Mortality in hypoplastic left heart syndrome: Review of 216 autopsy cases of aortic atresia with attention to coronary artery disease

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Objectives: Aortic atresia (AA) in hypoplastic left heart syndrome (HLHS) has been associated with increased mortality in several prior studies. We reviewed our autopsy series to explore the relationship of coronary abnormalities to anatomic subsets of HLHS with AA.

Methods: We retrospectively reviewed all pathology specimens with AA/MS (mitral stenosis) and AA/MA (mitral atresia) in the Cardiac Registry of Children's Hospital Boston between 1955 and 2009 including autopsy reports, operative notes, and imaging studies. Formalin-fixed hearts were examined, and cases found to have macroscopic coronary artery abnormalities were sectioned at mid-left ventricular level in the transverse plane and at mid-right ventricular level in the longitudinal plane for histologic analysis of coronary arteries using tissue sections stained with hematoxylin and eosin.

Results: A total of 216 autopsy cases were identified with AA/MS (134) and AA/MA (82). Coronary anomalies were found in 49 cases, left ventricle–coronary fistula in 39, all in AA/MS, and 10 other coronary abnormalities, all in AA/MA. Histologic study confirmed fistulas only in the AA/MS group with no evidence of fistulas in the AA/MA group.

Conclusions: The occurrence of left ventricle–coronary fistulas appears limited to the AA/MS group, and coronary fistula specimens were disproportionately more prevalent in postoperative specimens. Further clinical studies are required to validate this finding and to identify subgroups that carry a higher mortality risk. (*J Thorac Cardiovasc Surg* 2012;144:1301-6)

Prior reports on hypoplastic left heart syndrome (HLHS) at our and other institutions have found that the aortic atresia/mitral stenosis (AA/MS) subgroup was associated with a higher mortality. Vida and associates¹ reported a higher (29% vs 7.9%) mortality in the AA/MS variant of HLHS compared with other anatomic subtypes of HLHS. Glatz and colleagues² reported a 21% vs 3% mortality in the AA/MS subgroup vs the aortic atresia/mitral atresia (AA/MA) subgroup.

The pathophysiologic mechanisms underlying these findings have not been clearly defined, but a relationship to coronary abnormalities has been postulated. Several coronary abnormalities have been documented in HLHS, with the most common being coronary fistulas or ventricular–

coronary connections. O'Connor and coworkers³ in 1982 found that the AA/MS subgroup had a greater number of coronary abnormalities including ventricular–coronary connections. Baffa and associates⁴ reviewed 151 autopsy specimens, 89 with AA/MS and 52 with AA/MA. They identified 27 coronary–cameral fistulas in the AA/MS subgroup, 17 with associated tortuous epicardial vessels, and 3 specimens had single coronaries. Other abnormalities that have been described include intramural coronaries, high origin of coronaries, and anomalous origin of the left coronary artery from the pulmonary artery.⁵

We hypothesized that the occurrence of ventricular–coronary fistula would be more common in the AA/MS subgroup because of the frequent occurrence of hypertensive left ventricles (LVs) in this group. Ventricular–coronary fistulas could contribute to coronary steal and myocardial dysfunction and may contribute to mortality in this subgroup. To better understand the relationship between coronary disease and mortality, we undertook a review of all autopsies performed on patients with HLHS and AA at our center.

METHODS

We retrospectively reviewed, with institutional review board approval, all cases of AA subtype of HLHS that underwent autopsy in the Cardiac Registry of Children's Hospital Boston between 1955 and 2009. Clinical charts were reviewed for clinical history and operative data. Reports of all preoperative and postoperative imaging studies and autopsies were

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Abbreviations and Acronyms

AA	= aortic atresia
EFE	= endocardial fibroelastosis
HLHS	= hypoplastic left heart syndrome
LV	= left ventricle (ventricular)
LVEFE	= left ventricular endocardial fibroelastosis
MA	= mitral atresia
MS	= mitral stenosis
RV	= right ventricle (ventricular)
RVEFE	= right ventricular endocardial fibroelastosis

reviewed. In addition, all available formalin-fixed HLHS/AA heart specimens were examined, including gross examination of coronaries in all hearts.

