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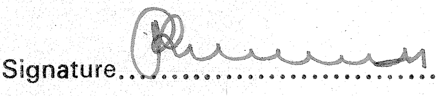
CERTIFICATE

I, Dr. M. SRINIVASAN hereby declare that I have actually performed all the procedures listed/carried out the project under report.

Signature 

Place: TRIVANDRUM

Name in capital letters M. SRINIVASAN

Date: 7.11.87

LIST OF ~~PROCEDURES~~ DONE

PROJECT REPORT

TITLE OF THE PROJECT: PULMONARY VASCULAR DISEASE IN CONGENITAL HEART DISEASE [SHUNT LEISONS] - HAEMODYNAMIC - PATHOLOGIC CORRELATIONS.

NAME: M. SRINIVASAN

PROGRAMME: D.M. CARDIOLOGY

MONTH & YEAR OF SUBMISSION: NOVEMBER 1987

Note:— (i) In the case compilation of procedures done, the contents and the subsequent pages should be made into different sections (a) Procedures done (b) Procedures assisted (c) Procedures participated (d) Procedures attended/participated etc in Other Centres. Each section should be preceded by a leaf carrying the name of the section that is succeeding.

(ii) The Contents page will carry into. as per model given under

PROCEDURES DONE

Closed Mitral valvotomy.................................124 (say)
Patent ductus arteriosus-ligation...............................10
Atrial septal defects...................................20
....
....

PROCEDURES ASSISTED

Closed Mitral valvotomy...............................100 (say)
....

(iii) In the subsequent pages details of each procedure done/assisted should be given in the format given below:—
Heading: **Closed mitral valvotomy**

Date	Name of the patient	Age	Sex	Patient No.

(iv) In the case of Project Report in the page immediately following the Certificate page the under-mentioned details should be given:—

(a) Title
(b) Duration
(c) Aim and scope
(d) 50 word summary of work done

CONTENTS

S U M M A R Y

In 46 patients aged 18 months to 29 years (25 cases of VSD, 11 cases of PDA 6 cases of ASD, 4 others) each with severe pulmonary artery hypertension (Pulmonary arterial pressure at least 75% of systemic pressure in most cases) and elevated pulmonary vascular resistance, haemodynamic meassurements and morphometric data obtained from open lung biopsy were correlated. Of the haemodynamic data PVR and left to right shunt correlated with Heath Edward grading. There was no correlation between PA pressure and arterial wall thickness. Decreased arterial density correlated with increasing Health Edward grade. All case less than Grade II had regression of PVR following surgery.

PULMONARY VASCULAR DISEASE IN CONGENITAL HEART DISEASE (SHUNT LEISONS) HAEMODYNAMIC - PATHOLOGICAL CORRELATIONS

AIM : To correlate Haemodynamic and Quantitative and qualifative pathological finding in lung biopsy - to derive prognostic indicators.

INTRODUCTION:

Pulmonary vascular disease is one of the most serious complications of many forms of congenital heart disease, particularly cyanotic or acyanotic lesions in which pulmonary blood flow is increased. The cause of pulmonary vascular obstructive disease (PVOD) in association with congenital heart disease (CHD) remains unknown. Certain factors known to be associated with PVOD include apart from increased pulmonary blood flow; increased pulmonary venous pressure, under - development of pulmonary microvasculature, chronic alveolar hypoxia and polycythaemia.

If the vascular disease is allowed to progress there will be increase in pulmonary vascular resistance that may interdict satisfactory surgical correction of cardiac defect. Natural history studies reveal that there are certain cardiac anamolies which place the patient at risk for developing PVOD quite early in life. Fifteen percent of large unresticted venticular septal defect (VSD) will experience an elevation of

pulmonary vascular resistance (PVR) occuring either late in infancy or early in child hood. However when surgical repair is carried out in the first two years of life this increase in PVR rarely persists. If correction is delayed longer the PVR does not return to normal following surgery and may even increase progressively. These patients may also exhibit an abnormal increase in PVR in response to exercise or stress. A similar incidence and course of development of increased PVR is seen in children with large patent ductus artereosus (PDA). Children with common artioventricular canal or truncus artereosus are at purticularly high risk for development of PVOD. Patients with atrial septal defects (ASD) are usually found to have a normal pulmonary artery pressure in childhood. If unrepaired approximately 20-30 percent will develop PVOD but this occurs late usually not until the third decade of life.

