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

Charles R. Cole, Pirooz Eghtesady

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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 boxelastosis reaction.

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

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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, coronary, endocardial boxelastosis, and pathogenesis. We searched from 1940 until the present, which 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 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 from its parents, rendering it unable to support systemic circulation. The presence of anatomical variations within the classic definition 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, 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. Saim 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 the aortic arch is stenotic. Systemic output is ductal dependent. In the setting of
combined 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 norm al 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 mitral valve dimensions, the aortic valve is usually atresic, which suggests that valvular development is also dependent on an adequate blood flow during development.

Third, hearts with isolated aortic atresia and patent mitral valve without a ventricular septal defect exhibit thickening of the left ventricular free wall, ventricular septum, and endocardium. As in combined mitral and aortic atresia, the ascending aorta and aortic arch are hypoplastic, and all systemic output is ductal-dependent. Fourth, hypoplastic left heart syndrome is heart with aortic valve stenosis and a patent mitral valve in an intact aortic arch with the aortic valve. The degree of ascending aortic and aortic arch hypoplasia is less than observed with aortic atresia. Fifth, in general, the degree of aortic arch hypoplasia correlates with the dimensions of the aortic root, but there is a subset of hypoplastic left heart syndrome patients with severe aortic arch hypoplasia that is not of proportion to the degree of aortic root hypoplasia. This subtype of hypoplastic left heart syndrome can have multiple combinations of mitral and/or aortic valve abnormalities.

Lev et al described some common qualities between subtypes of hypoplastic left heart syndrome. A detailed analysis of 230 hypoplastic left heart syndrome hearts revealed that specific endocardial cushions had an enlarged heart with an apex from 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 in pinnate orientation to the infundibular region. The right ventricle was hypertrophied and enlarged. Although right ventricular abnom alities are found in hypoplastic left heart syndrome, many of these abnom alities may be the result of the right ventricle persisting for an increased workload secondary to the presence of left ventricular outflow tract obstruction.

### Table 1. Morphologic subgroups of hypoplastic left heart syndrome

<table>
<thead>
<tr>
<th>No.</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mitral atresia</td>
</tr>
<tr>
<td>2</td>
<td>Mitral atresia with a patent aortic root and ventricular septal defect</td>
</tr>
<tr>
<td>3</td>
<td>Aortic atresia with patent mitral valve</td>
</tr>
<tr>
<td>4</td>
<td>Aortic stenosis and dysplasia with patent mitral valve</td>
</tr>
<tr>
<td>5</td>
<td>Left ventricular hypoplasia with orientation of the aortic arch</td>
</tr>
</tbody>
</table>

Myocardial histopathology of norm al hearts versus hypoplastic left heart syndrome hearts

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

Myocardial histopathology of left ventricle in hypoplastic left heart syndrome

Certain subtypes of hypoplastic left heart syndrome present with organized myocardial architecture at birth. Autopsy specimens of hearts with combined mitral and aortic atresia collected before the availability of effective surgical palliation demonstrate a normal aligned cell pattern without evidence of myocyte disarray in the left ventricular myocardium and rudimentary septum. In the event of mitral atresia with a large ventricular septal defect and a fully developed left ventricle chamber, myocardial base disarray is norm al. 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.
Endocardial/broelastosis

In an eloquent review, Lurie described endocardial/broelastosis as a reaction of the endocardium, not a disease state. Generally, the reaction is identified by 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/broelastosis is defined by thickening of the endocardium by layers of collagenous and elastic bases to >20 μm. Lurie described the endocardial/broelastosis reaction as a chronologic sequence of events during ventricular hypertrophy followed by their transformation and transition from the inner, sub-endocardial layers to the outer, sub-endocardial 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 base. The endocardial/broelastosis reaction is most active during fetal life and during periods of active growth.

