the left ventricle. This is an important observation because most cases of HLHS are considered to be caused by decreased prograde blood flow during development. The results of the study by deAlmeida et al give further support to the possibility of a mechanism for HLHS in which abnormal cardiac myocyte proliferation can be the primary defect. In this case, the defect may be because of abnormal signal transduction of normal blood flow that is critical for normal myocyte division and left ventricular growth. This potentially opens new areas of investigation for identifying novel therapeutic targets that can restore, or induce, normal myocardial signal transduction of blood flow in at risk patients.

There are, however, important limitations in the interpretation of the results of deAlmeida et al First, the model to generate HLHS is based only on hemodynamic perturbation. As mentioned above, in humans, HLHS has a strong genetic component. What if mutations in genes encoding factors involved in myocardial signal transduction of blood flow cause HLHS? In this case, restoration of normal prograde blood flow to the hypoplastic left ventricle may have no effect on left ventricle growth and cardiac myocyte division.

Second, because of technical constraints, these studies were not able to determine the duration of the effect of restoring normal blood flow to a hypoplastic left ventricle. In fact, the HLHS chicks were analyzed only 24 hours after right atrial clipping. It is possible that the response of the hypoplastic left ventricle to right atrial clipping is transient, and that over time the left ventricular growth and function could regress.

Third, the hemodynamic rescue model for treating HLHS is limited only to the HLHS hearts in which there is patency of both the mitral and aortic valves, which constitutes a small minority of patients with HLHS. Interestingly, studies\(^1\),\(^2\) have recently been published describing an in utero catheter-based intervention to relieve critical aortic valve stenosis (ie, before the development of complete atresia of the valve), thereby restoring normal inflow to the left ventricle. The results have been mixed, probably for numerous reasons. Some patients’ left ventricles seem to regress, or not improve, despite relief of critical aortic stenosis and presumably improved prograde blood flow to the left ventricle. Nonetheless, these studies suggest that early fetal intervention to relieve critical aortic stenosis before the development of complete valvar atresia may enable hemodynamic rescue of a larger subset of patients that are destined to develop HLHS.

Lastly, the mechanisms underlying a hemodynamic model for left ventricular hypoplasia in the chick may not apply to the human HLHS. In these studies, there was no evidence reported of hypoplasia or atresia of the other affected structures that comprise the human form of HLHS, specifically the mitral and aortic valves and the aorta. Thus, the relevance of the chick hemodynamic model to human HLHS must be questioned.

In summary, significant progress has been made in the treatment of HLHS. Nonetheless, there is still no cure, and long-term outcomes are uncertain. Although some patients may continue to do well with our current surgical approaches, it may be na"ive to think a single therapeutic approach is optimal for all HLHS patients. The genetic and anatomic heterogeneity of HLHS supports a rethinking of our current approaches, and new treatment strategies need to be investigated. Different and potentially complementary approaches combining surgical, catheter-based and medical therapies should be considered. These strategies should be based on a system of stratification that is derived from understanding the genetic, molecular and cellular mechanisms of HLHS.

Already, some centers are adopting a “hybrid” approach for a subset of HLHS patients as an alternative to the Norwood.\(^1\) In this case, in the newborn period a stent is placed to maintain patency of the ductus arteriosus, and the branch pulmonary arteries are banded to restrict pulmonary overcirculation. Thus, the hybrid approach can allow postponement beyond the newborn period before committing to a one versus two-ventricle repair.

Studies such as that of deAlmeida et al are critical for understanding the most basic and fundamental aspects of HLHS, as well as for devising new therapies. In the future, identification of genes causing HLHS, and the development of additional animal models for HLHS, such as in the mouse, should facilitate our progress in treating this group of patients with one of the most severe and challenging forms of congenital heart disease.

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References

5. Loffredo CA, Chokkalingam A, Sill AM, Boughman JA, Clark EB, Scheel J, Bremer J. Prevalence of congenital cardiovascular malformations among relatives of infants with hypoplastic left heart, coarctation...

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