Ventriculocoronary Connections in Hypoplastic Left Hearts: An Autopsy Microscopic Study

WILLIAM N. O’CONNOR, M.D., JAMES B. CASH, M.D., CAROL M. COTTRILL, M.D.,
GREGORY L. JOHNSON, M.D., AND JACQUELINE A. NOONAN, M.D.

SUMMARY Serial microscopic sections of the left ventricular myocardium were examined in 12 autopsy specimens of hypoplastic left heart syndrome. Multiple ventriculocoronary arterial connections, thick-walled coronary arteries, prominent endocardial fibroelastosis, myofiber disarray and focal calcification/scarring of the myocardium were noted in the cases with patent left ventricular inflow and obstructed outflow. The persistent embryonic microvascular pattern noted in these cases may be related to intrauterine outflow obstruction and could limit surgical attempts to produce a functional left ventricle in infants with hypoplastic left heart syndrome.

THE CONGENITALLY obstructed left ventricle with a patent mitral orifice is usually small, thick-walled and demonstrates endocardial fibroelastosis. Microscopically, sinusoids from the endocardial surface may extend into the myocardium. Beckman et al. postulated that these channels communicate with the myocardial veins, ramifications of the coronary arteries, or capillaries, and may represent the effect of high intracavitary pressure in utero on the development of the embryonic microvascular structure. We describe the findings in a serial section study of 12 autopsy specimens of hypoplastic left heart syndrome, with particular attention to intramyocardial vascular structure.

Materials and Methods

The clinical and autopsy findings of 32 infants with hypoplastic left heart syndrome who died at the University of Kentucky since 1969 were reviewed, 12 cases were selected for study. Excluded were cases in which there was not enough formalin-fixed tissue for detailed histologic study. For the purposes of microscopic examination, all specimens were sectioned in a similar manner. Each heart had originally been opened according to flow, and this allowed for a longitudinal section to be taken from both the right and left side. Then, starting at the left ventricular (LV) apex, three tissues sections 2 mm thick containing in one transverse plane part of the right ventricle, the interventricular septum and left ventricle were taken. Thus, the entire left ventricle was circumferentially studied, leaving less than 1 mm of basal myocardium adjacent to the mitral valve ring. These transverse blocks were serially sectioned at a thickness of 10μ and every fifth section was retained for microscopic examination. Stains for elastic, muscle and fibrous tissue aided in characterization of the connecting channels. Microscopic findings revealed that nine patients had multiple ventriculocoronary arterial connections, nine thick-walled coronary arteries, nine a thick-walled left ventricle with prominent endocardial fibroelastosis, 10 myofiber disarray; and 10 focal calcification/scarring of the myocardium.

Results

Clinical and Anatomic Data (table 1)

Ten patients were male and two were female. The age at death ranged from 1 to 12 days (mean 4.4 days). At autopsy, all specimens demonstrated a hypoplastic left heart (fig. 1). The mean LV chamber diameter was 15 × 9 mm and the mean right ventricular (RV) chamber diameter was 25 × 20 mm. LV wall thickness was 7 mm and RV wall thickness was 5.4 mm. Nine patients had aortic valve atresia, three critical aortic stenosis, 10 mitral valve hypoplasia, two mitral valve atresia, three premature closure of the foramen ovale, five stenosis of the foramen ovale (< 2 mm), four patent foramen ovale (≥ 2 mm), and five dilated coronary sinus.

Approximately 2000 slides were examined. Communication between the LV cavity and coronary vasculature was usually not apparent by microscopic examination of a single slide. However, with the serial section technique, luminal continuity between these structures could be readily demonstrated, and special stains for elastic, muscle and fibrous tissue aided in characterization of the connecting channels. Microscopic findings revealed that nine patients had multiple ventriculocoronary arterial connections, nine thick-walled coronary arteries, nine a thick-walled left ventricle with prominent endocardial fibroelastosis, 10 myofiber disarray, and 10 focal calcification/scarring of the myocardium.