Morphological and developmental aspects of pulmonary Vascular disease

Pulmonary vascular occlusive disease may result from anatomical changes in the pulmonary vascular bed secondary to increased pulmonary blood flow at high pressure for few years (e.g. large unrestricted

ventricular septal defect) or at low pressure for many years (e.g. secondum atrial septal defect). The vascular disease as classified by Heath and Edwards in 1958 consists of six grades of increasing severity.

Heath - Edwards classification

GRADES	Morphologic Features
REVESIBLE	
I	Medial Hypertrophy. The defenitive histological features lie in pulmonary artereoles and the muscular pulmonary arteries. The pulmonary artereoles less than 100 micron in diameter does not normally have muscular media. In grade I changes they have thick muscular media. The media of muscular arteries (100-1000 μ) is also thick.
II	Medial Hypertrophy plus cellular intimal proliferation. It is usually seen in smaller muscular arteries less than 300 micron.
Variably Reversible	
III	I and II plus intimal occlussion by fibroelastic tissue. Starts in smaller muscular pulmonary arteries and extends into medium sized arteries.
IRREVERSIBLE	
IV	I, II, III plus luminal occlussion by fibrous tissue with arterial dilatation.

V Angiomatoid formation and pulmonary haemosiderosis.

VI Fibrinoid necrosis

It is now apparent that pulmonary vascular disease producing pulmonary hypertension in children with congenital heart disease is a combination not only of the above described features but includes underlying developmental structural anomalies. The developmental anomalies include failure of the normal regression of perinatal musculature, extension of muscle peripherally into normally non muscular alveolar ductal wall arteries.

The relationship of these structural changes of the pulmonary vascular bed to the haemodynamic data for pulmonary blood flow, pulmonary artery pressure and pulmonary vascular resistance has enabled classification into three new grades of severity as given below. This new classification put forth by Sheila Howorth, Marlene Rabinovitch and Lynne Reid became essential because it was found that Heath and Edward analysis has certain draw backs.

(a) Grade IV and higher changes are unusual in first two years of life even in presence of severely elevated PVR.

(b) Advance grades are often spotty.

(c) There is no grading for very early changes.

RABINOVITCH CLASSIFICATION

Classification	Structure	Haemodynamics
A	Abnormal extension of muscle into peripheral arteries.	Increased Pulmonary blood flow.
B early	Abnormal extension & mild medial hypertrophy	Increased pulmonary blood flow, mild increase in pulmonary artery pressure.
B Late	Abnormal extension, severe medial hypertrophy and decrease artery size.	Moderate to severe increase in pulmonary artery pressure + mild increase in pulmonary vascular resistance.
C	All findings of late B and reduced artery number.	Moderate to severe increase in pulmonary vascular resistance.

MATERIALS AND METHODS

This is a retrospective analysis of the lung biopsis done between 1980 - 1986. The total number of cases were forty six. The biopsy specimen was obtained prior to corrective surgery in all cases of VSD and ASD and at the

time of ductal ligation for cases of PDA. The average interval between cardiac catheterisation and biopsy was six months (range three months to one year).

Biopsy Technique

The tissue was obtained from right upper lobe in 16 cases and from lingular segment of left lung in 30 cases. The lungs were inflated and two clamps were placed in the upper medial aspect of right lung. The tissue between the two clamps were incised and the distal clamp containing the inflated tissue was submerged for ten minutes in formalin or gluteraldehyde.

