Review Article

The pulmonary circulation in children with congenital heart disease: morphologic and morphometric considerations

Frederick A. Burrows MD FRCPC
Marlene Rabinovitch MD FRCPC

Pulmonary hypertension in infants, children and adolescents occurs in association with several clinical conditions (Table I). It is a common accompaniment of many congenital cardiac lesions and the status of the pulmonary circulation can be a major determinant in the clinical outcome of these patients.

This review discusses pulmonary hypertension in association with congenital heart disease, how its presence can be diagnosed and its severity assessed. The structural and morphological abnormalities, thinking concerning pathogenesis, the natural history of the disease and treatment modalities are outlined.

Elevated pulmonary artery pressure can result from increased pulmonary blood flow or increased resistance in the pulmonary vasculature or both. Increased resistance can be due to increased vascu-

lar tone and/or obstructive or obliterative changes, with a reduction in the cross-sectional area of the pulmonary vascular bed. The development of pulmonary hypertension in patients with congenital cardiac lesions is a combination of structural developmental abnormalities restricting the size of the pulmonary vascular bed with secondary obstructive or obliterative changes. In recent years there has been marked refinement of the perioperative and surgical management of children with congenital heart defects. This, as well as the enhanced awareness of the need for early operations on children with the potential for the development of pulmonary vascular obstructive disease have resulted in children undergoing corrective surgery in early infancy. The result has been a decreasing number of adolescents and adults with obliterative changes in the pulmonary vascular bed occurring as a consequence of delayed operation. Appreciation of the abnormal structural and morphological changes requires understanding of the normal growth and development of the pulmonary vascular bed.

Key words

HYPERTENSION PULMONARY: aetiology, diagnosis, pathology, complications, prevention and control

Normal growth and development of the pulmonary vascular bed

The main pulmonary artery arises with the partitioning of the truncus arteriosus, after which time the pulmonary arteries arise from the pulmonary trunk. The branch pulmonary arteries develop as derivatives of the sixth branchial arch arteries during the fifth to seventh weeks gestation. The left sixth branchial arch develops with the proximal part

From the Departments of Anaesthesia, Paediatrics and Pathology, The Hospital for Sick Children and University of Toronto, Toronto, Ontario.

Address correspondence to: Dr. F.A. Burrows, Department of Anaesthesia, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8.

TABLE 1 Causes of pulmonary hypertension in infants, children and adolescents

<i>Cause</i>	<i>Examples</i>
Congenital and acquired heart disease	<ul style="list-style-type: none"> – with increased pulmonary blood flow – with increased pulmonary venous pressure – with decreased pulmonary blood flow
Hypoxia	<ul style="list-style-type: none"> – acute hypoxia – chronic (high altitude) hypoxia – lung disease – obstructive <ul style="list-style-type: none"> – restrictive – upper airway obstruction – diminished ventilatory drive – disorders of the chest wall
Persistent pulmonary hypertension of the newborn	<ul style="list-style-type: none"> – underdevelopment of the lungs – maladaptation of the pulmonary vascular bed – maldevelopment of the pulmonary vascular bed
Thromboembolic disease	<ul style="list-style-type: none"> – sickle cell states – ventriculovenous shunts for hydrocephalus
Portal hypertension	<ul style="list-style-type: none"> – portal vein thrombosis – liver disease
Granulomatous disease	<ul style="list-style-type: none"> – Sarcoid
Collagen vascular disease	<ul style="list-style-type: none"> – rheumatoid arthritis – lupus erythematosus
Diet and drugs	<ul style="list-style-type: none"> – aminorex
Idiopathic pulmonary hypertension	<ul style="list-style-type: none"> – arterial abnormality – venous abnormality

From: *Rabinovitch M. Pulmonary hypertension in Moss' heart disease in infants, children and adolescents. 3rd Edition. Eds: FH Adams, GC Emmanouilides. Baltimore, William and Wilkins, 1983. Reproduced with permission.*

persisting as the left pulmonary artery and the distal part joining the left pulmonary artery to the dorsal aorta as the ductus arteriosus. The right sixth branchial arch artery develops with the proximal part persisting as the right pulmonary artery and the distal part degenerating. The peripheral pulmonary arteries develop within the lung buds.^{1,2}

The pulmonary veins develop, at four weeks gestation, from an evagination of the left atrium known as the primitive pulmonary vein. At five weeks, the primitive pulmonary vein joins with the capillary plexus of veins which forms in the lung buds and the single common pulmonary vein opens into the primitive left atrium.³ The atrium expands and the common pulmonary vein and the proximal portions of its branches become incorporated into the wall of the left atrium resulting in four pulmonary veins with separate openings into the atrium.¹