Ventriculocoronary Connections

The arterial connections were of the luminal, sinusoidal and specialized capillary subtypes as described by Blake et al. and were absent in cases 1–3 (table 1). A variable combination of all three types of ventriculocoronary connection was found in cases with patent inflow and obstructed outflow (cases 4–12). The subgroup with stenosis of the foramen ovale or premature closure of the foramen ovale had the greatest number of connections.

The arterioluminal subtype (figs. 2 and 3) connected the LV chamber directly to the vertically penetrating branches of the coronary arteries — the left anterior descending (LAD), obtuse marginal branch of the circumflex and the posterior descending (PDA) — irrespective of whether it arose off the right or left coro-
The site of connection was at a varying transmural distance within the myocardium and consisted of a primitive vascular tube (figs. 2D and 3E). In the interventricular septum, the connections were to the perforating branches of the LAD and PDA. The luminal orifices varied in caliber; in case 8 (fig. 2A), they represented the openings into grossly visible connections.

The arteriosinusoidal subtype (fig. 4) connected the LV chamber indirectly to smaller ramifications of the coronary arteries than did the arterioluminal subtype. These connections opened through primitive vessels into wider caliber channels (sinusoids) with multiple luminal orifices. The sinusoids formed a network of extensions of the ventricular cavity into the inner two-thirds of the myocardium beneath the posterior mitral leaflet (fig. 1), and externally were limited by a layer of compact myocardium. This region, beneath the posterior mitral leaflet, was devoid of direct arterioluminal connections even when such connections were prominent in the remainder of the LV wall.

The arteriocapillary subtype (fig. 5) connected the LV cavity indirectly to a rich network of thin-walled, capillary-sized vessels. This complex network had numerous connections to the terminal ramifications of the coronary arteries and also formed channels that connected to the epicardial coronary veins. This network had a mural distribution that was subendocardial and/or midzonal extending to form an interface with the outer compact myocardium (fig. 5B). Although sometimes present in the LV free wall and septum, the network frequently was located at the anterior and posterior junctions of these regions of the LV wall. Within the complex capillary zone, myocardial fibers were sparse and small (fig. 5C). In some cases, capillary congestion, edema and extravasation of red blood cells increased the prominence of this zone and correlated with grossly visible regions of discoloration, a finding that was consistently associated with dilatation of the coronary sinus.

**Thickened Coronary Arteries**

Epicardial and intramural thickening of coronary artery branches was limited to the LV free wall (figs. 6A and B) and septum (fig. 6C) and consisted of circumferential medial muscular hypertrophy, reduplicated elastic fibers, and focal intimal fibrous proliferation without significant luminal narrowing. These...
## TABLE 1. Clinical and Anatomic Findings in 12 Cases of Hypoplastic Left Heart Syndrome

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age at death</th>
<th>Clinical data</th>
<th>Anatomic data</th>
<th>Gross necropsy data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>3 days</td>
<td>AA, MA, PCFO, APVR</td>
<td>LV 2, RV 5</td>
<td>Slit 21 × 26</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>7 days</td>
<td>AA, MA, PFO</td>
<td>LV 3, RV 6</td>
<td>Slit 19 × 25</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>2 days</td>
<td>AA, AVC</td>
<td>LV 6, RV 4</td>
<td>5 × 7, 23 × 27</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>6 days</td>
<td>AA, MH, PFO</td>
<td>LV 12, RV 4</td>
<td>3 × 6, 28 × 20</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>6 days</td>
<td>AA, MH, SFO</td>
<td>LV 7, RV 6</td>
<td>5 × 9, 14 × 24</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>5 days</td>
<td>AA, MH, SFO</td>
<td>LV 8, RV 5</td>
<td>7 × 9, 21 × 23</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>2 days</td>
<td>AA, MH, SFO</td>
<td>LV 9, RV 5</td>
<td>9 × 3, 29 × 37</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>1.5 days</td>
<td>AA, MH, PCFO</td>
<td>LV 6, RV 4</td>
<td>10 × 10, 23 × 24</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>1 day</td>
<td>AA, MH, PCFO</td>
<td>LV 9, RV 3.5</td>
<td>8 × 7, 18 × 14</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>3 days</td>
<td>AS, MH, PFO</td>
<td>LV 9, RV 7</td>
<td>12 × 22, 16 × 21</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>4 days</td>
<td>AS, MH, SFO</td>
<td>LV 8, RV 6.5</td>
<td>14 × 13, 24 × 23</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>12 days</td>
<td>AS, MH, SFO</td>
<td>LV 8, RV 8.5</td>
<td>13 × 24, 12 × 31</td>
</tr>
</tbody>
</table>

