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Review Article

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

Charles R. Cole, Pirooz Eghtesady

Abstract: Hypoplastic left heart syndrome has the greatest mortality rate among all CHDs and without palliation is uniformly fatal. Despite noble efforts, the etiology 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, 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. Hypoplastic left heart syndrome is characterized by a diverse spectrum of malformations distinguished by underdevelopment of the left ventricle and its components, rendering it unable to support systemic circulation. The presence of anatomic variations within the classic classification of hypoplastic left heart syndrome yields a continuum of phenotypic heterogeneity that can be divided into broad subgroups. 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 any atrial arrangement, with situs solitus being the most common. It is necessary to analyze these subgroups individually because of their differing histological characteristics and the possibility for differing inciting events. Sedlmayer et al. provide an excellent breakdown of hypoplastic left heart syndrome subtypes, which appear in Table 1.

First, hearts with combined mitral and aortic stenosis present with a thin-walled, slit-like left ventricle. The ascending aorta and arch are extremely hypoplastic, and flow is retrograde. Systemic output is ductal dependent. In the setting of
combined mitral and aortic stenosis, 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 an isolated conotruncus. In the setting of a large ventricular septal defect, irrespective of mitral valve dimensions, the aortic valve is usually stenotic, which suggests that valvular development is also dependent to some degree on adequate blood flow during development. Third, hearts with isolated aortic stenosis and a patent mitral valve without a ventricular septal defect demonstrate thickening of the left ventricular free wall, ventricular septum, and endocardium. As in combined mitral and aortic stenosis, the ascending aorta and aortic arch are hypoplastic, and all systemic output is ductal dependent. Fourth, hypoplastic left heart syndrome with hypoplastic aortic valve stenosis and a patent mitral valve is a distinct anatomic variant recognized through the ascending aortic valve. The degree of ascending aortic and arch hypoplasia is less than observed with mitral stenosis. 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 hearts with severe aortic arch hypoplasia that is not of proportion to the degree of aortic root hypoplasia. This subset of hypoplastic left heart syndrome can have multiple combinations of mitral and/or aortic valve abnormalities. Lev et al described some common qualities between subsets of hypoplastic left heart syndrome. A detailed analysis of 230 hypoplastic left heart syndrome hearts revealed that some had an enlarged heart and 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 orifice was enlarged and imprinted upon the interventricular septum. The right ventricle was hypertrophied and enlarged. Although right ventricular abnormalities are found in hypoplastic left heart syndrome, many of these abnormalities may be the result of right ventricular overloading secondary to the presence of left ventricular outflow tract obstruction.

M yocardial histopathology of norm al hearts versus hypoplastic left heart syndrome hearts

Cardiac muscle cell orientation in non-diseased hearts exhibits a sin bar pattern in the embryo, fetus, child, and adult. N arrows, the majority portion of both ventricular walls and the mid portion of the interventricular septum have an ordered parallel arrangement of cells. Myocardial base disarray, defined as a lack of ordered parallel arrangement of myocardial fibers, has been described in hypoplastic left heart syndrome. M yocardial base disarray can be present in one of the following patterns: base branching at sharp angles to one another, groups of fibers cut longitudinally interspersed with base cut transversely, or base formation occurring with sharp angles to one another. These patterns may be found alone or in combination within the same heart. M yocardial base disarray is not unique to hypoplastic left heart syndrome but can be found to some degree in normal hearts and more extensively in hearts with conditions such as hypertrophic cardiomyopathy, pulmonary atresia, and tetralogy of Fallot.