By fourteen weeks gestation the main axial arteries are present but small. By sixteen weeks the major branching pattern of the pulmonary arteries (preacinar) is completed. The branching arteries

follow bronchi; collateral vessels are present, and are similar to the pattern seen in adults.⁴

From the early newborn period through childhood the peripheral arteries increase in number, at the same time as the alveoli proliferate, and also in internal diameter and length.⁵ Also, with increasing age, muscle is observed to extend more peripherally into intra-acinar arteries (Figure 1).⁶ At birth, the normally muscularized arteries, proximal to the terminal bronchioles (preacinar) are very thick-walled, but within a few days these arteries dilate, and their walls thin to adult levels. This process continues, to include the largest muscular pulmonary arteries, and is complete by four months of age⁵ (Figure 2). The pulmonary arteries grow in size and proliferate with advancing age. This development increases the cross-sectional area of the pulmonary arterial circulation and allows the pulmonary blood flow to increase at birth without an increase in pulmonary artery pressure or resistance. This proliferation is such that the ratio of alveoli to arteries decreases from a normal newborn value of

FIGURE 1 Extension of muscle into arteries accompanying respiratory structures within the acinus, from terminal bronchioli to alveoli, is shown to increase with age. The bar signifies the location at which 50 per cent of all arteries are muscular or partially muscular. wks = weeks, mths = months, yrs = years. (From: Hislop A, Reid L. Pulmonary arterial development during childhood: branching pattern and structure. *Thorax* 1973; 28: 129, with permission.)

20:1 to the adult value of 8:1 which is achieved in early childhood (Figure 3).

The pulmonary circulation in congenital heart disease

The causes of pulmonary vascular obstructive disease (PVOD) in association with congenital heart disease (CHD) remain unknown. Certain factors known to be associated with PVOD include: increased pulmonary blood flow, increased pulmonary venous pressure, and decreased pulmonary blood flow in association with systemic hypoxemia and polycythemia.⁷

Natural history studies reveal that there are certain cardiac anomalies which place patients at risk for developing PVOD quite early in life. Fifteen per cent of children with a large unrestricted ventricular septal defect (VSD) will experience an elevation in pulmonary vascular resistance (PVR) occurring either late in infancy or early in childhood.⁸⁻¹¹ 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.⁸⁻¹² These

FIGURE 2 Arterial wall thickness (WT) as a per cent of the external diameter (ED) calculated by $(2 \times \text{WT}/\text{ED}) \times 100$. In the foetus, the wall-thickness of pre-acinar and intra-acinar arteries is greatly increased. By three days of age, the wall thickness in arteries less than 200μ falls to adult levels, but the wall thickness of arteries greater than 200μ is still elevated until four months of age. (From: Reid LM. The pulmonary circulation: remodelling in growth and disease. *Am Rev Respir Dis* 1971; 119: 531, with permission.)

patients may also exhibit an abnormal increase in PVR in response to exercise or stress.¹³ A similar incidence and course of development of increased PVR is seen in children with a large patent ductus arteriosus.¹⁴ Children with a common atrio-ventricular canal or with truncus arteriosus are at a particularly high risk for the development of PVOD, and, if unrepaired often have a permanent increase in PVR by two years of age.^{15,16} Patients with atrial septal defects are usually found to have a normal pulmonary artery pressure in childhood. If unrepaired, approximately 20 per cent will develop PVOD, but this occurs late, usually not until the third decade of life.¹⁷ Certain forms of cyanotic congenital heart disease are also at particularly high risk for the development of PVOD, e.g., transposition of the great arteries; eight per cent, if there is an intact ventricular septum to 40 per cent if there is a large ventricular septal defect or patent ductus arteriosus.¹⁸⁻²⁰ In patients with transposition of the great arteries progressive elevation of PVR may occur after complete surgical repair, even in those patients who demonstrated normal PVR preoperatively.²¹

One of the considerations for earlier attempts at primary repair of cyanotic congenital heart defects, such as tetralogy of Fallot, is risk of the develop-