Left ventricular endocardial/broelastosis in hypoplastic left heart syndrome is hypothesized to be a reaction to abnormal blood flow patterns and results in reduced flow in the aorta and mitral valve. The incidence of endocardial/broelastosis sharply declined with the advent of balloon valvuloplasty. Endocardial/broelastosis reaction may also be seen in the setting of a patent midaortic valve and severely stenotic or atretic valve. Hearts that develop endocardial/broelastosis reaction are always under stress, either from pressure overload due to a mechanical obstruction or from volume overload due to cardiac mural disease. However, not every heart under stress will develop endocardial/broelastosis. In addition, endocardial/broelastosis is not seen within the left ventricle in the setting of combined mitral and aortic atresia or in cases of hypoplastic left heart syndrome when blood flow is absent from the left ventricle. There is strong evidence that prenatal infection could account for some cases of left ventricular hypoplasia with endocardial/broelastosis. Case studies and murine viruses were recognized as etiologic agents of endocardial/broelastosis in the 1960s and 1970s. Recently, endocardial/broelastosis reaction was identified in murine hearts when murine parovirus was administered intravenously. The incidence of endocardial/broelastosis sharply declined with the advent of the murine parovirus vaccine.

Infants with focal ventricular hypertrophy lack the endocardial/broelastosis reaction even though they are exposed to simlar mechanical stresses seen with certain subtypes of hypoplastic left heart syndrome (papillary muscle deficiency). Recent studies have highlighted the possibility that some cases of focal hypoplastic left heart syndrome may result from abnormal endocardial yococyte proliferation during development.
<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 mal and aortic atresia</td>
<td>36–46% *</td>
<td>Thin-walled, slit-like left ventricle; right ventricle; right atrium</td>
<td>Absent</td>
<td>Aortic atresia</td>
<td>Conally absent, mostly done endarterectomy; Aortic atresia pathology rarely documented.</td>
<td></td>
</tr>
<tr>
<td>M mal atresia with patent aortic and ventricular septal defect</td>
<td>NA</td>
<td>Larger the ventricular septal defect, the more closely the left ventricle will approach normal size</td>
<td>Absent</td>
<td>Thin friable valve leafs</td>
<td>Few ventricle-cavity stenoses left coronary arteries have increased tortuosity, but preserved left heart output</td>
<td></td>
</tr>
<tr>
<td>Aortic atresia with patent m. m. valve</td>
<td>20–29% *</td>
<td>Thicker left ventricular free wall and septum</td>
<td>Absent</td>
<td>Aortic atresia</td>
<td>Conally absent, mostly done endarterectomy; Aortic atresia pathology rarely documented.</td>
<td></td>
</tr>
<tr>
<td>Aortic atresia with dysplasia and patent m. m. valve</td>
<td>23–26% *</td>
<td>Thicker left ventricular free wall and septum</td>
<td>Absent</td>
<td>Aortic atresia</td>
<td>Conally absent, mostly done endarterectomy; Aortic atresia pathology rarely documented.</td>
<td></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>Fusion of valve leafs</td>
<td>Fusion of valve leafs</td>
<td>Proportional coronary artery stenoses in relationship to hypoplasia of vascular structures.</td>
<td></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 occurs, and both mechanical and immunologic factors 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, rather, may be a secondary event in the pathogenesis of the syndrome. In hypoplastic left heart syndrome, endocardial fibroelastosis 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 rather, may be a secondary event in the pathogenesis of the syndrome. In hypoplastic left heart syndrome, endocardial fibroelastosis is associated with postnatal outcome following in utero balloon valvuloplasty. Patients with more severe endocardial fibroelastosis have 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...
with mitral and aortic atresia. A congenital coronary artery stula is an abnormal direct communiation between any part of the coronary system and a cardiac chamber or great vessel, having bypassed the myocardial capillary bed. Mosaicorangiographic evaluation of hypoplastic left heart syndrome specimen n with ventriculo-coronary connections demonstrated that sinuses from the endocardial surface may extend into the myocardium. Blake categorized these ventriculo-coronary connections into three subtypes:

- **Aorto-luminal subtype**—connects the left ventricular chamber directly to the ventriculocoronal branches of the cardiac arteries.
- **Aorto-sinusoidal subtype**—connects the left ventricular chamber indirectly to an aneurysm of the coronary arteries.
- **Aorto-capillary subtype**—connects the left ventricular chamber indirectly to a rich network of thin-walled, capillary-sized vessels.

