Ped Cardiol 1:301-306, 1980

Pediatric Cardiology

Pulmonary Vascular Changes Associated With Hypoplastic Left Ventricle Syndrome

M. Paula Neumann, Kathleen P. Heidelberger, Macdonald Dick II, Amnon Rosenthal

Department of Pathology, and the Section of Pediatric Cardiology, Department of Pediatrics and Communicable Diseases, the University of Michigan Medical Center, Ann Arbor, Michigan

SUMMARY. **The lungs of ten newborn infants who died of hypoplastic left ventricle syndrome were studied by a morphometric technique that (1) determined the percentage wall thickness of injected pulmonary arteries, (2) determined the ratio between the number of alveoli per high-power field and the number of corresponding arteries, and (3) examined in detail the extension of medial smooth muscle to the vessels at the periphery of the acinus. The findings in the lung were related to the gross cardiac morphological changes and to echocardiographic and hemodynamic findings. The echocardiograms of eight neonates demonstrated small left ventricles. The aortic root was hypoplastic in seven and the left atrium was small in three of the eight. Pulmonary artery hypertension and elevation of the left atrial pressure were present in all infants in whom measurements were obtained. The mean percentage wall thickness of all vessels was greater in afflicted infants than in normal age-matched control subjects. There was a normal ratio between the number of alveoli per high-power field and the number of corresponding arteries, and all infants had extension of muscle to the peripheral vessels at the alveolar duct and alveolar wall levels. The pulmonary vascular abnormalities observed in the neonate with hypoplastic left ventricle syndrome may represent persistence of fetal vascular abnormalities associated with the abnormal fetal circulatory hemodynamics resulting from the malformation. These abnormalities may influence the success of surgery proposed for hypoplastic left ventricle syndrome.**

KEY WORDS: **Hypoplastic left ventricle—Abnormal pulmonary vasculature**

Hypoplastic left ventricle syndrome is one of the few remaining cardiovascular malformations for which adequate surgical therapy is currently not available. Since the status of the pulmonary vasculature is often crucial in the selection, timing, and successful outcome of cardiovascular surgery, we studied the morphological features of the small pulmonary arteries in patients with hypoplastic left ventricle syndrome. The anatomic changes were correlated with echocardiographic, hemodynamic, and gross pathological data.

The effect of hypoplastic left ventricle syndrome on the fetal pulmonary circulation is poorly defined. Some investigators, using different techniques, have described an increase [9, 14] and others a decrease [1, 13] in the amount of smooth muscle in the small pulmonary arteries. Using the techniques introduced by Davies and Reid [2] and Dunnill [3], we assessed the morphometric changes of the intra-acinar pulmonary vasculature in ten neonates with hypoplastic left ventricle syndrome. Previous work by Haworth and Reid [5] using similar techniques studied six patients with obstruction to left ventricular outflow (two each with aortic atresia, aortic

Supported in part by a grant from the Michigan Heart Association

This material was presented in part to the American College of Cardiology Annual Scientific Session, March 1979

Address reprint requests to: Kathleen P. Heidelberger, M.D., Department of Pathology, University of Michigan Medical Center, 1335 East Catherine Street, Ann Arbor, MI 48109

0172-0643/80/0001-0301 $01.20

Table. Hemodynamic data, diagnosis, and morphometric findings in patients with HLVS[a].

Case	Survival, days	Pressures, mm Hg			Diagnosis	% Wall, thickness[d]	ALV/ART ratio[e]
		LA[b]	PA[c]	Descending aorta			
1	3	. . .	59/40	59/40	Premature closure of foramen ovale	11.2	21:1
2	4	33/34 (25)	66/21	51/39	Aortic atresia	8.3	19:1
3	2	. . .	88/57	70/56	Aortic atresia	10.0	21:1
4	6	35/19 ($\overline{24}$)	71/52	73/55	Aortic atresia	15.0	21:1
5	6	28/25 ($\overline{17}$)	. . .	45/39	Mitral atresia	10.9	17:1
6	7	. . .	65/46	49/38	Aortic atresia	11.4	21:1
7	3	10/10 ($\bar{9}$)	77/43	62/44	Mitral stenosis	7.8	24:1
8	5	. . .	. . .	. . .	Mitral stenosis	6.9	23:1
9	1	. . .	111/51	51/45	Aortic atresia	8.1	19:1
10	5	20/20 ($\overline{17}$)	74/49	78/43	Aortic atresia	7.4	20:1

