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Charles R. Cole
University of Cincinnati

Pirooz Eghtesady
Washington University School of Medicine in St. Louis

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Review Article

The myocardial and coronary histopathology and pathogenesis of hypoplastic left heart syndrome

Charles R. Cole,1 Pirooz Eghtesady2

1University of Cincinnati, Cincinnati, Ohio; 2Washington University in St. Louis, St. Louis, Missouri, United States of America

Abstract: Hypoplastic left heart syndrome has the greatest mortality rate among all CHDs and without palliation is uniformly fatal. Despite noble efforts, the aetiology of this syndrome is unknown and a cure remains elusive. The genetic and anatomical heterogeneity of hypoplastic left heart syndrome supports a rethinking of old hypotheses and warrants further investigation into the histological and vascular variations recognized with this syndrome. In an effort to elucidate the pathogenesis of hypoplastic left heart syndrome, this review will focus on its unique myocardial and coronary pathology as well as evaluate the association of hypoplastic left heart syndrome with the endocardial broelastosis reaction.

Keywords: Hypoplastic left heart syndrome; endocardial broelastosis; coronary arteries; myocardial morphology; CHD

Methods

We performed a detailed review of PubMed for articles pertaining to hypoplastic left heart syndrome, which produced over 2700 articles that were then narrowed down to 67 articles based on relevance to histology, pathology, valve, myocardium, cranial, endocardial, broelastosis, and pathogenesis. We searched from 1940 until the present. We needed to evaluate articles dating back to 1940 because it was during that time period that much of the histological analysis for hypoplastic left heart syndrome was being performed. We also wanted to know the histologic appearance of specimens before any intervention. We included all articles we could locate pertaining to the pathogenesis of hypoplastic left heart syndrome.

Variable anatomy of hypoplastic left heart syndrome

Hypoplastic left heart syndrome is a severe and devastating heart defect that affects ~1 in 5-10,000 children born each year and accounts for up to 25% of all neonatal deaths from CHD.1 Hypoplastic left heart syndrome is characterized by a diverse spectrum of malformations distinguished by underdevelopment of the left ventricle and its concomitant chamber, rendering it unable to support systemic circulation.2,3 The presence of anatomic variations within the classic notion of hypoplastic left heart syndrome yields a continuum of phenotypic heterogeneity that can be divided into broad subgroups.1-4 These variations are dependent upon the presence or absence of the following: an inlet to the left ventricle, a patent outflow tract, a ventricular septal defect, and/or any other associated cardiac defects. Each subtype can be associated with an atrial arrangement, with situs solitus being the most common.5 It is necessary to analyze these subgroups individually because of their differing histological characteristics and the possibility for differing inciting events. Seidman et al. provide an excellent breakdown of hypoplastic left heart syndrome subtypes, which appear in Table 1.

First, hearts with combined mitral and aortic atresia present with a thin-walled, slit-like left ventricle.4 The ascending aorta and arch are extremely hypoplastic, and flow is retrograde.7 Systemic output is ductal dependent. In the setting of
combined mitral and aortic atresia, the ascending aortic arch hypoplastic, and all systemic outflow) displayed myocardial birefringence as newborns. Hypoplastic left heart syndrome e specimens that are exposed to increased left ventricular systolic hemodynamic pressure burden during development and the norm all myocardial architecture in these cases also suggests that the anatomy of these cases is likely vascular.

Hypoplastic left heart syndrome e specimens that are exposed to increased left ventricular systolic hemodynamic pressure burden during development and the norm all myocardial architecture in these cases also suggests that the anatomy of these cases is likely vascular.

Cardiac muscle cell orientation in non-diseased hearts exhibits a sin bar pattern in the embryo, fetus, child, and adult. Myocardial birefringence is not unique to hypoplastic left heart syndrome e, but can be found to some degree in normal hearts, and correlates extensively in hearts with conditions such as hypertrophic cardiomyopathy, pulmonic atresia, and tetralogy of Fallot.