O'Connell et al. found a variable combination of ventriculo-coronary connections in all cases of hypoplastic left heart syndrome with patent coronary arteries. The largest number of connections was found in the subgroup with either stenosis or complete closure of the foramen ovale. Nerv ventriculo-coronary connections were identified in the subgroup with m. infall and atroic atresia. Baffa et al. found ventriculo-coronary connections in 27 of 89 specimens with patent mitral and aortic atresia. Baffa et al. also found ventriculo-coronary connections in 27 of 89 specimens. O’Connell et al. noted increased tortuosity of the left coronary artery in m. infall and atroic atresia. Sauer et al. noted increased tortuosity of the left coronary artery in m. infall and atroic atresia. Sauer et al. also found that the ratio of coronary wall thickness relative to lumen diameter in the left coronary artery was significantly different from control hearts. Lloyd et al. also observed that the ventricular septal defect of the coronary arteries and ejection in hypoplastic left heart syndrome e were not different from control speices.

Anomalous coronary artery origins and coronary artery hypoplasia have been reported in hypoplastic left heart syndrome. Infrequently, case reports have described an anomalous origin of the left coronary artery from the right pulmonary artery in the setting of hypoplastic left heart syndrome. Lloyd et al. described a case of hypoplastic left heart syndrome with single coronary artery originating from the right pulmonary artery. Saroli et al. described three cases of hypoplastic left heart syndrome with superior origin of the left coronary artery. The origins of the right coronary artery from the descending thoracic aorta have been documented in one case of hypoplastic left heart syndrome. Dufour et al. described a case of hypoplastic left heart syndrome with the left coronary artery originating from the right pulmonary artery. Saroli et al. described 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. Dufour et al. described a case of hypoplastic left heart syndrome with the left coronary artery originating from the right pulmonary artery.

**Coronary artery patohology**

Physiologic coronary perfusion occurs in a cyclical manner, with the major contribution during diastole. In the setting of anatomic left ventricular obstruction ventricular, the coronary perfusion occurs during systole, as demystified 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 tortuosity in the epicardial coronary arteries and their intramyocardial branches. O'Connell et al. observed that diseased vessels were rare in the left ventricular free wall and septum. The histologic findings consisted of circumferential medial and mural hypertrophy, thickened elastic lamina, and focal intimal atherosclerosis without significant lumen narrowing. Sauer et al. found that specific e with m. infall and aortic atresia did not demystify histologic coronary artery abnormalities.

Coronary artery histopathologic findings are most prominent in arteries that are unilaterally supplied by the pulmonary artery. O’Connell et al. observed that diseased vessels were rare in the left ventricular free wall and septum. The histologic findings consisted of circumferential medial and mural hypertrophy, thickened elastic lamina, and focal intimal atherosclerosis without significant lumen narrowing. Sauer et al. found that specific e with m. infall and aortic atresia did not demystify histologic coronary artery abnormalities.
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 stenosis in other cases.44

In an autopsy report of 122 patients who died after a Norwood procedure, Bartram et al39 found impaired coronary artery perfusion to be the most frequent cause of death (83 patients, 27%). However, the cause of stenosis in the vast majority of these patients (91 of 33) was secondary to either intimal in situ stenosis at the anastomosis or external kinking of the graft.34,35 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 aberrant left circum ex coronary artery from the right pulmonary artery occurred in one case, resulting in biventricular infarction.39 Generalised coronary artery hypoplasia was also found in one patient.39 Despite the rare occurrence of coronary stenosis in hypoplastic left heart syndrome, detailed coronary artery assessment at an anamnesis 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 or tortuous in cases with high intraluminal pressure, but have a preserved lumen, and with rare exceptions are not primary to the pathogenesis of disease.