M yocardial histopathology of left ventricle in hypoplastic left heart syndrome

Certain subtypes of hypoplastic left heart syndrome present with organized myocardial architecture at birth. Autopsy studies of hearts with combined mitral and aortic stenosis collected before the availability of effective surgical palliation demonstrate a normal aligned cell pattern without evidence of myocardial disarray in the left ventricular myocardium and atrioventricular septum. In the event of mitral atresia with a large ventricular septal defect and a fully developed left ventricle, the myocardial architecture is normal. A common finding in both of these cases is that they likely do not have increased left ventricular cavity hemodynamic pressure burden during development. The norm al myocardial architecture in these cases also suggests that the anatomy of these cases is likely valvular. Hypoplastic left heart syndrome hearts that demonstrate 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 orifice was enlarged and imprinted upon the interventricular septum. The right ventricle was hypertrophied and enlarged. A thorough

<table>
<thead>
<tr>
<th>Table 1. Morphologic subgroups of hypoplastic left heart syndrome.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mitral and aortic stenosis</td>
</tr>
<tr>
<td>2. Mitral stenosis with a patent aortic root and ventricular septal defect</td>
</tr>
<tr>
<td>3. Aortic stenosis with patent mitral valve</td>
</tr>
<tr>
<td>4. Aortic stenosis and dysplasia with patent mitral valve</td>
</tr>
<tr>
<td>5. Left ventricular hypertrophy with elevation of the aortic arch</td>
</tr>
</tbody>
</table>

Cardiology in the Young January 2016
development.18,19 from abnormal cardiomyocyte proliferation during development and hypertrophy and fibrosis of the left ventricle.3 Cases of hypoplastic left heart syndrome may result in all left ventricle and right ventricle valve pathology. Postnatally, this subgroup can develop hypertrophy and fibrosis of the left ventricle. Characteristics of each subgroup are summarized in Table 2.

A recent histologic analysis of the myocardium of hypoplastic left heart syndrome hearts found large areas of random myocyte disorganization, disorganized bundles of myocardium with variable myocyte size found between bundles in all left ventricle and right ventricle samples (Fig 1).16 Although subgroup classifications were not documented in this report, all cases presented with myocyte disarray.16 Previously reported histologic studies observed organized myocardium in the subgroups with combined aortic/mitral atresia or m-truncus atresia with a ventricular septal defect.17 The obvious difference between the study groups was the age of the patients and the advancements in palliative techniques. In early publications, the patient’s mean lifespan was typically 1 week or less; in these cases, only cardiac study groups in which the lifespan was 6 days to 10 months. The cases in m-oliv patient were also exposed to isotropic support. This observation suggests that increased exposure to abnormal blood flow in the neonate will lead to myocardial disorganization and star formation in some hearts that perhaps had a histologically norm al myocardium at birth. The differing myocyte architecture observed between subtypes of hypoplastic left heart syndrome during development highlights the potential for differing inciting events between subtypes. The cases of hypoplastic left heart syndrome with abnormal myocyte architecture at birth may have a path way myocardial pathogenesis that alters blood flow patterns and results in abnormal development of the in utero valve structures. Recent studies have highlighted the possibility that some cases of hypoplastic left heart syndrome may result from abnormal cardiac myocyte proliferation during development.18,19

Endocardial fibroelastosis

In an eloquent review, Lurie20 describes endocardial fibroelastosis as a reaction of the endocardium, not a disease state. Generally, the reaction is identified as a pearly or opaque white appearance of the endocardium, especially of the valves.20 The normal endocardium is transparent and only around 10 μm in thickness.21 Endocardial fibroelastosis is described by thickening of the endocardium by layers of collagenous and elastic tissue to > 20 μm.20 Lurie20 described the endocardial fibroelastosis reaction as a chronologic sequence of an initial myocyte hyperplasia followed by their transition into amorphous state and translocation from the inner, sub-endocardial layers to the outer, intima myocardial layers (Fig 2). In the fetus, the endocardial lining is highly cellular, containing numerous smooth muscle cells and fibroblasts. Antepartum, the cellular characteristics disappear, leaving layers of collagen and elastic tissue. The endocardial fibroelastosis reaction is most active during fetal life and during periods of active growth. Left ventricular endocardial fibroelastosis in hypoplastic left heart syndrome is often found in the setting of a patent m-truncal valve and severely stenotic or atroventricular valve. Hearts that develop the endocardial fibroelastosis reaction are always under stress, either from pressure overload due to mechanical obstruction or from volume overload due to cardiac muscle disease.20,22 However, not every heart under stress will develop endocardial fibroelastosis.20 In addition, endocardial fibroelastosis is not seen within the left ventricle in the setting of combined m-truncus and atroventricular valve atresia or mitral atresia when blood flow is absent from the left ventricle21 but may affect the left atrium and mitral valve in the presence of m-truncal valve obstruction.21