MS was defined by documented flow across the mitral valve in imaging studies or by the presence of a well-defined mitral valve with a patent inflow into the LV and a measurable orifice.

Histologic examination of all AA hearts with coronary abnormalities noted on echocardiography, cardiac catheterization, or on gross autopsy examination was performed. In addition, coronary histologic examination was also carried out on an equivalent number of AA hearts matched for age and surgical status. Two representative tissue blocks, the first a cross section of the LV at mid cavity including the septum and the second a longitudinal section from the right ventricle (RV) at the acute margin, including the atrioventricular sulcus, were taken from intact heart specimens that had been fixed in 10% buffered formalin. The tissue was embedded in paraffin, and for each block, 5- μ m-thick sections were cut and stained with hematoxylin and eosin and examined with an Olympus BX400 microscope (Olympus Corporation, Tokyo, Japan) with field diameters calibrated using a stage micrometer. Measurements were made of (1) thicknesses of the ventricular wall, (2) thickness of the medial layer of coronary arteries having an outer diameter between 1100 μ m and 2200 μ m, and (3) thickness of any ventricular fibroelastosis approximated to the nearest fraction (1/6, 1/4, 1/3, 1/2, 2/3, or 3/4) of the microscopic field in which the thickness of interest was completely visualized (eg, fibroelastosis that spanned half of a 2200- μ m-wide microscopic field was determined to have a thickness of 1100 μ m). A fistula between a coronary artery and a ventricular cavity was considered present if there was an unambiguous connection on microscopic examination or if there was overlap of a coronary artery and a ventricular cavity in the plane of the slide. In histologically ambiguous cases or for cases in which fistulas were grossly identified but not seen in the initial hematoxylin and eosin slide, additional hematoxylin and eosin slides were prepared from the respective blocks at 10- μ m intervals and examined as above.

The hearts were classified into 4 groups:

- Group 1: AA/MS (aortic atresia, mitral stenosis)—hearts with a diagnosis of AA/MS confirmed by gross examination.
- Group 2: AA/MS/CF (aortic atresia, mitral stenosis, coronary fistula)—hearts in the AA/MS group that had coronary abnormalities on echocardiography, cardiac catheterization, gross examination, or histologic examination.
- Group 3: AA/MA (aortic atresia, mitral atresia)—hearts with diagnosis of AA/MA confirmed by gross examination.
- Group 4: AA/MA/CA (aortic atresia, mitral atresia, coronary abnormalities)—hearts in the AA/MA group that had coronary abnormalities on echocardiography, cardiac catheterization, gross examination, or histologic examination.

This grouping system was used for comparison between groups and for statistical analysis of histologic findings.

A nonparametric test (Mann-Whitney) was used to compare the median coronary artery medial thickness and thickness of LV endocardial fibroelastosis (LVEFE) among the 4 groups. The Pearson χ^2 test was used to compare the proportions of 4 groups in the pre-Norwood (preoperative) and post-Norwood (palliative surgical) eras. The statistics package used for analysis was PASW Statistics 18.0, SPSS Inc, Chicago, Ill.

RESULTS

A total of 216 hearts with the diagnosis of HLHS and AA were examined at the cardiac registry at Children's Hospital Boston between 1955 and 2009. Of these, 200 were autopsy specimens, and 16 were hearts explanted at orthotopic heart transplantation. All but 2 of the 216 hearts were available for reexamination. One hundred thirty-four (62%) were of the AA/MS subtype and the remaining 82 (38%) were of the AA/MA subtype. Thirty-nine (29%) of 134 specimens of the AA/MS subtype had coronary abnormalities, and all were fistulas between the ventricle and coronary arteries, with 38 LV–coronary fistulas and 1 RV–coronary fistula. **Figure 1, A and B**, shows representative cardiac catheterization images of LV–coronary fistulas. In the AA/MA group, 10 specimens had coronary abnormalities (12%), but none had coronary fistulas. The abnormalities noted in the AA/MA group included anomalous origin of the left coronary artery from the pulmonary artery in 1, single coronary artery in 3 (1 with an atretic left coronary ostium), aneurysmal right coronary artery in 1, high takeoff and intramural right coronary artery in 1, intramyocardial left anterior descending coronary artery in 1, coronary ostial stenosis in 1, hypoplastic coronaries in 1, and high takeoff and oblique ostium of left coronary artery in 1.