[a] HLVS, hypoplastic left ventricle syndrome
[b] LA, left atrium
[c] PA, pulmonary artery
[d] Normal values for age: wall thickness $\leq$ 5%
[e] Normal values for age: alveolar/artery (ALV/ART) ratio, 20:1

stenosis, and coarctation of aorta with ventricular septal defect). The four of these with aortic atresia and stenosis had similar findings, viz, increased numbers of intra-acinar arteries that, along with the veins, were more muscular than normal in extent and medial thickness. Three structural features were used in the analysis: extension of smooth muscle into the peripheral arteries, percent wall thickness of all arteries, and the ratio of the number of alveoli to small arteries. The demonstrated increase in the extent of the muscularization and wall thickness of individual pulmonary vascular changes in the fetus are similar to those taking place in the postnatal period and in patients with large left-to-right shunts [12].

Methods

Diagnosis of hypoplastic left ventricle syndrome was made at cardiac catheterization and confirmed at necropsy in all cases (Table). Detailed histological quantitative morphometric changes of the intra-acinar pulmonary vasculature were studied in lungs obtained at necropsy in the ten study patients by the method described by Davies and Reid [2]. The pulmonary artery and main stem bronchus were cannulated and the lung incubated to reach 37°C. The pulmonary artery was then injected with a mixture of barium sulphate and gelatin at 60°C for five to seven minutes at constant pressure of 100 cm H_2O. The bronchial catheter was then infused with 10% buffered formalin at room temperature at a pressure of 45 cm H_2O until the pleura was tense and bulging.

The fixed lung was sliced into sections 0.5 cm thick. Using a random numbers guide [3], 1.0 × 1.0-cm tissue blocks, usually 12 per lung, were taken for sectioning. The tissue blocks were processed routinely, imbedded in paraffin, sectioned, and stained with hematoxylin and eosin, Verhoeff's elastic, and Mallory's trichrome stains.

The resulting slides were examined using quantitative morphometric analysis [2, 5, 7]. A calibrated eyepiece was used to measure (1) external diameter of arteries (the distance between external elastic lamina across the shorter axis of the vessel) and (2) the medial wall thickness (the distance between internal and external elastic lamina in each side of the vessel at the diameter). The values were added and a mean obtained. These measurements were used to calculate a percent wall thickness:

$$\frac{2 \times \text{mean wall thickness}}{\text{external diameter}} \times 100 = \% \text{ wall thickness}$$

Also noted was the structure of the vessel wall (ie, muscular, partially muscular, and nonmuscular) and the location of each artery with respect to its accompanying airway (pre-acinar bronchus, terminal bronchiole, respiratory bronchiole, alveolar duct, and alveolar wall). The number of alveoli and arteries greater than 10 μm were counted in ten high-power fields per slide and expressed as a simple ratio of alveoli to arteries. Arteries were grouped according to size and location. Muscularity was assessed on the basis of percent wall thickness and the extension of smooth muscle into smaller and more peripheral arteries.

A mean of 133 (81 to 191) arteries were examined per patient. The arteries analyzed varied in size from 12 to 2,000 μm in external diameter. The histological data obtained from the hypoplastic left ventricle syndrome patients were compared with data from two age-matched control subjects (2 days and 6 days of age). The controls had no clinical or pathological evidence of cardiovascular or pulmonary abnormalities and had died of metabolic defects.

Results

The pertinent clinical diagnosis and gross cardiac pathological findings are outlined in the Table. All

infants died within the first week of life. Mean age at death was 4.2 days. Severe hypoplasia or atresia of the left ventricular inflow, sinus, or outflow was present in each infant. The left atrium was small in all but one patient and the ascending aorta markedly hypoplastic in all. Pulmonary artery hypertension and elevation of left atrial pressure were demonstrated in all infants in whom appropriate pressure measurements could be obtained at the cardiac catheterization (Table). Selective injections of contrast material through an umbilical artery catheter placed in the thoracic aorta at the level of the ductus arteriosus were diagnostic in the patients with aortic atresia. Selective left atrial cineangiograms were diagnostic in the patients with mitral atresia or stenosis. The diagnosis of hypoplastic left ventricle syndrome was suspected from the echocardiogram in all cases in which the study was performed before catheterization. The size of the left atrium, left ventricle, and aortic root determined from the echocardiograms is shown in Fig. 1.