Abbreviations: LV = left ventricle; RV = right ventricle; AA = aortic atresia; MA = mitral atresia; PCFO = premature closure of foramen ovale; APVR = anomalous pulmonary venous return; PFO = patent foramen ovale; AVC = atrioventricular canal; MH = mitral hypoplasia; SFO = stenotic foramen ovale; AS = aortic stenosis; 0 = absent; + = present, moderate; ++ = present, extensive.

### FIGURE 2. Case 8. Sites of origin of the arterioluminal type of ventriculocoronary connection. (A) Gross photograph of cut surface of heart shows thick-walled left ventricle (LV) with endocardial fibroelastosis. Note luminal cleft-like opening in outlined anteroseptal region. RV = right ventricle; POST = posterior cardiac surface. (B and C) Photomicrographs of serial sections, 40 μ apart, from the region outlined in A. Note endocardial fibroelastosis (dark-stained) and primitive channel extending from left ventricular chamber toward epicardial branches of left anterior descending coronary artery (LAD). LV = lumen of left ventricle. Elastic stain; magnification × 10. (D) Region outlined in C. Note condensation of muscle (dark-stained) in wall of primitive channel and disarrayed bundles of surrounding myocardium. Arrows indicate continuity of channel with LV lumen. Trichrome stain; magnification × 80.
### Table 1. (Continued)

<table>
<thead>
<tr>
<th>Ventriculocoronary connections</th>
<th>Microscopic findings in left ventricle</th>
<th>Thickened coronary arteries</th>
<th>Endocardial fibroelastosis</th>
<th>Myofiber disarray</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterioluminal</td>
<td>Arteriosinusoidal</td>
<td>Arteriocapillary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

**Figure 3.** Case 8 — site of intramural anastomosis of an arterioluminal connection. (A and B) Photomicrographs of cross sections of heart 610 μ apart showing connection between left ventricular chamber (LV) and obtuse marginal artery (OM). Arrowheads indicate multiple sites of origin of documented arterioluminal connections. Elastic tissue stain; magnification × 2. (C and D) Photomicrographs of region outlined in B with luminal continuity demonstrated. C — elastic stain and D — trichrome stain; magnification × 8. (E) Photomicrographs of area outlined in D showing intraluminal projections of intimal tissue at connection site. Trichrome stain; magnification × 100.
changes were seen in all cases with ventriculocoronary arterial connections (table 1), and were most prominent in arteries that communicated directly with the lumen (arterioluminal subtype) and less prominent in those that communicated indirectly with the lumen (arteriosinusoidal and arteriocapillary subtypes). In case 8, who had grossly visible arterioluminal connections, the associated epicardial coronary artery branches were cord-like and tortuous on the external surface of the left ventricle, which was dimpled where the branches entered the myocardium.

