Double inlet ventricle

Lung biopsy findings and implications for management

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SUMMARY The lung was biopsied in 20 children with double inlet ventricle and pulmonary hypertension aged 2 months to 14 years. Eleven patients had two patent atrioventricular valves, three atresia of the right valve, and six hypoplasia of the left valve. Severe pulmonary arterial medial hypertrophy occurred in the nine children <1 year of age. The findings did not suggest a period of normality after birth when the pulmonary artery might have been banded most effectively. Of the 11 older patients, eight had medial hypertrophy and three intimal proliferation with medial atrophy. Six patients with medial hypertrophy had some reduction in pulmonary arterial pressure after banding.

It is recommended that the pulmonary artery be banded as early as possible, and rebanded early if a satisfactory result is not obtained, particularly in patients destined for a Fontan-Kreutzer procedure. Early atrial septectomy should reduce the arterial and venous abnormalities seen in left atrioventricular valve hypoplasia.

The development of pulmonary vascular disease in patients with double inlet ventricle and an excessive pulmonary blood flow is thought to be similar to that seen in patients with a large isolated ventricular septal defect. Pulmonary vascular resistance is high after birth, reaches a nadir at six months, and is high in older children.¹ Banding of the pulmonary artery is recommended to prevent the development of pulmonary vascular obstructive disease and to allow regression of any arterial medial hypertrophy that is already present. Recent advances in surgical technique, however, demand a more precise understanding of the development of pulmonary vascular disease in this condition. A double inlet ventricle may be repaired by septation of the main chamber or by connecting the right atrium to the pulmonary artery with, if necessary, closure of the right atrioventricular valve, the Fontan-Kreutzer procedure.^{2,3} The risk of septation is increased when pulmonary vascular resistance is raised, although the severity of pulmonary vascular disease that characterises the increase in mortality is not known.⁴ There are two reports of mortality being significantly higher after a Fontan-Kreutzer procedure

in patients with a "single ventricle" than in those with classical tricuspid atresia, without there being an obvious explanation.^{4,5}

A recent small study suggested that the risk of a Fontan procedure is higher in patients with a double inlet ventricle and an increase in pulmonary blood flow than in those with classical tricuspid atresia and hypoperfusion because pulmonary vascular smooth muscle can be increased in such patients even when the pulmonary artery has been banded and the criteria for a Fontan operation have been largely fulfilled.⁶ These observations suggest that it is crucial to band the pulmonary artery at an age when there is the greatest likelihood of achieving a normal pulmonary vascular bed subsequently. We have therefore studied the pulmonary vascular changes in lung biopsy specimens from 20 patients with a double inlet ventricle, usually before the pulmonary artery was banded. Eleven patients had two patent atrioventricular valves, three atresia of the right valve, and six hypoplasia of the left atrioventricular valve.

Patients and methods

The 20 patients were aged between 2 months and 14.5 years. Nine were boys and 11 girls. Table 1 shows the clinical and haemodynamic data. Eighty per cent of

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Table 1 Double inlet ventricle in patients with two patent atrioventricular valves and in those with atresia of the right or left atrioventricular valve