Quantitative histological measurements of the pulmonary arteries at postmortem disclosed marked extension of smooth muscle into the small arteries and an increase in percent wall thickness of all arteries in patients with hypoplastic left ventricle syndrome. On the average, 50% of the aveolar wall arteries and 86% of the alveolar duct arteries were completely muscularized (Fig. 2), as compared with 0% and 4%, respectively, in the control subjects. Ninety-nine percent of the respiratory bronchiole arteries ($\geq$ 100 μm) examined were fully muscularized vs 29% in normal controls. Percent wall thickness was increased in all size vessels in eight of ten patients (Fig. 3). The average percent wall thickness for arteries in hypoplastic left ventricle syndrome patients was 9.7% (range, 6.9% to 15%). The value in the control group was 4%. Alveolar to artery ratio ranged from 17:1 to 24:1 (mean, 20:1 to 21:1). These values did not differ significantly from the mean value of 20:1 (range, 20:1 to 21:1) found in the normal controls. The size of the intra-acinar arteries, landmarked according to the accompanying airway, was similar to controls.

There was no direct relationship between the exact anatomic diagnosis, eg. aortic atresia vs hypoplasia, and the severity of smooth-muscle extension or percent wall thickness of the pulmonary arteries. The smallest ratio of alveoli to arteries occurred in the patient with mitral atresia.

Discussion

Quantitative morphometric analysis of the pulmonary arteries in ten neonates dying with hypoplastic left ventricle syndrome disclosed marked and progressive extension of smooth muscle to the smallest pulmonary arteries and an increase in the thickness of the arterial walls (Fig. 2 and 3). These changes, although varying in severity, were present in each case and occurred regardless of the exact type of anatomic left-heart malformation.

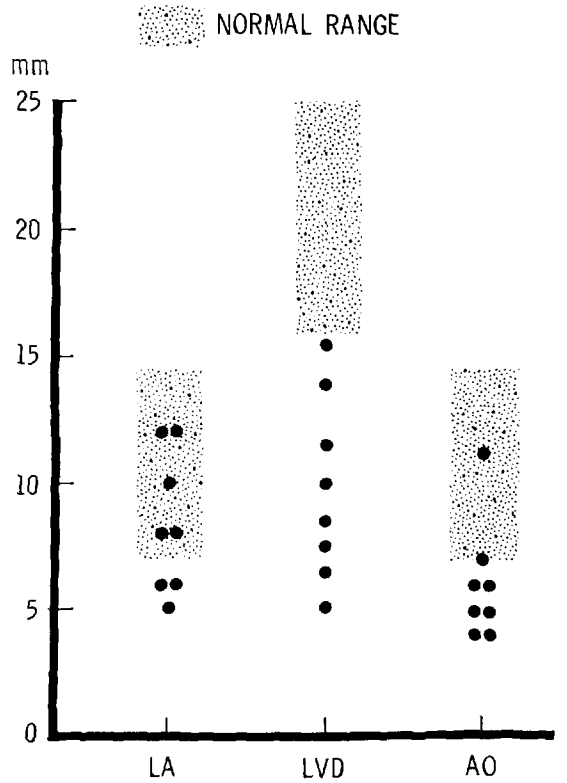

Fig. 1. Echocardiographic measurements of left atrium *(LA)*, left ventricular diastolic dimensions *(LVD)*, and aortic root *(Ao)* in eight infants with hypoplastic left ventricle syndrome. Range of normal values from Solinger et al [15].

Previous investigators using different techniques [14] have shown normal thickness of the media but increased total muscularization owing to increased numbers of muscularized arteries in neonates (younger than 5 days) with hypoplastic left ventricle syndrome [14]. Rudolph [13] described his findings of dilated and relatively thin-walled arterioles in two infants with hypoplastic left ventricle syndrome. Similarly, hypertrophy of the smooth muscle in pulmonary arterioles was not observed by Damman and Ferencz [1].