**Endocardial Fibroelastosis**

Endocardial fibroelastosis (EFE) was absent in the left ventricle of both cases with combined aortic and mitral atresia as well as case 3, but was present in all nine cases with a patent mitral orifice (fig. 1). When present, it diffusely thickened the endocardial layer, with the exception of the endocardium beneath the posterior mitral leaflet. Beneath the leaflet where arteriosinusoidal connections dominated, the EFE was consistently less striking than elsewhere in the left ventricle in all nine cases (table 2). Within the main portion of the LV cavity, where arterioluminal and arteriocapillary connections predominated, the diffuse fibroelastosis sometimes appeared to narrow the endocardial orifices of the ventriculocoronary connections (figs. 3B and 5A).

**Myofiber Disarray**

LV myofiber disarray consisting of areas of cellular disorganization was seen in all 10 cases with patent inflow and obstructed outflow (cases 3–12). The distribution of disarray was generally in the inner two-thirds of the myocardium of the LV free wall (figs. 2D, 3C and D and 4B) and septum (the region containing the ventriculocoronary connections) and did not involve the outer compact myocardium or the right ventricle.

**Focal Calcification/Scarring of the Myocardium**

Small areas of calcification or scarring were noted in 10 cases. This finding was limited to the subendocardial region of the left ventricle, and involved the interventricular septum and the papillary muscles. It was absent in both cases with combined mitral and aortic atresia.

---

**TABLE 2. Regional Distribution of Microscopic Connections and Endocardial Fibroelastosis in Left Ventricular Wall**

<table>
<thead>
<tr>
<th>Location in LV wall</th>
<th>Type of ventriculocoronary connection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arterioluminal</td>
</tr>
<tr>
<td>Beneath posterior mitral leaflet</td>
<td>0/12</td>
</tr>
<tr>
<td>Remainder of cavity</td>
<td>9/12</td>
</tr>
</tbody>
</table>

Abbreviations: LV = left ventricular; EFE = endocardial fibroelastosis.
FIGURE 5. Arteriocapillary connections in case 5. (A) Photomicrograph of whole-mount transverse section with pale staining of inner myocardium in left ventricular free wall. LV = lumen of left ventricle. Elastic stain; magnification × 2. (B) Region solidly outlined in A with normally developed outer compact myocardium (CM), endocardial fibroelastosis (EFE) and pale-staining specialized capillary network (SCN). Elastic stain; magnification × 8. (C) High-power micrograph of region outlined in B, with dilated vascular channels, edema, and paucity of myofibers. Trichrome stain; magnification × 100. (D) Region with interrupted outline in A showing a subendocardial focus of primitive channels (arrows), which were associated with the specialized capillary network. Elastic stain; magnification × 12.

Discussion

In the developing human embryo, the coronary arteries arise in early prenatal life as solid angioblastic buds. These buds are visible before conotruncal partitioning is complete and later extend through the epicardium, dividing into their usual anatomic components by the middle of the seventh week of gestation. The smaller branches of the coronary arteries join a rich capillary network which already has connected to the veins and the coronary sinus. This specialized capillary network is connected to the LV lumen.25, 26 Some branches of the coronary arteries communicate with the intramyocardial trabecular spaces, which are relatively large during early cardiac development.26, 27 These spaces in turn connect either directly or indirectly with the ventricular lumen, forming natural ventriculocoronary communications in the embryo which later shrink as the outer compact myocardium develops.28

A trabeculated pattern is normally prominent in the developing RV wall and assumes postnatal significance in pulmonary valve atresia with intact ventricular septum type I, where a competent tricuspid valve is associated with a small right ventricle.29 The chamber wall is thick, has prominent trabeculations that recapitulate an embryonic pattern, and exhibits endocardial fibroelastosis. Sinusoidal channels within the myocardium, by connecting with the lumen, may allow for egress of blood from this obstructed high-pressure chamber during systole. The relatively high incidence of reported ventriculocoronary communications in association with hypoplastic right heart syndrome is considered to be a related developmental phenomenon.30 The obstructed chamber in hypoplastic left heart syndrome may predispose in a similar way to the persistence of an embryonic microvascular pattern and would allow for egress of blood from this high-pressure obstructed chamber. Our study supports this concept.