FIGURE 3 Schema showing morphometric changes: extension of muscle into peripheral arteries, per cent wall thickness and artery number (alveolar/arterial ratio) as they relate to age. Upper panel shows normal development. Lower panel shows abnormalities in all three features in a two-year-old child with a hypertensive ventricular septal defect. TB = artery accompanying a terminal bronchiolus, RB = artery accompanying an alveolar duct, AW = artery accompanying an alveolar wall, ALV/Art = alveolar/arterial ratio. (From: Rabinovitch M, Haworth SG, Castaneda AR, Nadas AS, Reid LM. Lung biopsy in congenital heart disease: a morphometric approach to pulmonary vascular disease. *Circulation* 1978; 58: 1107, with permission of the American Heart Association, Inc.)

ment of PVOD after palliative systemic to pulmonary shunts. However, such changes occur in less than ten per cent of cases with a Blalock-Taussig (subclavian-pulmonary artery) anastomosis, but is present in greater than 30 per cent of patients with a Waterston (ascending aorta-right pulmonary artery) or Potts (descending aorta-left pulmonary artery) anastomosis.²²

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 a few years (e.g., large unrestricted ventricular septal defect) or at low pressure for many years (e.g., secundum atrial septal defect). The vascular changes as classified by Heath and Edwards in 1958 consist of six grades of increasing severity.²³ Changes consisted of medial hypertrophy with no intimal reaction (Grade I), the addition of cellular intimal proliferation (Grade II), occlusion of the vessel lumen by continued hypertrophy of the media with intimal hyalinization and fibrosis (Grade III) formation of vessel dilatation (Grade IV), angiomatoid formation (Grade V), and ultimately arterial necrosis (Grade VI). Grades I and II are felt to be largely reversible with the restoration of pulmonary blood flow and pulmonary artery pressure to normal; Grades IV to VI irreversible. Grade III is variably reversible. This appears to depend upon the proportion of vessels that are involved and the degree of intimal hyalinization and fibrosis. Medial hypertrophy, even if severe, does not preclude reversibility. Concentric-laminar intimal fibrosis is a more significant finding but its significance also is dependent upon its severity and extent (Table II).²⁴ Patients with Grades IV to VI changes are judged at high risk for surgery.

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 of obliterative vascular disease but includes underlying developmental structural anomalies.^{4,6,25-29} The developmental anomalies include failure of the normal

TABLE II Heath-Edwards Classification²³

Grades	Morphologic features
Reversible	
I	Medial hypertrophy
II	Medial hypertrophy plus cellular intimal proliferation
Variably reversible	
III	I, II, plus luminal occlusion by fibroelastic tissue
Irreversible	
IV	I, II, III, plus luminal occlusion by fibrous tissue with arterial dilatation
V	Angiomatoid formation
VI	Fibrinoid necrosis

TABLE III Structural features quantified in congenital heart defects

<i>Congenital heart defects</i>	<i>Artery size</i>	<i>Artery number</i>	<i>Extension of muscle</i>	<i>Medial wall thickness</i>
Ventricular septal defect	↓	↓	↑	↑
Hypoplastic left heart	N	↑	↑	↑
Coarctation of the aorta	N	N	↑	↑
Total anomalous pulmonary venous connection	N	N	↑	↑
Tetralogy of Fallot	↓	N or ↑	N	↓ or ↑
Pulmonary atresia	↓	↓	N	↓

↑ = increased, above normal; ↓ = decreased, below normal; N = normal.

From: *Rabinovitch M, Reid LM. Quantitative structural analysis of the pulmonary vascular bed in congenital heart defects in Pediatric Cardiovascular Disease. Ed: MA Engle. Philadelphia, FA Davis, 1981. Reproduced with permission.*

TABLE IV Classification of structural changes of pulmonary vascular bed by quantitative analysis

<i>Classification</i>	<i>Structure</i>	<i>Haemodynamics</i>
A	Abnormal extension of muscle into peripheral arteries	Increased pulmonary blood flow
B (early)	Abnormal extension and mild medial hypertrophy	Increased pulmonary blood flow, mild increase in pulmonary artery pressure
B (late)	Abnormal extension, severe medial hypertrophy and decreased 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

From: *Rabinovitch M, Reid LM. Quantitative structural analysis of the pulmonary vascular bed in congenital heart defects in Pediatric Cardiovascular Disease. Ed: MA Engle. Philadelphia, FA Davis, 1981. Reproduced with permission.*

regression of perinatal musculature, extension of muscle peripherally into normally non-muscular alveolar ductal wall arteries, and reduced size and growth in number of all intra-acinar arteries (Figure 3) (Table III). Alveolar number and differentiation are normal.^{30,31}

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 the classification of the structural changes into three classes or grades of severity as demonstrated in Table IV.