Patient Population

Total No. of cases	:	46
VSD	:	25
PDA	:	11
ASD	:	6
Trumcus Artereosus	:	1
Aorto-Pulmonary Window	:	1
Total Anomalous Pulmonary Venious drainage	:	1
Trans position with VSD	:	1

Age ranged from 18 months to 29 years.

Haemodynamic features (Table Ia, Ib, Ic)

Ventricular Septal defect: All Patients had unrestrictive single VSD. Mean age is 8.5 ± 7

Patient Ductus artereosus: Mean age is higher (14 ± 10). All had severe elevation of pulmonary vascular resistance.

Atrial Septal Defect: All cases had only secondum atrial septal defect with normal mitral valve. The mean age was still higher (25 ± 10).

Morphometric measurements:

The total number of arteries in each field was counted. The arteries were grouped according to the size measured. All the measurements were made with caliberated eye piece micrometer. The diameter of the artery was measured from external elastic lamina across the short axis of the vessel. The arteries were grouped into two categories. Those with the diameter above 100 microns and those with diameter below 100 microns.

Wall thickness was measured between external and internal elastic lamina seperately for vessels above 100 micron and below 100 micron. The mean thickness in each group was taken for analysis. Percentage of wall thickness was calculated as

$$\frac{2x \text{ wall thickness} \times 100}{\text{External diameter}} = \text{Percentage of wall thickness.}$$

Mean percentage of wall thickness for each group (for vessels above 100 micron and below 100 micron) was used for analysis.

Previous workers (Reid, Sheila Howarth) have established he following normal values.

In the distented vessels of 50-100 micron diameter the ercentage of wall thickness of eight percent is considered ormal in children younger than four months of age and four ercent is considered normal in older children.

Because specimen were injected a correction factor of .5 is applied, and increased muscularity is considered to e present if the percentage of wall thickness was greater han 20 percent before first four months and greater than 10 ercent there after.

The arterial density was expressed as alveolar arterial atio. Alveoli were counted radially from the centre of each ield. Alveolar arterial ratio varies with age; In the neonate t is 20:1, at the age of two years 12:1, and 6:1 by age of 10.

Based on the morphometric criteria, the biopsy was ategorised into grade A, B or C (of Rabinovitch).

Each biopsy was also graded according to Heath and Edward ystem. The biopsy data of each group is given in table II , b and c.

esults

aemodynamic Data Obtained at Cardiac Catheterisation

(Table I a, b, c)

entricular Septal Defect: Pulmonary arterial systolic ressure was greater than 90 percent of systemic pressure in

Table I A VSD

&	PAS	PA (M)	PAS / AOS %	QP / QS	PVR	PVR / SVR
2	75	50	94	2.8:1	4.46	0.28
4	65	40	72	4.5:1	0.98	0.1
5	82	50	100	1.9:1	4.4	0.37
2	80	43	80	4.7:1	0.73	0.03
18	105	58	95	2:1	6.2	0.5
14	100	70	90	1.8:1	5.3	0.37
4	72	55	92	4.6:1	1.4	0.16
4	110	69	96	1.4:1	7.7	0.35
5	85	55	100	1.5:1	4.46	0.56
2½	97	65	100	1.3:1	4.5	-
14	98	70	85	1.7:1	10.1	0.47
20	105	70	95	2.4:1	6.2	0.25
7	90	60	100	2:1	7.2	0.79
15	109	73	100	1:4	13.7	0.57
16	115	75	100	3.5:1	6.1	0.20
12	100	62	80	2.5:1	4.5	0.24
2	68	50	75	2.4:1	1.9	0.2
19	120	67	100	2.5:1	7.3	0.26
3	90	70	90	1.9:1	6.1	0.4
3	74	48	85	2.7:1	3.2	0.32
7	65	48	60	3.2:1	1.5	0.11
12	68	42	77	2.4:1	2.52	0.14
11	81	67	90	1.75:1	6.9	0.4
15	98	75	100	1.8:1	1.2	0.61
20	65	42	55	1.4:1	7.3	-