First, all specimens with patent inflow and obstructed outflow contained numerous microscopic ventriculocoronary connections (table 1), which were of the arterioluminal, arteriosinusoidal and specialized arte-
riocapillary types as described in the human embryo by Blake et al.\textsuperscript{54} The individual subtypes had regional distribution (table 2), and together formed a network that presumably allowed for decompression of the ventricular chamber.

Second, there were changes in many of the coronary artery branches proximal and distal to these connections (table 1). The wall thickening we noted in some of the epicardial coronary arteries and their intramyocardial branches (fig. 6) has been ascribed to high-pressure perfusion or excessive flow in several forms of congenital heart disease.\textsuperscript{31, 32} For example, in supravalvular aortic stenosis, where the unprotected coronary ostia are situated below the site of outflow obstruction, similar changes secondary to antegrade high-pressure blood flow during ventricular systole are seen. In hypoplastic left heart syndrome, we noted thickening of the coronary arteries, which spared the RV branches and suggested high-pressure or excessive perfusion of coronary artery branches proximal to their ventricular connections. These observations correspond to the findings of others, detected by angiography,\textsuperscript{33} by gross inspection of the epicardium,\textsuperscript{4, 10, 13, 16, 17, 19, 23, 31} and by microscopic examination.\textsuperscript{16, 17, 21, 27} Implied also in the morphologic alterations is an interference with the usual cyclic perfusion of the coronary arteries, the major component of which is passive and normally during diastole. In hypoplastic left heart syndrome, the recognizable coronary perfusion angiographically is during systole, being ductus dependent, and flowing proximally through the ascending aorta.\textsuperscript{33} Thus, in the setting of an anatomically obstructed left ventricle with microscopic lumen-to-artery connections and thickened surface epicardial coronary arteries, systolic egress of blood at high pressure from the ventricle into the overlying coronary arterial vasculature could occur. Without the availability of left ventriculography,\textsuperscript{33} angiographic flow along the line of lowest resistance into the distal arterial vessels and their epicardial collaterals may have been hitherto undetectable.

The tendency toward regional distribution of the individual types of communications, accompanied by a variable degree of endocardial fibroelastosis (table 2), suggests that regional differences in flow, pressure and oxygenation may exist in the left ventricle in hypoplastic left heart syndrome.\textsuperscript{34-39} Beneath the posterior mitral leaflet, the prominent arteriosinusoidal connections to the ventricular cavity with sparse EFE (fig. 1) may relate developmentally to the abnormal anatomy of the valve apparatus. As a result of shortened and fibrotic chordae and papillary muscles, the endocardium and underlying myocardium in this region may be relatively protected from the inflowing blood in diastole. In the remainder of the ventricle, however, where arteriosinusoidal connections were virtually absent, inflowing blood in diastole may, in part, be the basis for the thick EFE. EFE is a process considered by others\textsuperscript{34, 35} to predispose to closure of the ventricular openings of the thebesian veins. Since arterioluminal connections predominate in the myocardium adjacent to thick EFE (table 2) and are most prominent in those cases with complete outflow tract obstruction (table 1), the persistent patency of this type of connection may

![Figure 6. Coronary artery thickening in two different cases.](http://circ.ahajournals.org/)