Morphologic subgroups of hypoplastic left heart syndrome e

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Description</th>
</tr>
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</table>
| 1 | Mitral and aortic atresia, if a ventricular septal defect is present, a large left ventricular cavity will develop and the wall of the left ventricle will be proportionately thicker. The larger the ventricular septal defect, the more closely the left ventricle will approach normal dimensions. The observation that left ventricular dimensions are proportional to the size of the inlet suggests that myocardial development is dependent on adequate blood flow during development. Second, mitral atresia can also occur with a stenotic aortic valve, patent aortic root, and ventricular septal defect. These cases are characterized by a hypoplastic ascending aorta with a widely patent ductus arteriosus. In the setting of a large ventricular septal defect, irrespective of the valve dimension, the aortic valve is usually atretic, which suggests that valvular development is also dependent on adequate blood flow during development. Third, hearts with isolated aortic atresia and a patent mitral valve without a ventricular septal defect develop thickening of the left ventricular free wall, ventricular septum, and endocardium. As in combined mitral and aortic atresia, the ascending aorta and aorta are hypoplastic, and all systemic outflow is ductal-dependent. Fourth, hypoplastic left heart syndrome e is characterized by a hypoplastic aortic valve, stenosis, and a patent mitral valve in a small anterograde outflow through the aortic valve. The degree of ascending aortic and arch hypoplasia is less than observed with mitral atresia. Fifth, in general, the degree of aortic arch hypoplasia correlates with the dimensions of the aortic root, but there is one subset of hypoplastic left heart syndrome e with severe aortic arch hypoplasia that is cut of exception to the degree of aortic root hypoplasia. This subset of hypoplastic left heart syndrome e can have multiple combinations of mitral and/or aortic valve abnormalities.

Lev et al described some common qualities between atypical hypoplastic left heart syndrome e. A detailed analysis of 230 hypoplastic left heart syndrome e hearts revealed that specimens had an enlarged heart with an apex forming the right ventricle. In all cases the right atrium was hypertrophied and enlarged, the left atrial appendage was small, and the tricuspid annulus was enlarged and in pitted upon the infundibular region. The right ventricle was hypertrophied and enlarged. Although right ventricular abnomalities are found in hypoplastic left heart syndrome e, many of these abnomalities may be the result of the right ventricle compensating for an increased workload secondary to the pulmonary left ventricular atresia.
endothelial fibroelastosis

in an eloquent review, Lurie describes endocardial fibroelastosis as a reaction of the endocardium, not a disease state. Gently, the reaction is identified as a pearly or opaque white appearance of the endocardium, especially of the ventricles. The normal endocardium is transparent and only around 10 μm in thickness. Endocardial fibroelastosis is defined by thickening of the endocardium by layers of collagenous and elastic tissue to > 20 μm. Lurie described the endocardial fibroelastosis reaction as a chronicologic sequence of events in the development of the endocardial fibroelastosis reaction. It is also possible that in

Left ventricular endocardial fibroelastosis in hypoplastic left heart syndrome is often found in the setting of a patent mitral valve and severely stenotic or atretic aortic valve. Hearts that develop endocardial fibroelastosis reaction are always under stress, either from pressure overload due to mechanical obstruction or from volume overload due to cardiac muscle hypertrophy. However, not every heart under stress will develop endocardial fibroelastosis. In addition, endocardial fibroelastosis is not seen within the left ventricle in the setting of congenital mitral and aortic atresia when blood flow is absent from the left ventricle but may affect the left atrium and mitral valve in the presence of mitral valve obstruction. There is strong evidence that prenatal infection could account for some cases of left ventricular hypoplasia with endocardial fibroelastosis. Coronaviruses and mumps viruses were identified as etiologic agents of endocardial fibroelastosis in the 1960s and 1970s. These findings were further supported when mumps cases were identified with mumps in the mumps vaccine. The incidence of endocardial fibroelastosis sharply declined with the administration of the mumps vaccine. Infants with ventricular septal defect may have a patent mitral valve and severe left ventricular outflow tract obstruction in the first trimester of pregnancy. Recent studies have highlighted the possibility that some cases of hypoplastic left heart syndrome may result from abnormal ventricular septation during development. Endocardial fibroelastosis
<table>
<thead>
<tr>
<th>Subtype</th>
<th>Frequency</th>
<th>Gross anatomy</th>
<th>Histopathology of left ventricle</th>
<th>Endocardial fibroelastosis</th>
<th>Aortic valve pathology</th>
<th>Coronary artery pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>M ventral and aortic atresia</td>
<td>36–46% *</td>
<td>Thinner-walled, slit-like left ventricle. Right ventricle thin-walled, small in size.</td>
<td>No abnormalities detected.</td>
<td>Absent</td>
<td>Atretic</td>
<td>Coronary shunts are mainly ductus-arteriosus.</td>
</tr>
<tr>
<td>M ventral stenosis with NA and ventricular septal defect</td>
<td>NA</td>
<td>The largest the ventricular septal defect, the more closely the left ventricle will approach normal dimensions.</td>
<td>No abnormalities detected.</td>
<td>Absent</td>
<td>Thinned, friable valve leaflets.</td>
<td>Few ventriculo-coronary stenoses.</td>
</tr>
<tr>
<td>Aortic stenosis with a patent m. ventricle</td>
<td>20–29% *</td>
<td>Thickened left ventricular free wall and septum</td>
<td>Present ventricular free wall and septum. Myocyte disarray generally in the inner two-thirds of the myocardium that does not involve the outer compact myocardium. Areas of focal calcification and scarring.</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Aortic valve stenosis and dysplasia with patent m. ventricle</td>
<td>23–26% *</td>
<td>Thickened left ventricular free wall and septum</td>
<td>M. arched myocardiopathy of the left: Present ventricular free wall and septum. Myocyte disarray generally in the inner two-thirds of the myocardium that does not involve the outer compact myocardium. Areas of focal calcification and scarring.</td>
<td>Nodular, thickened, and dysplastic valve leaflets. Fusion of valve leaflets.</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Left ventricular hypoplasia with coarctation of the aorta</td>
<td>24–80% of hypoplastic left heart syndrome &amp; coarctation **</td>
<td>Proportional hypoplasia of left ventricle in relation to hypoplasia of vascular structures.</td>
<td>Fibrosis is not evident.</td>
<td>Absent</td>
<td>Fusion of valve leaflets.</td>
<td>Proportional coronary shunt development in relation to hypoplasia of vascular structures.</td>
</tr>
</tbody>
</table>