PA SYSTOLIC BP,
: PA mean BP
PAS / AOS : PA SYSTOLIC / AO SYSTOLIC
QP / QS : Pulmonary blood flow / Systemic blood flow
PVR : Pulmonary vascular Resistance, SVR. Systemic vascular Resistance

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TABLE I - B - PDA

. & e	PA S	PS (M)	PA/AO S	QP/QS	PVR	PVR/SVR
-13	125	82	100	1.8:1	12	0.38
-20	110	75	75	3.9:1	4.2	0.24
-17	118	90	100	2.8:1	9.1	0.31
-14	95	65	73	2.6:1	4.9	0.31
-19	125	93	100	1.1:1	15.3	0.95
-27	85	57	78	5.2:1	2.5	0.11
-22	110	82	93	1.9:1	11.2	0.9
-5	90	65	100	1.4:1	7.7	0.89
-18	100	70	83	2.1:1	6.5	0.51
-12	85	65	90	3:1	3.8	0.25
-15	145	105	100	3:1	7.05	0.23
-22	130	90	92	1.1:1	30.3	1.0

bbreviation as in Tab I A;

TABLE I - C - ASD

o.& Age	PA S	PS M	PA/AO S	QP/QS	PVR	PVR/SVR
1-29	70	40	-	3.2:1	35	-
2-23	96	54	83	1.1:1	11.9	-
3-14	80	57	72	1.5:1	8.9	0.42
4-39	92	56	65	2.1:1	10.6	-
5-23	80	66	57	1.4:1	12.7	-
5	72	48	65	1.9:1	10.1	-

Abbreviations as in Tab. I A

19 of 25 patients (76% of cases). Mean QP/QS was 2.48 ± 1.4. PVR was elevated in all patients (5.7 ± 3.5) PVR/SVR was 0.31 ± .18.

Patent Ductus artereosus: In 5 cases out of 11 (45%) PA systolic was equal to systemic pressure. In three cases it was above 90%. Mean QP/QS was 2.45 ± 1.26 PVR was elevated in all cases (9.77 ± 7.86) PVR/SVR was 0.46 ± 0.31.

ASD: All cases had secondum ASD only. PA systolic pressure was above 50 percent of systemic messure in all cases. Mean QP/QS was 1.7 ± 0.43. PVR was high in all cases (9.62 ± 3.28).

Structural Data Obtained at biopsy

Ventricular Septal Defect: In six of 25 cases Heath Edward grade was III or greater indicating obstruction of arterial lumen. Seven cases were in Grade C indicating decreased arterial density. The mean percentage of wall thickness of vessels above 100 micron was at least thrice normal mean. (35 ± 14.4). The percentage of wall thickness of vessels below 100 microns was above twice normal mean (26.6 ± 10.5). Mean arterial density was 9.1 ± 4.5, only 4 of the 25 cases were in Group C. This may be due to technical reasons. Biopsies done in early years were not very ideal for studying alveolar arterial ratio.

Patent Ductus Artereosus: In six of the eleven cases (55%) Heath Edward Grade was III or greater (3 cases were Grade IV).

STRUCTURAL FEATURES

Table II A (VSD)