A total of 96 hearts were examined histologically: 31 in AA/MS, 37 in AA/MS/CF, 16 in AA/MA, and 10 in AA/MA/CA groups. **Figure 2, A and B**, shows histologic images of coronary fistulas.

Tables 1 and 2 give an outline of management strategies that had been used before the time of death/explant, and management stage at death/explant, in the 4 anatomic subgroups. Tables 3 and 4 document coronary medial thickness and EFE thickness in the 4 groups.

On comparison of the 4 groups on the basis of historical era, ventricular–coronary fistulas were found much more frequently in the AA/MS group in the postoperative era than in the era before first attempts at surgical palliation ($P < .031$). This finding of a higher percentage of autopsied hearts in the operated groups compared with the nonoperated specimens suggests an unfavorable impact of ventricular–coronary fistulas on surgical palliative procedures. The presence of LVEFE was significantly higher ($P > .0001$) in the AA/MS and AA/MS/CF groups than in the AA/MA and AA/MA/CA groups. However, there was no significant difference between the AA/MS and the AA/MS/CF groups in thickness of the LVEFE. Interestingly, there was a higher

FIGURE 1. A, Anteroposterior view of a left ventricular angiogram demonstrating retrograde filling of the left coronary artery via the fistula. Arrow points to the fistula. B, Lateral view of the same left ventricular angiogram demonstrating the coronary fistula filling the left coronary artery on injecting the left ventricle. Arrow points to the fistula.

occurrence of RV endocardial fibroelastosis (RVEFE) in the AA/MS/CF group than in the AA/MS group ($P < .030$).

DISCUSSION

Since first description of the pathophysiology of HLHS by Bardeleben in 1851,⁶ this disease complex has been extensively studied. HLHS was a uniformly fatal condition until palliative procedures were developed and perfected in the 1970s and early 1980s. In 1981 Norwood and coworkers⁷ reported their experience with 16 consecutive infants with HLHS in whom staged palliation was attempted. Of interest,

FIGURE 2. A, Histologic section of the left ventricle stained with hematoxylin and eosin (H&E) at 40× magnification. Coronary artery and ventriculo–coronary connections are marked by solid black arrows. B, Elastic-stained histologic section of the left ventricle at 100× magnification. The coronary artery opening into the ventricular cavity is marked by solid arrows.

3 of these patients had LV–left anterior descending coronary artery fistulas, which are included in our series. Our series includes specimens obtained after a variety of palliative procedures, including the first Norwood procedures.

Clinical and Pathologic Distribution of the AA/MS and AA/MA Subtypes

In contrast to the current pathologic series, most clinical series of HLHS with AA have had a higher occurrence of AA/MA subtype. Mahle and his group⁸ in their series of 840 HLHS patients found 520 patients with AA; 61% of this group had AA/MA whereas 39% had AA/MS. A similar distribution of 65% AA/MA vs 35% AA/MS was reported by Glatz and colleagues.²

Some early autopsy series have also reported a similar distribution. Van Praagh and associates,⁹ in their review of nearly 3000 hearts in the cardiac registry at Children's Hospital Boston, reported 102 cases of HLHS with AA with 63% in the AA/MA subgroup and 37% in the

TABLE 1. AA management strategy

Management	AA/MS (n = 134)	AA/MS/CF (n = 39)	AA/MA (n = 82)	AA/MA/CA (n = 10)
I no surgery (before Norwood era)	49*	8*	32	4
II surgical palliation	85†	31†	50	6
P value	.031 (I vs II)		NS (I vs II)	

This table represents the distribution of the hypoplastic left hearts with aortic atresia in the 3 subgroups in the preoperative and postoperative eras. There is a significantly higher proportion of hearts with AA/MS and ventricular–coronary fistulas in the postoperative era. AA, Aortic atresia; MS, mitral stenosis; CF, coronary fistula; MA, mitral atresia; CA, coronary anomalies other than coronary fistula; NS, not significant. *Ex-planted heart from primary orthotopic heart transplantation = 1. †Hybrid stage I = 4.