* Frequencies documented before Norwood procedure.12,13
** Frequencies unrelated to Norwood procedure.6,14,15
genetically susceptible patients contribute from both mechanical and immunologic factors are necessary for pathology. In hypoplastic left heart syndrome, a two-hit phenomenon may contribute to the expression and/or severity of the endocardial fibroelastosis reaction.

In the past, endocardial fibroelastosis was thought to be a primary disease that could potentially lead to left ventricular hypoplasia and the "contracted type" of primary endocardial fibroelastosis. The current understanding is that endocardial fibroelastosis does not cause hypoplastic left heart syndrome, but its presence and severity worsen the prognosis. Mcelhinney et al. recently reported that the severity of endocardial fibroelastosis, as determined by prenatal echocardiography in patients with aortic stenosis and evolving hypoplastic left heart syndrome, had an association with postnatal outcomes following in utero balloon valvuloplasty. Patients with more severe endocardial fibroelastosis had a lower probability of postnatal biventricular volume. They also reported that from pre-intervention to late gestation, the time-indexed change in left ventricular end-diastolic volume was significantly greater in fetuses with mild endocardial fibroelastosis compared with those with severe endocardial fibroelastosis. Although our understanding of endocardial fibroelastosis has improved greatly over the last half century, many questions remain regarding the fascinating relationship between hypoplastic left heart syndrome and endocardial fibroelastosis.

Congenital coronary artery fistulas

We now shift focus to the coronary artery histopathology found in hypoplastic left heart syndrome and its contribution to the pathogenesis of the syndrome. We will first evaluate coronary artery

Figure 1. Hypoplastic left heart syndrome. Disorganised bundles of myocytes, large areas of bands, and abnormal vascular formations (left ventricle from 3-month-old hypoplastic left heart syndrome patient, trichrome stain, original magnification 25x). Courtesy of Bohlmeyer.16

Figure 2. (a) Histologic stained section of endocardium (4x20), showing dense fibers of collagen and elastic typical of endocardial fibroelastosis. Reproduced from Am J Pathol 1972;66:483–496, Figure 3; with permission from the The American Society for Investigative Pathology and kind cooperation of G moe M. Hutchins, MD. (b) In contrast to the parallel diagram derived from electron microscopy showing cellular activity that generates the fibroelastosis. 1. Dark smooth muscle cell; 2. light smooth muscle cell; 3. light smooth muscle cell with loss of basement membrane; 4. leio myoid cell; and 5. fibroblast. Adapted from the Archives of Pathology Laboratory Medicine 1979; 103: 218, Figure 8; Copyright 1979 American Medical Association. All rights reserved. Courtesy of Lurie.20
...studies, followed by more coronary artery disease or mitral valve disease, and will naturally elevate the mortality rate.