se	Heath Edward Grade	Alveolar arterial ratio	Morpho-metric Grade A, B, C.	% of Medial thickness arteries above 100μ	% of medial thickness arteries Below 100μ
1	II	8:1	B	50	--
2	I	5:1	B	18 ± 3	18 ± 3
3	II	10:1	B	23 ± 9	40
4	II	8:1	B	23 ± 5	17 ± 5
5	I	6:1	B	28 ± 4	18 ± 4
6	I	6:1	B	24 ± 4	18 ± 4
7	III	13:1	C	49 ± 2	24 ± 2
8	III	10:1	C	38 ± 3	22 ± 3
9	III	18:1	C	23 ± 4	25
0	I	8:1	B	28 ± 9	33 ± 8
1	IV	20:1	C	29 ± 4	41 ± 18
2	I	4:1	B	19 ± 6	14 ± 0
3	I	6:1	B	18 ± 5	23 ± 7
4	II	8:1	B	19.5	33
5	I	7:1	B	17 ± 9	25
6	III	20:1	C	28 ± 5	--
7	I	8:1	B	26 ± 5	24 ± 2
8	I	6:1	B	21 ± 3	21 ± 3
9	I	6:1	B	18 ± 6	29 ± 6
0	I	7:1	B	17 ± 8	21
21	I	8:1	B	28 ± 20	50
22	I	6:1	B	17 ± 6	30
3	III	20:1	C	9 ± 6	19
24	I	8:1	B	23 ± 5	17
25	II	6:1	B	31 ± 4	18

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TABLE II B PDA

Heath Edward Grade	Alveolar arterial ratio	Morphometric Grade A, B, C,	% of Medial chickness arteries abobve 100 μ	% of medial thickness arteries Below 100 μ
III	18:1	B	21	25
I	8:1	B	15 ± 4	--
IV	18:1	C	13 ± 3	23 ± 4
I	8:1	B	28	25 ± 10
IV	20:1	C	25 ± 9	40 ± 0
I	10:1	B	38 ± 5	40
II	--	B	21 ± 5	25 ± 0
I	8:1	B	27 ± 3	26 ± 0
I	8:1	B	27 ± 3	26 ± 0
III	17:1	C	28 ± 2	28 ± 7
IV	16:1	C	41 ± 12	40 ± 1

ASD Table II C

Heath Edward Grade	Alveilar arterial ratio	Morphometric Grade A, B, C.	% of Medial thickness arteries above 100 μ	% of medial thickness arteries Below 100 μ
I[I]	7:1	B	26 ± 8	60
III	16:1	C	47 ± 65	45
IV	10:1	C	21 ± 8	42 ± 14
III	10:1	C	25 ± 18	--
II	10:1	B	21 ± 7	19 ± 7
0	6:1	A	14 ± 5	4 ± 1

ll the Grade III cases fall in to group C.

Mean percentage of arterial thickness of arteries above 00 microns and below 100 micron are 24.6 ± 9, and 30 ± 30 espectively. Comparisions of wall thickness ratio of arteries n Grade III and above with lesser grade did not reveal any ignificant difference (P=1.33).

trial Septal Defect: Three of six cases were in Grade III.

orrelation between structural and Functional Parameters:

With increasingly severe Heath Edwards changes pulmonary lood flow was less, the left to right shunt decreasing. r = -.58, P = 001). The resistance ratio increased directly ith Heath Edward grade (r = .72). No significant correlation as found between (1) Mean pulmonary artery pressure and wall hickness (r value .02).

2) Pulmonary vascular resistance and wall thickness (r value .16)

3) Alvelar arterial arterial ratio and pulmonary vascular resistance (r = 0.22)

4) QP/QS and wall thickness ratio did not show linear correlation (r = .19).

lveolar arterial ratio is higher (decrease in arterial density) n severe Heath Edward grades.

14 of 15 cases (93%) with Heath Edward Grade III or more ad alveolar arterial ratio greater than 12:1.

17 of 25 cases with Grade I and II (68%) had alveolar arterial ratio less than 10:1.

Structual changes and vascular reactivity:

In sixteen cases pulmonary vascular reactivity was assessed during haemodynamic study either with oxygen or Tolazoline by standard technique. Six cases showed fall in PA mean pressure and PVR. There was no difference in histological grading between the two groups.

Correlation between post operative Haemodynamics:

Post operative haemodynamic data were available in ten cases. All cases showed fall in pulmonary artery mean pressure. Only in six cases there was significant fall in pulmonary vascular resistance (minimum of 10% and maximum of 60%). All six cases were Grade I or II. In two cases there was more than seventy percent increase in PVR and both cases were in grade III as also two cases which did not show any change in PVR.