AA/MS subgroup. This finding is likely related to the fact that the majority of cases reported in this series were from the era before attempts at surgical palliation. However, later autopsy series have contained a higher percentage of AA/MS hearts. Bartram and colleagues¹⁰ reported 88 cases of AA with a distribution of 49% AA/MA and 51% AA/MS in their postmortem series of 122 deaths after modified Norwood procedures. Bharati and Lev¹¹ looked at 230 hearts with HLHS. They reported 200 cases of AA, 95 (48%) with AA/MA, and 105 (52%) with AA/MS.

In our series of 216 autopsy cases of HLHS/AA, we found a much higher percentage of specimens with AA/MS compared with AA/MA (62% vs 38%). This finding is potentially related to the significantly higher number of coronary abnormalities seen in the AA/MS group, 29% vs 12% in the AA/MA group ($P < .004$) and to the inclusion of a large number (63%) of postoperative specimens. The only coronary abnormality we found in the AA/MS subgroup was ventricular–coronary fistula. The AA/MA group had several types of coronary abnormalities but none had coronary fistulas.

Coronary Morphology

Prior studies of the coronary arteries in HLHS suggested that coronary morphology was a possible contributor to

TABLE 2. AA stage at death

Outcome	AA/MS (n = 134)	AA/MS/CF (n = 39)	AA/MA (n = 82)	AA/MA/CA (n = 10)
Unoperated (before Norwood era)	49*	8*	32	4
Stage I	59	20	30	5
OHT after stage I	8	7	0	0
Interstage death	4	0	13	1
After BDG death	4	2	3	0
OHT after BDG	0	0	3	0
After Fontan death	6	0	1	0
OHT after Fontan	4	2	0	0

This table represents the proportion of hearts in the 4 subgroups based on stage at death. Again there is higher proportion of hearts with AA/MS and ventricular–coronary fistula in the postoperative era, particularly after the initial palliation. AA, Aortic atresia; MS, mitral stenosis; CF, coronary fistula; MA, mitral atresia; CA, coronary anomalies other than coronary fistula; OHT, orthotopic heart transplantation; BDG, bidirectional Glenn. *Ex-planted heart after orthotopic heart transplantation.

TABLE 3. Histology of coronary arteries—medial thickness

Coronary artery medial thickness (μm)				
	AA/MS	AA/MS/CF	AA/MA	AA/MA/CA
n	31	37	16	10
Median	37	55	37	37
Range	37-165	37-110	37-110	37-110
P value	.22-.55 between groups			

This table compares the coronary artery medial thickness in the 4 groups of hypoplastic left hearts with aortic atresia. There is no significant difference in the medial thickness of coronary arteries noted. AA, Aortic atresia; MS, mitral stenosis; CF, coronary fistula; MA, mitral atresia; CA, coronary anomalies other than coronary fistula.

mortality. Lloyd, with Evans and Marvin¹² and with Marvin,¹³ compared 51 autopsy specimens with HLHS with 18 normal controls and found no difference in coronary ostial size or diameters in the 2 groups. A subsequent study of 59 HLHS heart specimens, all from patients who died within the first 90 days after birth (11 surgically palliated), demonstrated a significant survival advantage for larger coronaries, greater RV mass, and coronary/RV mass ratio. They concluded that adequacy of myocardial perfusion was essential for survival. Sauer and colleagues¹⁴ compared the epicardial coronaries in 9 AA/MA hearts, 19 AA/MS hearts, and 10 normal hearts. They noted that LVEFE was present in all AA/MS hearts and that coronaries in AA/MS hearts were thicker and more tortuous on macroscopic examination. Although there was no difference in external diameters of the coronaries in the groups, some AA/MS hearts did show an increase in medial thickness, particularly in the left coronary system. They hypothesized that these coronary abnormalities may increase risk of mortality.