...with mitral and aortic atresia. A congenital coronary artery stula is an abnormal direct connection between any part of the coronary system and a cardiac chamber or great vessel, having bypassed the normal coronary ostia.2,7

...lesions consisted of circumferential myocardial hypotrophy, thickened elastic limit, and focal intima hyperplasia without significant luminal narrowing.11 Sauer et al.29 found that stulae with mitral and aortic atresia did not demonstrate histological coronary artery abnormalities.

...and aortic atresia.28 Baffa et al.28 noted increased tortuosity of the left coronary artery in patients with either aneurysm or atroventricular canal. N of ventricular coronary connections were identified in the subgroup with mitral and aortic atresia.11 Baffa et al.28 found ventricular coronary connections in 27 of 89 specimens with mitral and aortic atresia and in 2 out of 52 specimens with mitral and aortic atresia. M of the connections in hypoplastic left heart syndrome are the arterio-sinusoidal subtype, rather than the direct arterio-luminal subtype.28,29 The arterio-sinusoidal subtype frequently occurs with endocardial hypocontractility of the left ventricle.28

...cushion with poststenotic dilatation. The regional distribution of myocardial ischemia supports the concept that vascularisation parallels myocardial organisation in the developing heart.30 It has been postulated that elevated left ventricular intracavitary pressure inclines the persistence of omphalomesentric vasculature from around the developing aortic arch and circumflex artery to the left coronary artery in mitral stenosis/aortic atresia.22,33

...arter applyMiddleware ischaemia during ventricular systole may lead to wall thickening and tautness in the epicardial coronary arteries and their intra myocardial branches.12,30 Fig 3. O Connor et al. observed that diseased vessels were limb to the left ventricular free wall and septum.

...reported corona angiography in prior studies of hypoplastic left heart syndrome with superior origin of the left coronary artery. Sarosi et al.15 reported three cases of hypoplastic left heart syndrome with superior origin of the left coronary artery. The origin of the right coronary artery from the descending thoracic aorta has been documented in one case of hypoplastic left heart syndrome.22

...artery, pulmonic artery stula associated with common mitral and aortic atresia and a ventricular septal defect.24 The authors concluded that the coronary stula was the primary cause of hypoplastic left heart...
syndrome in this case because of the existence of a ventricular septal defect that nullified the intraventricular pressure gradient, which is typical of hypoplastic ventricles and thought to be responsible for the secondary development of stenosis in other cases.44

In an autopsy report of 122 patients who died after a Norwood procedure, Bartram et al.39 found impairment of coronary artery perfusion to be the most frequent cause of death (33 patients, 27%). However, the cause of stenosis in the vast majority of these patients (31 of 33) was secondary to either intraluminal stenosis at the anastomosis or external kinking of the graft.44,45 The poor coronary perfusion in these cases was therefore the result of the surgical technique and was not the underlying coronary disease. Surgical kinking of an absent left circumflex coronary artery from the right pulmonary artery occurred in one case, resulting in biventricular infarction.49 Generalised coronary artery hypoplasia was also found in one patient.49 Despite the rare occurrence of coronary anomalies in hypoplastic left heart syndrome, detailed coronary artery assessment at necropsy ended part of the routine echocardiographic evaluation of hypoplastic left heart syndrome before surgical intervention.37 The coronary arteries in hypoplastic left heart syndrome may become thickened or tortuous in cases with high intraluminal intraventricular pressure, but have a preserved lumen, and with rare exception are likely not primary to the pathogenesis of disease.

M Microvasculature

Focusing on the microvasculature of hypoplastic left heart syndrome, Salih et al.45 described an interesting finding that unoperated hearts with hypoplastic left heart syndrome have a higher mean and maximal diffusion distance from any arbitrary point to the nearest capillary than do normoalae normatral hearts. No differences were noted between left and right ventricles or between subtypes. The authors believe the reduction in capillaryisation may be an inherent abnormality of hypoplastic left heart syndrome that may have implications for ventricular development. Rakusan et al.46 noted that congenital
acetic stenosis and coarctation of the aorta are characterized by an increase in capillary supply proportional to myocardial volume, maintaining capillary density similar to control hearts. They observed that pressure-overload left ventricular hypertrophy in children demarcates proportional capillary angiogenesis, whereas in adults hypertrophy appears to be associated with failure of capillary angiogenesis.

Could the pathogenesis of hypoplastic left heart syndrome stem in part from premature failure of capillary angiogenesis? Jacobs suggested that the decreased capillarisation observed by Salihe et al. might not be an unalleviable inherent abnormality of hearts with hypoplastic left heart syndrome, but rather a snapshot of the supply-demand mismatch that may occur later in gestation.55,56 Recent hypotheses also question whether immune, infectious,5,24 autoimmune insults to genetically susceptible hosts may contribute to left ventricular hypoplasia from either diastolic myocardial injury or secondary to reduced left ventricular blood flow through damaged valves.