Case No	Additional diagnosis	Age at biopsy	Cardiac catheterisation results at lung biopsy						Outcome
			PAP (mm Hg)	SAP (mm Hg)	Qp:Qs	Rp:Rs	Rpa (units m ²)	% Oxygen saturation	
Patent atrioventricular valves									
1	TGA	3 mnth	75/30	75/40	2.8	0.36	5.4	88	PAB (twice), alive
2	Dextrocardia	5 mnth	66/10	70/40	—	—	1.8	—	Died during PAB
3	TGA, PDA	5.5 mnth	80/40	80/50	1	0.90	10.4	75	Alive*
4	PDA	7 mnth	60/25	70/35	8.2	0.10	2.1	—	Alive*
5	TGA	8 mnth	80/30	80/50	—	—	—	67	Alive*
6	PS	8 mnth	45/?	80/?	—	—	—	—	Died during Fontan procedure, aged 7.5 yr
7	—	1.5 yr	90/45	90/45	2.4	0.35	3.4	87	PAB (twice), alive
8	—	1.9 yr	70/35	70/40	0.9	1.00	13.3	69	Blalock-Hanlon septectomy performed at time of lung biopsy, alive*
9	TGA, PS	3.5 yr	46/28	88/?	2.5	—	—	—	Alive*
10	—	5 yr	90/50	90/50	—	—	—	—	Alive*
11	—	7.5 yr	68/42	75/54	4.5	0.15	2.7	89	Died during Fontan procedure, aged 8 yr
Atresia of right atrioventricular valve									
12	TGA	6 mnth	85/40	100/70	2.1	0.32	11.0	77	Alive*
13	—	1.9 yr	100/40	100/60	1.8	1.00	13.0	68	Died during PAB
14	—	5.3 yr	80/40	85/40	4.3	—	3.0	95	Alive*
Hypoplasia of left atrioventricular valve									
15	—	2 mnth	70/?	75/45	—	—	—	—	Blalock-Hanlon septectomy performed at time of lung biopsy. Died during Fontan procedure, aged 5 yr
16	Coarctation†	2.5 mnth	70/35	70/35	3.4	0.2	5.2	91	Died during Blalock-Hanlon septectomy
17	—	3.7 yr	28/15	86/52	—	—	—	72	PAB at 9 mnth, alive
18	—	4.9 yr	85/65	85/50	0.7	1.8	20.5	77	Alive*
19	—	8.8 yr	75/40	88/58	0.8	0.9	16.0	75	Blalock-Hanlon septectomy performed at time of lung biopsy, alive*
20	CHB	14.5 yr	103/39	98/67	0.9	—	9.0	88	Blalock-Hanlon septectomy performed at time of lung biopsy, alive*

*Having had banding of the pulmonary artery.

†Mean pressure gradient 10 mm Hg.

CHB, complete heart block; PAB, pulmonary artery band; PAP, pulmonary arterial pressure; PDA, persistent ductus arteriosus; PS, pulmonary stenosis; Qp:Qs, pulmonary to systemic blood flow ratio; Rpa, pulmonary arteriolar resistance; Rp:Rs, pulmonary to systemic resistance ratio; SAP, systemic artery pressure; TGA, transposition of great arteries.

patients were on or below the twenty fifth centile for weight, 45% being below the third centile. All the patients were or had been in cardiac failure. The chest radiograph showed cardiac enlargement and an increase in pulmonary vascular markings in all patients except one (case 6), who had mild pulmonary stenosis. Nineteen patients had pulmonary hypertension (Table 1). The pulmonary arteriolar resistance was 1.8–5.4 units m² in seven patients and at least 9 units m² in seven, three with and four without left atrioventricular valve hypoplasia. In 18 patients the lung was biopsied at thoracotomy for banding the pulmonary artery or electively in unbanded patients to help decide the management of the case, or in one

patient (case 20) at the time of insertion of a pacemaker and a Blalock-Hanlon operation. In one other patient (case 16) lung tissue was obtained when the patient died immediately after atrial septectomy. Only in one patient (case 17) had the pulmonary artery been banded before the lung was biopsied. The time interval between cardiac catheterisation and biopsy was short, less than one month in 17 cases and four months in two cases. To date 14 patients are alive and well without corrective surgery, the pulmonary artery having been banded in all except one (case 20). Two children died immediately after the pulmonary artery was banded, one (case 16) after atrial septectomy and three immediately after a Fontan proce-

Table 2 Haemodynamic effect of banding the pulmonary artery

Case No	Age at biopsy and banding	Pre-banding mean PAP:SAP ratio	Time interval	Post-banding mean PAP:SAP ratio	Rpa
1	3 mnth	0.9	2 mnth	0.5	3.1
6	7 mnth	0.8	3 yr	0.2	—
7	1.5 yr	1.0	2 yr	0.6†	—
12	7 mnth	0.7	6 mnth	0.5	3.6
15	2 mnth*	—	9 mnth	0.4	4.7
17	9 mnth†	—	2.8 yr	0.3	—
19	8.8 yr*	0.7	6 mnth	0.4	3.1

*Blalock-Hanlon operation.

†Banded before biopsy performed.

‡One year after a second banding operation the mean pressure ratio was 0.2.