Baffa and coworkers,⁴ in their series of 151 hearts, reported no difference in coronary artery wall thickness between AA/MS, AA/MA, and AS/MS hearts. Sugiyama and associates¹⁵ described a higher occurrence of abnormal findings, including myocardial necrosis, interstitial fibrosis, and calcification, in the MS subgroups of HLHS, which could possibly contribute to RV dysfunction and thus poorer prognosis. Recent studies by Salih, Sheppard, and Ho¹⁶ on unoperated HLHS hearts from patients dying in the first 2

TABLE 4. Histology of LV endocardium

EFE thickness (μm)				
	AA/MS	AA/MS/CF	AA/MA	AA/MA/CA
n	31	37	16	10
Median	225	225	0	0
Range	0-1833	0-1833	0-73	0-73
P value	<.0001 vs AA/MA		<.0001 vs AA/MA/CA	

This table compares the thickness of the left ventricular endocardium in the four groups of hypoplastic left hearts with aortic atresia. There is a significant difference in the occurrence of left ventricular fibroelastosis in the subgroup with aortic atresia and mitral stenosis. LV, Left ventricle (ventricular); EFE, endocardial fibroelastosis; AA, aortic atresia; MS, mitral stenosis; CF, coronary fistula; MA, mitral atresia; CA, coronary anomalies other than coronary fistula.

months after birth found that capillarization (as measured by diffusion distance) in both the RV and LV was reduced compared with normal hearts. They hypothesized that increased diffusion distances could affect ventricular development inasmuch as tissue aerobic metabolism is dependent on diffusion distance from capillary beds.

Our series showed no significant differences in coronary artery medial thickness between the various subtypes of HLHS with AA, but capillary density and capillary diffusion distances were not examined.

Coronary Fistula

Occurrence of coronary fistulas in AA was reported as early as 1932 by Bellet and Gouley.¹⁷ Raghbi and colleagues¹⁸ described a case of AA with premature closure of the foramen ovale, with egress of LV blood through sinusoids and coronary fistulas and ultimately via the coronary sinus to the right atrium. They compared this with RV–coronary fistulas seen with pulmonary atresia and intact ventricular septum. More recently, LV–coronary fistulas in HLHS have been successfully diagnosed on prenatal echoes.¹⁹ Extensive ventricular–coronary connections to both coronary artery systems was recently reported by Roberson and his group.²⁰ Their patient underwent hybrid stage I palliation and died at 5 weeks of age of ischemia-induced ventricular tachyarrhythmia. The left circumflex system had a proximal obstruction and was exclusively supplied through fistulous communication from the LV.

In our series we had only 1 heart with AA/MS with demonstrable coronary ostial occlusion on cardiac catheterization and coronaries filling entirely from the hypertensive LV via fistulous communication. Although 2 of the hearts in our AA/MA subgroup had coronary ostial atresia or stenosis, it is interesting to note that neither had coronary fistula.

Sathanandam and coworkers,²¹ in a 4-year prospective study, reported 15% incidence of ventricular–coronary connections in 100 consecutive HLHS cases, with 56% of the AA/MS subtype having ventricular–coronary connections. Mortality was limited to those cases with extensive ventricular–coronary connections. Recent work by Scheurer and colleagues²² at our institution retrospectively reviewed all cases of AA/MS over a 42-month period beginning in January of 2007 with a significantly lower transplant-free survival (34%) in those with LV–coronary fistulas compared with 100% in those without fistulas. In our series, AA/MS hearts with ventricular–coronary fistulas were disproportionately represented among the specimens in the AA/MS subgroup after palliation. This finding suggests that the presence of LV–coronary fistulas may have contributed to mortality in the AA/MS subgroup in our series. [Appendix Table 1](#) outlines the percentage of coronary fistulas in AA/MS group and coronary abnormalities in the AA/MA group distributed over 10-year periods. [Appendix Table 2](#) outlines