There is strong evidence that prenatal infection could account for some cases of left ventricular hypoplasia with endocardial fibroelastosis.21 Coxsackie virus and mumps virus were recognized as etiologic agents of endocardial fibroelastosis in the 1960s and 1970s.20 These findings were further supported by the consistent identification of mumps virus in the m-oliv in cases of severe left ventricular outflow tract obstruction in the first trimester. All fetuses had elevated end-diastolic pressure, but none developed endocardial fibroelastosis.20 This finding suggests that m-oliv stress alone does not always cause endocardial fibroelastosis. Lurie hypothesized that in the conditions that increase contractility, such as hypoxic cardiomyopathy, the endocardium may inhibit the endocardial fibroelastosis reaction. It is also possible that in
<table>
<thead>
<tr>
<th>Subtype</th>
<th>Frequency</th>
<th>Gross anatomy</th>
<th>Histoopathology of left ventricle</th>
<th>Endocardial histopathology</th>
<th>Aortic valve pathology</th>
<th>Coronary artery pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. atal and aortic atresia</td>
<td>36–46% *</td>
<td>Thin-walled, slit-like left ventricle. Right ventricle 1-2 mm in diameter.</td>
<td>N. ciliary arranged cell pattern</td>
<td>Absent</td>
<td>Aortic</td>
<td>Coronary atresia usually documented. N. histologically normal coronary arteries</td>
</tr>
<tr>
<td>M. atal stenosis with patent aortic root and ventricular septal defect</td>
<td>NA</td>
<td>The larger the ventricular septal defect, the more closely the left ventricle will approach normal.</td>
<td>In the event of a large ventricular septal defect and fully developed ventricular chamber, myocardi al base orientation will be normal.</td>
<td>Absent</td>
<td>Aortic</td>
<td>Few ventriculo-crown stenoses. Left coronary arteries have increased tortuosity, but preserved left main stem.</td>
</tr>
<tr>
<td>Aortic stenosis with a patent m. atal valve</td>
<td>20–29% *</td>
<td>Thickened left ventricular free wall and septum</td>
<td>M. asked n. myocardi al base disarray of the left. Present ventricular free wall and septum. M. myocardi al disarray generally in the inner two-thirds of the myocardium that does not involve the inner two-thirds of the myocardium.</td>
<td>Absent</td>
<td>Aortic</td>
<td>Aortic</td>
</tr>
<tr>
<td>Aortic valvular stenosis and dysplasia with patent m. atal valve</td>
<td>23–26% *</td>
<td>Thickened left ventricular free wall and septum</td>
<td>M. asked n. myocardi al base disarray of the left. Present ventricular free wall and septum. M. myocardi al disarray generally in the inner two-thirds of the myocardium that does not involve the inner two-thirds of the myocardium.</td>
<td>Absent</td>
<td>Aortic</td>
<td>Coronary stenoses, ranging from 32 to 100%.</td>
</tr>
<tr>
<td>Left ventricular hypoplasia with coarctation of the aorta</td>
<td>24–80% of hypoplastic left heart syndrome</td>
<td>Proportional hypoplasia of left ventricle in relation to hypoplasia of vascular structures</td>
<td>Fibrocalcific myxomatous valve</td>
<td>Absent</td>
<td>Fusion of valve leaflets</td>
<td>Proportional coronary atresia in relation to hypoplasia of vascular structures</td>
</tr>
</tbody>
</table>

*Frequencies documented before Norwood procedure

**Frequencies unrelated to Norwood procedure
genetically susceptible patients, contributions 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, termed 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. McCrindle et al. recently reported that the severity of endocardial fibroelastosis, as determined by prenatal echocardiography, in patients with aortic stenosis and excluding hypoplastic left heart syndrome, had an association with postnatal outcome following in utero balloon valvuloplasty. Patients with more severe endocardial fibroelastosis had a lower probability of postnatal biventricular outcome. 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
Coronary artery pathology