Genetic factors that alter valve development have been proposed as the etiology in hypoplastic left heart syndrome.57,58 Mutations in the signaling and transcription regulator, NOTCH1, have caused early

CD31 has also been associated with cancer angiogenesis.48 Recent work suggests that CD31 has a novel role in arteriogenesis and collateral xenotransplantation.59 CD31 has also been identified as the rst molecule that determines pre-existing collateral dian ete.60 These findings highlight the possibility that abnormally high CD31 expression might be an attempt by the myocardium to induce angiogenesis secondary to the decreased capillarisation seen in hypoplastic left heart syndrome. Alternatively, the abnormal capillarisation in hypoplastic left heart syndrome could be the product of abnormally high CD31 expression within the myocardi um.

Pathogenesis of hypoplastic left heart syndrome

The etiological mechanisms leading to hypoplastic left heart syndrome are largely unknown. A bout one-fourth of hypoplastic left heart syndrome cases occur in the context of recognized genetic disorders including, but not limited to, Turner, Jacobs, Noonan, and Holt–Oram syndromes. However, studies involving non-syndromic infants have suggested that heritability is complex. No single disease-causing pathway has yet been identified.23,31 Clinical observations indicate that obstruction of blood flow through the left ventricle in an otherwise normal four-chambered fetal heart, caused by either aortic and/or mitral stenosis, leads to the development of left ventricular hypoplasia.52 Prenatal diagnosis of hypoplastic left heart syndrome can be made as early as 14 weeks' gestation,53 but numerous cases of hypoplastic left heart syndrome have presented with normal or even dilated left ventricular cavities on routine foetal ultrasound at >19 weeks' gestation.49 The unifying pathogenetic explanation is that the growth and development of vascular structures are dependent to some degree on the relative quantity and quality of blood flow during development.5 Recent studies have shown that hypoplastic left heart syndrome emyocytes are well differentiated, but have prolonged expression of fetal or “heart failure” genes.1,24,30 These findings suggest that intrauterine insult to the fetus may occur after 19 weeks' gestation and highlights the possibility that fetal development of hypoplastic left heart syndrome may occur later in gestation.5,1,24,30 Recent hypotheses also question whether immune, infectious, autoimmune insults to genetically susceptible hosts may contribute to left ventricular hypoplasia from either aortic or mitral valvular injury or secondary to reduced left ventricular blood flow through damaged valves.

Inappropriate expression of platelet-endothelial cell adhesion molecule-1, also known as CD31, has been identified in hearts with either hypoplastic left heart syndrome or “heart failure” genes. Recent studies have shown that hypoplastic left heart syndrome emyocytes are well differentiated, but have prolonged expression of fetal or “heart failure” genes. These findings suggest that intrauterine insult to the fetus may occur after 19 weeks’ gestation and highlights the possibility that fetal development of hypoplastic left heart syndrome may occur later in gestation.5,1,24,30 Recent hypotheses also question whether immune, infectious, autoimmune insults to genetically susceptible hosts may contribute to left ventricular hypoplasia from either aortic or mitral valvular injury or secondary to reduced left ventricular blood flow through damaged valves.

Genetic factors that alter valve development have been proposed as the etiology in hypoplastic left heart syndrome.57,58 Mutations in the signaling and transcription regulator, NOTCH1, have caused early
acoustic valve defects in animal models.\(^5\) Genetic involvement in downstream NOTCH signaling and cardiac gene expression have been implicated in familial form of hypoplastic left heart syndrome.\(^6\) A recent study showed a shared genetic linkage with hypoplastic left heart syndrome and bicuspid aortic valve.\(^7\) Bicuspid aortic valve is very common, affecting 1% of the general population, and is a known risk factor for aortic valve disease. It is possible that a small subset of patients with aortic valve defects and hypoplastic left heart syndrome have distinct genetic susceptibilities.\(^8\) Genetic factors are clearly present, but epigenetic mediates and/or environmental influences in ventricle might be necessary for the phenotypic expression of hypoplastic left heart syndrome.\(^9\)

The complex etiologies of hypoplastic left heart syndrome suggests the potential for environmental contributions to the observed phenotype. M. trunal upper respiratory tract infection during the first trimester has been documented as a significant risk factor for hypoplastic left heart syndrome.\(^10\) Population-based studies in the Baltimore-Washington region have identified environmental risk factors for hypoplastic left heart syndrome, including maternal exposure to organic solvents.\(^11\) A recent study showed a seasonal pattern in the presentation of hypoplastic left heart syndrome with peak occurrence in summer months consistent with an environmental risk factor.\(^12\) These findings suggest a role for environmental factors in the etiology of hypoplastic left heart syndrome.