Correlation of biopsy with findings at autopsy:

Of the 10 VSD cases which died autopsy data were available in four cases. In three cases autopsy grading and biopsy grading was same. In the fourth case autopsy grading was IV and biopsy showed grade III changes.

...tion between structural and Functional Parameters with Post
...e outcome: of the 25 cases of VSD operated 10 cases
died either -

because of failure to come off by pass or in the immediate post pperative period. Comparision between the groups showed that there was no significant difference between the haemodynamic para meters (PVR, QP/Qs, PVR/SVR). Of the clinical parameters age was the only significant factor. Mean age of patients who succumbed was 5.8± 5.5, where as mean age of alive cases was 12.4±5.3 (p=0.003).

Among the structural criteria absolute wall thickness below 100 microns was higher in cases who died. Wall thickness in expired cases was 31.3±11.1 wall thickness in alive cases 9.3±3.5 (P=0.00001). Other parameters were comparable in both groups.

Discussion:

Arterial changes in the pulmonary vascular bed are less severe in those with only an increase in pulmonary blood flow or small raise in pulmonary artery pressure than in those with higher pressure or higher increase in pulmonary resistance. Pulmonary vascular obstructive disease is indicated by pulmonary artery hypertension in presence of only a small or no increase in pulmonary blood flow. Three common shunt lesions studied here showed pulmonary vascular disease occurs at younger age group in VSD, and at older age in ASD.

In all group of patients irrespective of age there was precocious muscularisation of peripheral pulmonary arterial

bed and increase in wall thickness of muscular arteries (Grade B) were found. Density of arteries were not uniformly decreased as reported in other studies. Recently Howarth et al reported little change in arterial density after six months of age cautioning that density measurements may be affected by the part of the acinus sampled, the plane of sectioning or the number of fields counted. In those with most severe Heath Edward changes pulmonary flow was lower and resistance was higher. There was a significant inverse correlation between severety of Heath Edward changes and arterial density.

With a defect of given size individual predisposition rather than age probably governs the rate of development and severity of structural changes (GROVER).

Medial hypertrophy is an early structural change of pulmonary arteries exposed to increased pulmonary blood flow and pressure has been present in all cases. (Rabinowitch). In our study we could not confirm thinning of media as the Heath Edward grade worsens - possibly due to small number.

Our study has also shown, the Heath Edward grade, III or more, or the alveolar arterial ratio of more than 20:1 are good predictors of non reversibility of pulmonary vascular disease. In fact significant number of them will continue to have progressive pulmonary vascular disease.

This study has also shown that in patients with ventricular septal defect associated with severe pulmonary

hypertension, the haemodynamic data do not predict the out come of surgical closure. Where as structural changes may throw light but this needs further investigation. When pulmonary arterial hypertension is produced in dogs by creating anastamosis between a systemic artery and the pulmonary artery, there is no relation between either the pulmonary blood flow or the pulmonary artery pressure generated and the presence of pulmonary vascular leisons including medial hypertrophy and intimal proliferation (Geer JC). Clinical studies have also shown an inconstant relation between pre operative and post operative pulmonary artery pressure or resistance (Rabino witch).

Even though recent studies have suggested that ventricular septal defects operated by the age of two years, pulmonary artery pressure and pulmonary vascular resistance return to normal, there is higher operative mortality in younger age group in our series. Rabinovitch et al have shown that those operated below nine months of age always have shown complete normalisation of pulmonary haemodynamics the same does not hold good after nine months of age.

Conclusion:

The morbidity of oper lung biopsy is low, lingular segment is fairly reflective of changes in the whole pulmonary

vasculature. and in patients with high pulmonary artery pressure and pulmonary vascular resistance Heath Edward changes of no more than grade II and at least an alveolar arterial ratio of less than 10:1 were predictive of drop in pulmonary artery pressure post operatively. The long term changes in pulmonary artery pressure at rest or with exercise are not known.

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