Microvasculature

Focusing on the microvasculature of hypoplastic left heart syndrome, Salih et al45 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 al46 noted that congenital...
cardiac 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 causes anatomical 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 primary failure of capillary angiogenesis? Jacobs suggested that the decreased capillarisation observed by Salihe et al. might not be an unavoidable inherent abnormality of hearts with hypoplastic left heart syndrome, but rather a snapshot of the supply–demand mismatch encountered with unscarred hypoplastic left heart syndrome anatomy. Assisted previously, perfusion of the myocardium in unoperated hearts with hypoplastic left heart syndrome occurs primarily in systole, rather than in diastole, as there is considerable diastolic runoff into the pulmonary circulation. Coronary perfusion is further limited by excessive myocardial wall tension. Eliminating the diastolic runoff by means of closure of the system to pulmonic artery shunt at the time of the second-stage surgery results in the restoration of macroscopic diastolic coronary perfusion, as well as reduction in the volume of oedema of the ventricle. Jacobs suggested that the hypoplastic left heart syndrome could contribute to the limited capillary supply. Inappropriate expression of platelet-endothelial cell adhesion molecule-1, also known as CD31, has been shown to be increased in hearts with hypoplastic left heart syndrome. CD31 has been associated with cell migration and cancer angiogenesis. Recent work suggests that CD31 has a novel role in arteriogenesis and collateral remodelling. CD31 has also been identified as the rst molecule that determines pre-existing collateral flow. These findings highlight the possibility that abnormally expressed 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 abnormally expressed CD31 expression within the myocardium.

Pathogenesis of hypoplastic left heart syndrome

The aetiologic mechanisms leading to hypoplastic left heart syndrome are largely unknown. About one-fifth of hypoplastic left heart syndrome cases occur in the context of recognised genetic disorders including, but not limited to, Turner, Jacobsen, Noonan, and Holt–Oram syndromes. However, studies involving non-syndrome 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-chamber 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 rare cases of hypoplastic left heart syndrome have been described with normal or even dilated left ventricular cavities. Postnatal observation of hypoplastic left heart syndrome may occur at any stage of development, but abnormal development of vascular structures is dependent to some degree on the relative quantity and quality of blood flow during development. Recent studies have shown that hypoplastic left heart syndrome is associated with abnormal expression of CD31, cardiac myocytes have been shown to express CD31 at any stage of development or in any disease state. These findings support the hypothesis that inappropriate expression of CD31 or a related gene under the aortic regulatory control may be responsible for the disorganisation of hypoplastic left heart syndrome cardiac myocytes and potentially the higher-order cardiac structural anomalies associated with this disease.
aortic valve defects in animal models. Genes involved in downregulation of NOTCH signaling and cardiac gene expression have been implicated in familial forms of hypoplastic left heart syndrome. A recent study showed a shared genetic linkage with hypoplastic left heart syndrome and bicuspida aortic valve. 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 disease has a distinct genetic susceptibility. Genetic factors are clearly present, but environmental and/or genetic factors have been identified that may contribute to the observed phenotype. M. straminial upper respiratory infection during the 6th to 8th week of gestation has been shown to be 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 pronounced in summer months in contrast to the random pattern observed in other left-sided heart diseases. These findings support a role for an environmental factor in the pathogenesis 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. Our lab recently demonstrated that transplacental transfer of maternal autoantibodies to the fetus leads to structural myocardial disorders as a result of altered cardiovascular development. Interestingly, some phenotypes of hypoplastic left heart syndrome seen in the fetus have been identified that could contribute to the observed pathological changes. These findings support the concept that infection-mediated changes in fetal myocardial development can lead to the observed phenotype. Future studies should evaluate the role of maternal autoantibodies in the development of hypoplastic left heart syndrome.

Conclusion: Because of the variability in subtypes and presentation of hypoplastic left heart syndrome, a common cardiac phenotype is unlikely. Genetic and environmental factors are likely working in concert to create the spectrum of phenotypes observed. Cases of hypoplastic left heart syndrome with mitral atresia and aortic atresia or with mitral atresia, a ventricular septal defect, and an intact aortic arch have been shown to have normal myocardial architecture at birth, with normal coronary anatomy, which suggests that these subtypes are likely due to prenatal vascular pathogenesis. Future research efforts in these subtypes should look for genetic and environmental causes of valvular agenesis. Subtypes of hypoplastic left heart syndrome with patent inow tract and obstructed outow tract present with the spectrum of phenotypes observed. As stated previously, the regional distribution of maternal disease supports the concept that vascularisation parallels myocardial organisation in the developing heart. Future studies should evaluate the role of maternal autoantibodies in the development of hypoplastic left heart syndrome, a common cardiac phenotype.
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 conflict of interest with the submitted article.

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