Our study corroborates and extends further the observations by Naeye [9] that smooth muscle in the arterioles is markedly increased. The increase in muscularity is due to both muscularization of the small peripheral arteries and an increase in percent wall thickness of individual vessels.

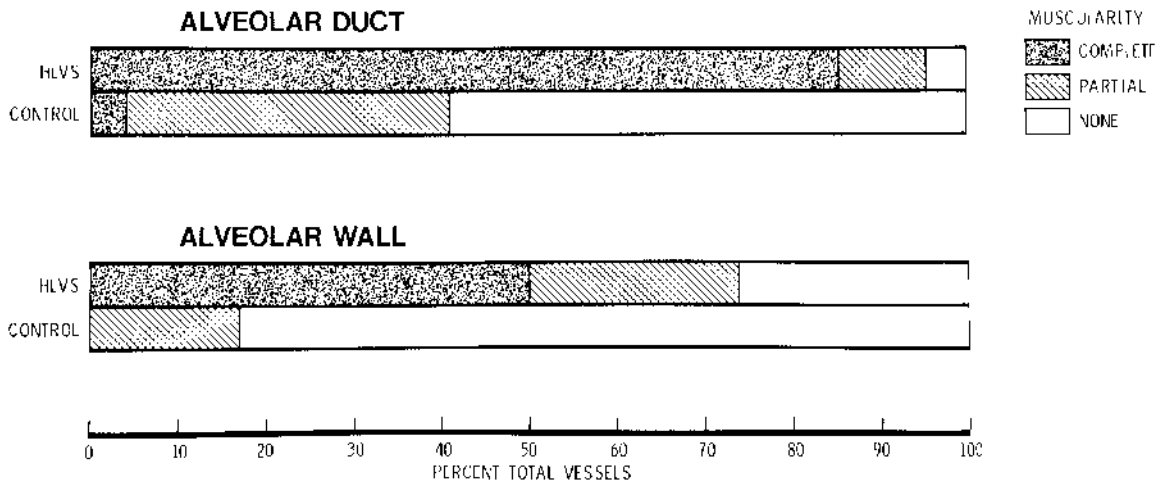

Fig. 2. Percent of total vessels that are nonmuscular, partially muscular, or completely muscular at the alveolar duct and alveolar wall levels. *HLVS* indicates hypoplastic left ventricle syndrome.