Physiologic coronary perfusion occurs in a cyclical pattern, with the major contribution during diastole. In the setting of an anteriorly obstructed left ventricle, the coronary perfusion occurs during systole, as documented by selective aortic root angiography in prior studies of hypoplastic left heart syndrome. The high-pressure blood flow during ventricular systole may lead to wall thickening and tautness in the epicardial coronary arteries and their intramyocardial branches. Coronary arterial insufficiency may result from intimal thickening and fibrosis, decreased arterial compliance, or reduced coronary perfusion. In cases of hypoplastic left heart syndrome, the coronary arteries may be small and tortuous, with increased wall thickness and narrowing of the lumen. The coronary arteries may also be disconnected from the myocardium, with direct connections to the aorta or pulmonary artery. Microvascular abnormalities may include hypoplasia, dysplasia, or obstruction, leading to ischemia and myocardial dysfunction. The coronary arteries may also be connected to the pulmonary artery, as in the case of the arterial switch operation for hypoplastic left heart syndrome. The coronary arteries may also be connected to the aorta, as in the case of the arterial switch operation for hypoplastic left heart syndrome.
syndrome in this case because of the existence of a ventricular septal defect that nullified the intra-ventricular pressure gradient, which is typical of hypoplastic ventricles and thought to be responsible for the secondary development of stenoses in other cases.44

In an autopsy report of 122 patients who died after a Norwood procedure, Bastian et al.39 found impairment of coronary artery perfusion to be the most frequent cause of death (63 patients, 27%). However, the cause of stenosis in the vast majority of these patients (91 of 122) was secondary to either intraluminal stenoses at the anastomosis or external kinking of the graft.43,45 The poor coronary perfusion in these cases was therefore the result of the surgical technique and was not the underlying coronary disease. Surgical ligation of an aberrant left circumflex coronary artery from the right pulmonary artery occurred in one case, resulting in biventricular infarction.43 Generalised coronary artery hypoplasia was also found in one patient.46 Despite the rare occurrence of coronary anomalies in hypoplastic left heart syndrome, detailed coronary artery assessment at necropsy ended as 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 arterialis in cases with high intraluminal pressure, but have a preserved lumen, and with some exception are not primary to the pathogenesis of disease.

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 normal age-matched control hearts. No differences were noted between left and right ventricles or between subtypes. The authors believe the reduction in capillarisation may be an inherent abnormality of hypoplastic left heart syndrome that may have implications for ventricular development. Rakusan et al.46 noted that congenital

Figure 3.
Coronary artery wall thickening observed in cases of hypoplastic left heart syndrome with patent ductus arteriosus. (a) Photomicrograph of a branching posterior descending artery in the epicardial groove, Magnification 14×. (b) Artery outlined in (a) shows a prominent muscularis zone (M). Eccentric intimal thickening (I) is apparent but does not appear to significantly narrow the lumen, Magnification 120×. (c) Low-power view of interventricular septum with prominent muscularised arteries (arrow), Magnification 10×. All elastic stain. Courtesy of O’Connor.47 LV = left ventricle; PD = patent ductus; RV = right ventricle.
CD31 has also been associated with cell migration and cancer angiogenesis. Recent work suggests that CD31 has a novel role in arteriogenesis and collateral xenotransplantation. CD31 has also been identified as the rat/mouse allele that determines pre-existing collateral dictum et al. These findings highlight the possibility that aberrant 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 atypical capillarisation in hypoplastic left heart syndrome could be the product of aberrant CD31 expression within the myocardium.