PAP, pulmonary artery pressure; SAP, systemic artery pressure; Rpa, pulmonary arteriolar resistance.

ture. The time interval between the pulmonary artery banding and the Fontan operation was six years in case 6, six months in case 11, and four years in case 15.

Six patients in whom the lung was biopsied and the pulmonary artery banded underwent cardiac catheterisation two months to three years later, and all showed a reduction in pulmonary arterial pressure (Table 2).

PATHOLOGICAL STUDIES

The lung biopsy specimens were taken when the lung was at least partially inflated and were fixed with the small airways and alveoli inflated. Paraffin embedded sections, 4 μ m thick, were stained with haematoxylin and eosin, with Miller's elastic stain counter stained with Van Gieson's stain, and with Perl's stain for iron. In each biopsy specimen pulmonary vascular structure was analysed using quantitative morphometric techniques and the findings compared with the normal for age.^{7,8} Pulmonary arterial muscularity was assessed by determining the mean percentage arterial medial thickness of arteries in different size ranges. The proportion of muscular, partially muscular, and non-muscular arteries accompanying terminal and respiratory bronchioli and alveolar ducts was also assessed in order to discover if muscle had differentiated in more peripheral arteries than is normal for age. In each biopsy specimen the size of the intracinar (respiratory unit) arteries was determined by measuring the external diameter of all arteries seen accompanying terminal and respiratory bronchioli and alveolar ducts and estimating the mean external diameter at each airway level. The number of arteries was estimated by counting the number of alveoli and arteries within as many different microscopic fields as possible and calculating the mean ratio of alveoli to arteries.

In each case the percentage arterial medial thickness in arteries of different size ranges was compared with the normal for age using two way non-orthogonal analysis of variance. Student's unpaired *t* test was used when comparing arterial size.

Results

All 20 patients showed a significant increase in mean percentage arterial medial thickness (Figure) ($p < 0.0001$). In the 11 patients (cases 1–11) with two atrioventricular valves mean percentage arterial medial thickness was greatest in the seven without either pulmonary stenosis or atrophy of the pulmonary arterial walls. The three patients (cases 12–14)

Figure Mean percentage pulmonary arterial medial thickness related to external diameter (μ m) in lung biopsy specimens taken from 20 patients with double inlet ventricle compared with normal. Numbers indicate case numbers. Arrows indicate those patients who subsequently had a reduction in pulmonary arterial pressure after banding. *The only patient to have undergone banding before the lung was biopsied.

with atresia of the right atrioventricular valve tended to show a less pronounced increase in muscularity than the 11 patients without. In the six patients (cases 15–20) with left atrioventricular valve hypoplasia muscularity was similar to that seen in cases 1–11 except for the banded case (case 17) in which muscularity was relatively low. In each of the 20 patients the proportion of entirely muscularised arteries at each level was greater than expected for the age of the child, indicating that muscle had differentiated in more peripheral arteries than normal.

Circumferential intimal proliferation tended to occur in the older patients aged ≥ 1.9 years and was found in the preacinar or the intra-acinar arteries or both of cases 8–11, 14, 18, and 20. The most severe intimal changes were present in case 8, and in this case and in cases 11 and 18 the media of alveolar duct and alveolar wall arteries was atrophied distal to thick walled arterial segments containing intimal proliferation. Mild intimal proliferation was also present in the alveolar duct arteries of three younger patients (cases 3, 4, and 6).

In 14 of the 20 cases the preacinar veins were abnormally thick walled, and the small veins had developed an external elastic lamina and were "arterialised." The veins in five patients (cases 9, 10, and 18–20) showed intimal fibrosis. The lungs of the three oldest patients with left atrioventricular valve hypoplasia (cases 18–20) had the greatest increase in vein wall thickness and intimal fibrosis.

The mean external diameter of arteries accompanying respiratory bronchiolar and alveolar duct arteries was normal in five cases, significantly increased at one or both of those positions in 12 ($p < 0.01$), and reduced in three (cases 18–20), the reduction being statistically significant in alveolar duct arteries ($p < 0.001$). The mean alveolar to arterial ratio was normal for age in 14 of the 18 patients in whom it could be determined accurately. In the four abnormal cases (cases 8, 10, 17, and 18) the mean ratio was 12.4–13.8 above the normal mean level for age (8.4–10.9) but within 1 standard deviation of the normal mean value, suggesting that in no case was there a significant reduction in the number of arteries per unit area of lung tissue.