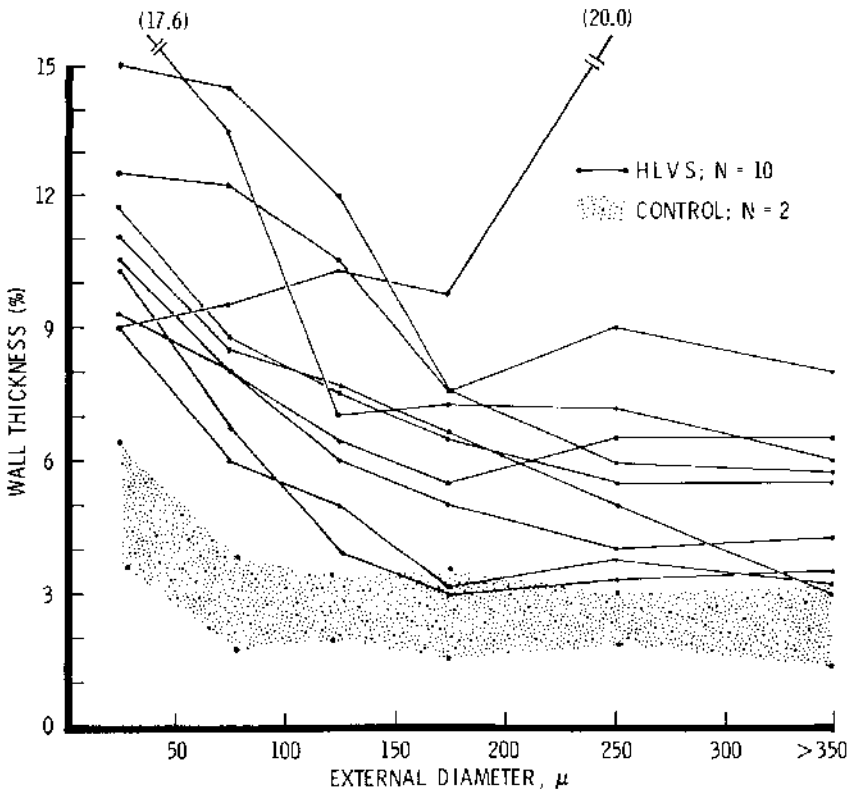

Fig. 3. Mean percent wall thickness of arteries in neonates with hypoplastic left ventricle syndrome *(HLVS)* compared with controls. Percent wall thickness is plotted against external diameter of vessels. Each size category of vessels is thicker than controls, except in two patients, where there is minor overlap at 151 to 200 μ size.

The morphometric changes observed in newborns with hypoplastic left ventricle syndrome are similar to those described in infants and young children with large intracardiac left-to-right shunts [12], aortic stenosis, or coarctation [5] with pulmonary artery hypertension [12]. Progressive extension of smooth muscle and increased percent wall thickness have been described in patients with ventricular septal defect, transposition of the great arteries, and atrioventricular canal [12]. With advancing age, these changes become more severe and may be associated with progressive increase in alveolar to artery ratio. Newborns dying of persistent fetal circulation syndrome have also been shown to have simi-

lar morphometric changes of the pulmonary arteries [10].

The cardiovascular hemodynamic abnormalities in neonates with hypoplastic left ventricle syndrome include pulmonary artery hypertension and, when the foramen ovale is patent, a large left-to-right shunt at the atrial level. However, the pathological changes observed in the first week of life are likely to be the result of the intrauterine fetal circulation pattern. An explanation for findings observed in the neonate with hypoplastic left ventricle syndrome must be related to the circulatory pattern expected in the fetus. Experimental evidence and theoretical consideration suggest that the fetal circulation pattern in hypoplastic left ventricle syndrome is associated with an obligatory increase in P_{O_2} of blood perfusing the lung, pulmonary artery hypertension, and left atrial hypertension [13]. Severe hypoplasia of the left heart structures results in complete mixing of the venous blood in the right ventricle and increased oxygenation of the blood directed to the pulmonary artery circulation. The increased P_{O_2} in blood perfusing the pulmonary arteries may thus act in the same way as it does in patients with large left-to-right shunts to produce extension to and increased muscularization of the peripheral pulmonary arteries. This, however, seems an unlikely explanation, since a similar increase in P_{O_2} of pulmonary arterial blood occurs in the fetus with pulmonary atresia, yet examination of the pulmonary arteries indicates that they are smaller in caliber and less muscularized [6]. The increased flow through the main pulmonary artery and ductus arteriosus in the fetus with hypoplastic left ventricle syndrome may also result in an increase of pulmonary artery pressure. The ductus may not be able to accommodate the increase in flow through the main pulmonary artery.

The presence of prenatal pulmonary artery hypertension is supported by the observation that such infants have right ventricular hypertrophy at birth [11]. The pulmonary artery hypertension may be further augmented by the increased resistance to pulmonary venous flow through the smaller left atrium [9] or an obstructed foramen ovale. Endocardial thickening of the left atrium [9, 14] suggests that these infants have high left atrial pressure in fetal life. Microangiographic studies on lungs of infants with hypoplastic left ventricle syndrome show prominent tortuosity of the intralobular arteries in those with an obstructive foramen ovale, suggesting, again, congenital pulmonary hypertension [4]. The combination of these factors leading to pulmonary hypertension in utero may then lead to pulmonary vascular changes not unlike the corresponding response observed in the lung vessels in the postnatal state. Infants with hypoplastic left ventricle syndrome surviving beyond the first week of life show persistence or increase in arteriolar muscle [9, 14]. Another possible explanation for the vascular changes is that they, as well as the cardiac malformation, are the direct or indirect result of intrauterine hypoxemia. Chronic fetal hypoxemia has been shown to produce an increased muscularization of small arteries and is known to cause cardiac malformations [8]. However, infants with complete endocardial cushion defect (unpublished data), truncus arteriosus, or single ventricle have normal pulmonary arterial muscularization in the immediate neonatal period [9].