(A) Case 9 — Photomicrograph of branching posterior descending artery (PD) in epicardial groove. Magnification × 14. (B) Case 9 — vessel outlined in A shows a prominent muscular elastic zone (M). Eccentric intimal thickening (I) is present but does not appear to significantly narrow the caliber of the lumen. Magnification × 120. (C) Case 5 — low-power view of interventricular septum with prominent muscularized arteries (arrows). Magnification × 10. All elastic stain.
be related to elevated systolic intracavitary pressure. Irrespective of the regional distribution within the ventricle, the consistent subendocardial and midzone localization of the complex capillary network at the junction with outer compact myocardium suggests a developmental relationship to local hemodynamic factors in the LV wall. Furthermore, an acute alteration of in vivo hemodynamics is suggested by the association of capillary congestion, edema and hemorrhage in this zone, with coronary sinus dilatation. These histologic changes between myofibers may be secondary to increased hydrostatic pressure at the venous end of the specialized capillary network due to the effects of increasing right atrial pressure as the right heart fails agonally.7,14,40 The paucity of myocardial fiber development in the specialized capillary zone (fig. 5C) may also have implications for mural kinetics in regions in which the abnormality is extensive.

All types of connections were prominent when stenosis or premature closure of the foramen ovale occurred with a patent mitral orifice and without other recognizable routes of pulmonary venous drainage (table 1), suggesting that the connections may have allowed for intracavitary blood to reach not only the coronary arteries, but also the coronary sinus. This alternate anomalous pathway for obstructed pulmonary venous return has been described by others in hypoplastic left heart syndrome.13,23 Myocardial fiber disarray in the septum and LV free wall was limited to cases with a patent mitral orifice and outflow obstruction (table 1).41-43 The anatomic distribution was similar to 15 cases of aortic atresia with intact septum reported by Bulkley et al.,41 who noted associated intramural coronary artery thickening. The ‘‘IHSS-type’’ histologic changes were felt by these authors to be secondary to altered wall stress produced by the excessive isometric systolic contraction that is a feature of ventricular function common to both hypoplastic right and left heart syndromes and primary muscular subaortic obstruction.41 Because of the zonal distribution of fiber disarray (figs. 2D, 3C and D and 4B), it would appear that in hypoplastic left heart syndrome, differentiation of the myocardial fibers may relate not only to contractile characteristics of the wall, but also to the abnormally developing microvascular structure.

Our findings support the rationale of current surgical management of hypoplastic left heart in which the small left ventricle is bypassed and remains nonfunctional.44-47 In most cases, production of a functional left ventricle is likely to be limited by the inhibitory effect of extensive underlying structural abnormalities on LV performance and subsequent growth of the myocardium. However, consideration of surgical production of a functional left ventricle might be given in the future to those specific cases in which less extensive structural changes or a combination of more favorable anatomic defects48 can be recognized.

In summary, although a variety of histologic abnormalities of the LV endocardium,18,21,35,36 myocardium,17,23,31,41-43 and vessels16,17,21,31,32 have been reported by others in cases of severe congenital left ventricular outflow obstruction, no clearcut recognition of their regional distribution and extent or apparent relationship to developmental anatomy and hemodynamics has emerged. We have documented in this study the postnatal persistence of elements of the embryonic microvascular structure in the left ventricle of the hypoplastic left heart syndrome. Numerous microscopically patent ventriculocoronary connections were noted in association with zonal morphologic abnormalities of the endocardium and myocardium. The abnormalities appear to relate to the intrauterine hemodynamic derangements implied by the combination of left-sided patent inflow and obstructed outflow.

Acknowledgment

We thank Janis Atlee for preparation of figure 1 and Glenn Porter for secretarial assistance in preparation of the manuscript.

References

21. Essed CE, Klein HW, Kredit P, Vorst Jr: Coronary and endocar-
dial fibroelastosis of the heart in the hypoplastic left and right heart syndromes. Virchows Arch [Pathol Anat] 368: 87, 1975
25. Grant RT: Development of the cardiac coronary vessels in the rabbit. Heart 13: 262, 1926
Ventriculocoronary connections in hypoplastic left hearts: an autopsy microscopic study.
W N O’Connor, J B Cash, C M Cottrill, G L Johnson and J A Noonan

Circulation. 1982;66:1078-1086
doi: 10.1161/01.CIR.66.5.1078

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/66/5/1078.citation