Discussion

In these 20 patients with double inlet ventricle there was a striking increase in pulmonary vascular smooth muscle that was rather less in those with atresia of the right atrioventricular valve than in those with two patent valves or left atrioventricular valve hypoplasia. The intra-acinar arteries were normal or even increased in size for age, and the number of intra-acinar arteries per unit area of lung was within normal limits. Only three of the 20 patients showed

significant obstructive pulmonary vascular disease, all were at least 1.9 years old and one had an obstructed left atrioventricular valve. Severe medial hypertrophy with little if any intimal proliferation was seen in patients < 1 year of age. Excluding cases with right atrioventricular valve atresia, the increase in muscularity in patients with double inlet ventricle and an increased pulmonary blood flow was greater than is usually seen in ventricular septal defect during the first year of life, although like patients with a ventricular septal defect intimal proliferation was uncommon at this age.

Six patients whose lung biopsy specimens showed severe pulmonary arterial medial hypertrophy were recatheterised after banding the pulmonary artery, and it was reassuring to find that all had a reduction in pulmonary arterial pressure. Two of these six cases, however, had had to be rebanded in order to obtain a mean pulmonary to systemic arterial pressure ratio of ≤ 0.5 . In addition, at recatheterisation at least four cases had a mean pulmonary arterial pressure and arteriolar resistance that exceeded or barely fulfilled the Fontan criteria. Given the pronounced increase in pulmonary vascular smooth muscle seen in the infant cases it is perhaps surprising that it may be difficult to band the pulmonary artery satisfactorily on the first occasion. The age at which the pulmonary artery is first banded might be important in this respect. If pulmonary vascular smooth muscle could be shown to regress significantly after birth before showing a secondary increase in response to the high arterial pressure and flow then there might be an optimal age at which the pulmonary artery should be banded. In this series, however, the muscularity was high in four patients with double inlet ventricle without atresia or hypoplasia of either atrioventricular valve (aged 5–8 months) and was similar to that seen in the older patients. This suggests that there is no ideal age at which to band the pulmonary artery, rather it should be banded as soon as possible. The risk of pulmonary artery banding is now low.^{4,9} Stefanelli *et al* banded 11 patients with no hospital deaths and a 10 year actuarial survival of 74%.⁴ Banded patients with ventriculo-arterial discordance can develop subaortic obstruction,¹⁰ but the only alternative to banding the pulmonary artery appears to be an intracardiac repair in infancy.

The present study demonstrates the difficulty of predicting pulmonary vascular structure and "operability" from the haemodynamic data. Two patients in the present study who had been banded died after a Fontan procedure with a mean pulmonary arterial pressure immediately before operation ≤ 20 mm Hg. Three patients previously reported died with a preoperative mean pulmonary arterial pressure of 14–25 mm Hg, and at necropsy all three cases showed

a significant increase in muscularity.⁶ It seems probable that a low pulmonary arterial pressure in these banded patients does not necessarily imply a structurally normal pulmonary vascular bed, and if this is so and muscularity is increased then an intracardiac repair giving a ventricular rather than a atrial dependent pulmonary circulation might be associated with a lower operative morbidity and mortality. When the main chamber is septated, however, the outcome is less satisfactory in patients who do not have pulmonary stenosis.^{4,5} It appears that whatever type of intracardiac repair is expected every effort should be made to achieve a structurally normal pulmonary vascular bed beforehand. This may necessitate banding the pulmonary artery on two separate occasions or even ligating the pulmonary artery and performing an aortopulmonary anastomosis.

In patients with double inlet ventricle and left atrioventricular valve hypoplasia pulmonary venous obstruction exacerbates the pulmonary arterial hypertension. In the present series the three oldest patients with left atrioventricular valve hypoplasia showed a pronounced increase in vein wall as well as in arterial wall thickness and venous intimal fibrosis. Early atrial septectomy should help reduce such damage. In a recently published series there were no deaths in the 14 patients undergoing atrial septectomy, and the 10 year actuarial survival was 76%.⁴

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