Hypoplastic left ventricle syndrome represents, perhaps, the last major frontier for the thoracic surgeon dealing with congenital heart disease. There are few reports of successful surgical therapy for infants with hypoplastic left ventricle syndrome [16, 17]. The observed vascular changes in the neonate with hypoplastic left ventricle syndrome reported here may have implications in planning future surgical intervention for these infants. Attempts at pulmonary perfusion via any direct atrial to pulmonary artery anastomosis (if the right ventricle is to be the systemic ventricle) are unlikely to succeed because the low pressure generated will not be sufficient to overcome increased pulmonary vascular resistance associated with the increased muscularization of the pulmonary vessels. Palliative surgical procedures that will not protect the lung from excessive flow or pressure will also be more likely to result in acceleration of the vascular disease. Hopefully, a combination of medical therapy, with alprostadil (prostaglandin E_1) used to keep the ductus arteriosus open, and palliative surgery will permit involution of the pulmonary vascular changes to allow more definitive operation at a later age.

References

1. Damman JF Jr, Ferencz C: The significance of the pulmonary vascular bed in congenital heart disease: III. Defects between the ventricles of great vessels in which both increased pressure and blood flow may act upon the lungs and in which there is a common ejectile force. *Am Heart J* 52:210-231, 1956
2. Davies G, Reid L: Growth of the alveoli and pulmonary arteries in childhood. *Thorax* 25:669-681, 1970
3. Dunnill MS: Quantitative methods in the study of pulmonary pathology. *Thorax* 17:320-328, 1962
4. Grant CA, Robertson B: Microangiography of the pulmonary arterial system in 'hypoplastic left heart syndrome.' *Circulation* 45:382-388, 1972
5. Haworth SG, Reid L: Quantitative structural study of pulmonary circulation in the newborn with aortic atresia, stenosis or coarctation. *Thorax* 32:121-128, 1977
6. Haworth SG, Reid L: Quantitative structural study of pulmo-

nary circulation in the newborn with pulmonary atresia. *Thorax 32*:129-133, 1977
7. Hislop A, Reid L: Intrapulmonary arterial development during fetal life-branching pattern and structure. *Circulation 113*:35-47, 1972
8. Levin DL, Hyman AI, Heymann MA, Rudolph AM: Fetal hypertension and the development of increased pulmonary vascular smooth muscle: A possible mechanism for persistent pulmonary hypertension of the newborn infant. *J Pediatr 92*:265-269, 1978
9. Naeye RL: Perinatal vascular changes associated with underdevelopment of the left heart. *Am J Pathol 41*:287-295, 1962
10. Needleman H, Dick M, Crowley D, Heidelberger KP: D-transposition of the great arteries associated with syndrome of persistence of fetal circulation. *Pediatr Res 13*:345, 1979
11. Noonan JA, Nadas AS: The hypoplastic left heart syndrome: An analysis of 101 cases. *Pediatr Clin North Am*, November 1958, pp 1029-1056
12. Rabinovitch M, Haworth SG, Castaneda AR, Nadas AS, Reid LM: Lung biopsy in congenital heart disease: A morphometric approach to pulmonary vascular disease. *Circulation 58*:1107-1122, 1978
13. Rudolph AM: *Congenital Disease of the Heart*. Chicago, Year Book Medical Publishers, 1974, p 552
14. Wagenvoort CA, Edwards JE: The pulmonary aterial tree in aortic atresia with intact ventricular septum. *Lab Invest 10*:924-933, 1961
15. Solinger R, Elbl F, Minhas K: Echocardiography in the normal neonate. *Circulation 47*:108-117, 1973
16. Norwood WI, Kirklin JK, Sanders SP: Hypoplastic left heart syndrome: Experience with palliative surgery. *Am J Cardiol 45*:87-91, 1980
17. Doty DB, Knotts HW: Hypoplastic left heart syndrome: Experience with and operation to establish functionally normal circulation. *J Thorac Cardiovasc Surg 74*:624-30, 1977