Pathogenesis of hypoplastic left heart syndrome

The aetiology of embryonic leading to hypoplastic left heart syndrome is largely unknown. A commonality of hypoplastic left heart syndrome cases occurs in the context of recognized genetic disorders including, but not limited to, Turner, Jacobsen, Noonan, and Holt-Oram syndromes. However, studies involving non-syndromic familial members have suggested that heritability is complex. No single disease-causing pathway has yet been identified. 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. Prenatal diagnosis of hypoplastic left heart syndrome can be made as early as 14 weeks’ gestation, but runx2a cases of hypoplastic left heart syndrome have been presented with normal or even dilated left ventricular cavities on routine fetal ultrasound at >19 weeks’ gestation. The unifying aetiological explanation is that the growth and development of vascular structures are dependent on the relative quantity and quality of blood ow as well as the degree of relative neovascularization and the rate of myocardial growth and development. Recent studies have shown that hypoplastic left heart syndrome myocardium is well differentiated, but have prolongation of expression of fetal or “heart failure” genes. These findings suggest that intrinsic defects in the fetus may occur after embryogenesis and highlights the possibility that fetal development of hypoplastic left heart syndrome may occur later in gestation. Recent hypotheses also question whether in utero, infectious or autoimmune insults to genetically susceptible hosts may contribute to left ventricular hypoplasia from either direct myocardial injury or secondary to reduced left ventricular blood ow through damaged valves.

Genetic factors that alter valve development have been proposed as the aetiology in hypoplastic left heart syndrome. Mutations in the signalling and transcription regulator, NOTCH1, have caused early...
affecting 1% of the general population, and is a known risk factor for aortic valve disease. Aortic valve stenosis 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 m ost restrictive bicuspid aortic valves progress to hypoplastic left heart syndrome. Isolated aortic valve atresia and congenital aortic stenosis do not always progress to hypoplastic left heart syndrome, suggesting that aortic valve defects and hypoplastic left heart syndrome have distinct genetic susceptibilities. Genetic factors are clearly present, but epigenetic modifications are also involved in the development of hypoplastic left heart syndrome.

The complex heritability of hypoplastic left heart syndrome suggests the potential for environmental contributions to the observed phenotype. M etabolic, upper respiratory infection during the first trimester has been documented as a significant risk factor for hypoplastic left heart syndrome. Population-based studies in the Baltimore-Washington region have identified environmental risk factors for hypoplastic left heart syndrome, including maternal exposure to organic solvents.

A recent study showed a seasonal pattern in the presentation of hypoplastic left heart syndrome with postnatal onset in the winter, in contrast to the random pattern observed in other left-sided heart diseases. These findings support a role for an environmental contaminant 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 crossreact with human aortic and mitral valve antigens through a mechanism known as molecular mimicry. O ur lab recently demonstrated that transplacental transfer of maternal anti-cardiac myocyte antibodies leads to structural congenital cardiac defects in affected progeny that included diminished left ventricular cavity dimension.

Postnatal development of hypoplastic left heart syndrome e-like phenotype had elevated serum levels of anti-β adrenergic receptor antibodies as well as increased protein kinase A activity, suggesting a potential role for the observed pathological changes.

These findings provide evidence that prenatal viral infection could account for a small percentage of cases of hypoplastic left heart syndrome with endocardial fibroelastosis. Viral infection is a well-accepted cause of cardiac pathology. Studies have reported that viral RNA is present in myocardial samples from fetuses with aortic valve stenosis.

A leukocytic mechanism for the pathogenesis of hypoplastic left heart syndrome has been suggested, in which abscam antibodies are present in maternal sera. These antibodies can be detected in aortic valve and myocardium in utero and have been reported to cross-react with human aortic valve and myocardium. They are thought to result from cardiac myocyte hyperplasia during development. These antibodies may contribute to the pathogenesis of hypoplastic left heart syndrome.

Conclusion

Because of the variability in subtypes and presentation of hypoplastic left heart syndrome, it is clear that many subtypes have a shared genetic link with myocardial disease. Studies have shown that antinuclear antibodies and CD31 are present in myocardial samples from fetuses with aortic valve stenosis. These findings suggest that viral infection and environmental factors may contribute to the pathogenesis of hypoplastic left heart syndrome.

Future studies should evaluate the potential for environmental and genetic factors to contribute to the pathogenesis of hypoplastic left heart syndrome.
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

The authors have no relationships with industry or financial associations that might pose a conlict of interest with the submitted article.

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