An immune-mediated mechanism for the pathogenesis of hypoplastic left heart syndrome has been proposed where antibodies cross-react with human valvular and myocardial antigens through a mechanism known as molecular mimicry.\(^13\) Our lab recently demonstrated that transplacental transfer of maternally derived antibodies leads to structural congenital cardiac defects in affected progeny that included diminished left ventricular cavity dimensions.\(^14\) Furthermore, a study showed elevated serum levels of anti-β adrenergic receptor antibodies in neonates with hypoplastic left heart syndrome.\(^15\) These findings suggest a potential role for immune-mediated mechanisms for the observed pathological changes.\(^16\)

The evidence that prenatal viral infection could account for some cases of left ventricular hypoplasia with endocardial hypoplasia remains to be fully elucidated.\(^17\) Viral infection is a well-accepted cause of cardiovascular disease. Studies have reported that viral RNA is present in myocardial biopsies from fetuses with aortic valve atresia.\(^18\) A heritable mechanism for the pathogenesis of hypoplastic left heart syndrome has been suggested in which abnormal valvular or myocardial prolapse may be the primary defect. In this case, left ventricular hypoplasia is thought to result from altered cellular signal transduction, which is critical for normal myocyte division and left ventricular growth.\(^19\) Conversely, the thickening of the left ventricular myocardium in subtypes of hypoplastic left heart syndrome with a patent left ventricle thought to result from advanced myocardial hypertrophy.\(^20\) The abnormal thickening of the left ventricular myocardium could lead to reduced left ventricular cavity size, and valvular abnormalities as a result of altered haemodynamic forces. M. Marfan syndrome has a distinct genetic basis, and can be inherited in a dominant fashion.

The complex heritability of hypoplastic left heart syndrome is likely due to a combination of genotypic and environmental factors.\(^21\) The pathogenesis of hypoplastic left heart syndrome is likely due to a combination of genetic and environmental factors.\(^22\) Further research efforts in these subtypes should focus on identifying genetic and environmental causes of valvular abnormalities. Subtypes of hypoplastic left heart syndrome with patent left ventricle or obstructed outflow tract are particularly challenging. A recent study showed a shared genetic link with M. trunal left ventricular hypoplasia and left ventricular growth.\(^23\) Conversely, the thickening of the left ventricular myocardium in subtypes of hypoplastic left heart syndrome has been proposed as a result of altered haemodynamic forces. M. Marfan syndrome is inherited in a dominant fashion.

Conclusion

Because of the variability in subtypes and presentation of hypoplastic left heart syndrome, a common etiology for all subtypes is unlikely. Genetic and environmental contributions are likely working in concert to create the spectrum of phenotypes observed. Cases of hypoplastic left heart syndrome with a patent left ventricle and left ventricular growth are an interventricular septal defect, and an intact aortic arch have been shown to have normal myocardial architecture at birth and normal myocardial function, which suggests that these subtypes are likely due to a primary valvular pathology. Future research efforts in these subtypes should focus on genetic and environmental causes of valvular abnormalities. Subtypes of hypoplastic left heart syndrome with patent left ventricle or obstructed outflow tract are particularly challenging. Further research efforts in these subtypes should focus on identifying genetic and environmental causes of valvular abnormalities. Subtypes of hypoplastic left heart syndrome with patent left ventricle or obstructed outflow tract are particularly challenging. Further research efforts in these subtypes should focus on identifying genetic and environmental causes of valvular abnormalities. Subtypes of hypoplastic left heart syndrome with patent left ventricle or obstructed outflow tract are particularly challenging. Further research efforts in these subtypes should focus on identifying genetic and environmental causes of valvular abnormalities. Subtypes of hypoplastic left heart syndrome with patent left ventricle or obstructed outflow tract are particularly challenging. Further research efforts in these subtypes should focus on identifying genetic and environmental causes of valvular abnormalities.
this abnormality is warranted. If the pathogenesis of this disease is uncovered, the possibility for more effective treatment or perhaps even the prevention of certain subtypes of hypoplastic left heart syndrome may one day become reality.

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Conflicts of Interest
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