the distribution in the pre-Norwood and post-Norwood era. As depicted in the tables, the occurrence of coronary abnormalities in autopsies in the AA/MA group is essentially unchanged over time, but the occurrence of coronary fistulas in autopsies and explanted hearts in the AA/MS group has gradually increased from 12.5% in the preoperative/pre-Norwood era to nearly 60% in the current era. However, because this is an autopsy series and the true denominator is unknown, we can only speculate that occurrence of coronary fistulas in the AA/MS group confers a higher risk of mortality.

The mechanism by which these ventricular–coronary connections/fistulas could contribute to an increased mortality risk remains unclear, particularly in patients after stage I palliative procedures. In contrast to patients with pulmonary atresia and RV-dependent coronary circulation, in whom proximal coronary stenosis or atresia is associated with higher mortality,²³ patients with AA/MS and ventricular–coronary fistulas did not demonstrate proximal obstructions. Inasmuch as there was a high incidence of restrictive atrial septum in these patients with coronary fistulas, it is tempting to speculate that the atrial septectomy that is carried out as part of a typical Norwood or Sano stage I palliative procedure alters LV filling and thus coronary perfusion through ventricular–coronary fistulas. In addition, it is known that the AA/MS subgroup generally has a hypertensive LV with suprasystolic pressures, which may lead to reversal of flow in coronaries and coronary malperfusion. This high pressure in the LV cavity may also lead to subendocardial ischemia and fibrosis because of abnormal transmural gradients.²⁴

Limitations

This study has limitations in that it is an autopsy series, data were collected retrospectively from a single center, and physiologic relationship between coronary fistula and mortality cannot be clearly established.

CONCLUSIONS

Coronary fistulas appear to be the most common coronary abnormality in this autopsy series of AA in HLHS. Ventricular–coronary fistulas are limited to the AA/MS group. Patients with AA/MS and coronary fistulas were overrepresented in the autopsies from the postoperative era compared with the preoperative era. The exact relationship between abnormal coronaries, particularly LV–coronary fistulas, and mortality cannot be conclusively established, but it seems likely that coronary fistulas may have contributed to coronary ischemia and mortality in this series. Further investigation of this link between LV–coronary fistula and mortality is required.

The presence of coronary fistula on preoperative imaging studies should raise awareness of potentially increased mortality risk, and optimal management strategies need to be

developed. The roles of preferential use of a Sano shunt for stage I palliation or a hybrid stage I palliation vs primary transplantation for neonates with significant LV–coronary fistulas should be considered in future management of patients with MS/AA and coronary fistula. Follow-up study on survivors with coronary fistulas in HLHS will help us gain a better understanding of the natural history of the coronary fistula inasmuch as there has been a recent case report of regression of fistula.²⁵

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APPENDIX TABLE 1. Distribution of various groups based on era

Era	AA/MS total	AA/MS/CF	AA/MS/CF (% of total)	AA/MA total	AA/MA/CA	AA/MA/CA (% of total)
Before 1980	48	6	12.5%	14	2	14%
1981–1990	47	10	21%	38	3	8%
1991–2000	29	17	57%	19	3	16%
2001–2009	10	6	60%	11	2	17%

AA, Aortic atresia; MS, mitral stenosis; CF, coronary fistula; MA, mitral atresia; CA, coronary anomalies other than coronary fistula.

APPENDIX TABLE 2. Distribution of various groups based on pre-Norwood (before 1980) and post-Norwood (after 1980) era

Era	AA/MS total	AA/MS/CF	AA/MS/CF (% of total)	AA/MA total	AA/MA/CA	AA/MA/CA (% of total)	P value
Before 1980	48	6	12.5%	14	2	14%	1.0
After 1980	86	33	38%	68	8	12%	.002
P value			.0015			1.0	

AA, Aortic atresia; MS, mitral stenosis; CF, coronary fistula; MA, mitral atresia; CA, coronary anomalies other than coronary fistula.