Because of this failure of normal growth and development of the pulmonary circulatory bed, there is a deficiency in the cross-sectional area of the pulmonary vascular bed. This results in a high pulmonary artery pressure at birth due to inability of the pulmonary arterial circulation to accommodate the increase in pulmonary blood flow. It is secondary to the elevated pulmonary blood flow and pulmonary artery pressure that the anatomic changes described by Heath and Edwards develop.

Clinical and haemodynamic assessment of pulmonary vascular disease

The ability to determine which patients will develop severe pulmonary hypertension or those which will do so particularly early in life is difficult. Clinical features include shortening and softening of a heart murmur, decreased splitting of the second heart sound and increased intensity of the pulmonic component. These features are subtle early on and may not be recognized until the condition is advanced.

Electrocardiographic³² and vectorcardiographic³³ features are useful in early detection of right ventricular hypertrophy. Such studies however provide little information as to the severity of the hypertrophy and as to the severity of any co-existing pulmonary hypertension.

Imaging techniques are equally as insensitive. Radiologic features may show an enlarging main pulmonary artery, tortuosity and "pruning" of the intrapulmonary arteries, but these are generally late manifestations.^{34,35} M-mode echocardiography can only indicate the presence of right ventricular

TABLE V Pathologic, haemodynamic, radiographic correlation in the development of pulmonary vascular disease

Grade	Pathology	Physiology			Wedge angiogram
		Qp	Ppa	Rp	
A	Abnormal extension of muscle into small arteries ± mild medial hypertrophy	↑	N	N	Slow tapering of axial arteries
B	"A" + severe medial hypertrophy	↑	↑	N	Abrupt tapering
C	"B" + ↓ arterial number and size	± ↑	↑	↑	Very abrupt tapering

↑, increased, above normal; ↓, decreased, below normal; Ppa, mean pulmonary arterial pressure; Qp, pulmonary blood flow; Rp, pulmonary vascular resistance.

From: Rabinovitch M. Pulmonary hypertension in Moss' heart disease in infants, children and adolescents. 3rd Edition. Eds: FH Adams, GC Emmanouilides. Baltimore, William and Wilkins, 1983. Reproduced with permission.

hypertrophy by features such as prolongation of right ventricular systolic time intervals, prolongation of right ventricular isovolumic contraction time or early closure of the pulmonic valve, but this provides little information as to severity.³⁶ Radio-nuclide assessment of right ventricular wall thickness using thallium-201 is useful solely as a screening test for pressure overload states and provides little additional information as to the severity of ventricular hypertrophy and pulmonary hypertension.³⁷ Pulsed doppler studies, identifying abbreviated diastolic flow as in patent ductus arteriosus, again only predict the presence rather than the severity of pulmonary hypertension.³⁸

Early and frequent cardiac catheterization is currently the best technique to follow the level of pulmonary vascular resistance. The aim of cardiac catheterization in these patients is to measure and compare pulmonary and systemic flows and resistances. Calculated from the ratio of pressure gradient to flow across the pulmonary bed, the estimation of PVR by the Fick principle is most precise when oxygen consumption is measured.³⁹ It is important to emphasize that any such measurement reflects the state of the pulmonary vasculature at only one point in time, and this value can be affected by many factors such as level and type of sedation,⁴⁰ the haematocrit,⁴¹ the presence of pulmonary disease producing hypoxia,⁴² and the amount of flow through systemic collateral vessels.⁴³ In spite of these limitations, an index of pulmonary vascular resistance can be obtained. As well, estimates can be obtained as to the potential reversibility of the elevated PVR by assessing the response to 100 per cent oxygen or the intravenous administration of tolazoline which is a histamine agonist, an α -adre-

nergic antagonist and may have a direct relaxant effect on vascular smooth muscle.⁴⁴ A reduction in PVR, indicating it is not fixed, suggests that potentially reversible vasoconstriction has contributed to the high PVR, and suggests a more favourable outcome postsurgical repair.^{45,46}

With the limitations of these studies, borderline cases of suitability for corrective surgery will still exist. This has resulted in the efforts to apply the structural analysis, described previously, to the operative problem of patients with borderline catheterization results. The aim is to identify those whose pulmonary vascular disease may be expected to remain unchanged or worsen, and as such not be candidates for surgical repair, from those who can be expected to benefit from surgical repair with regression of their pulmonary vascular disease and pulmonary hypertension. One technique is the use of high definition magnification wedge angiography preoperatively to assess the structural state of the pulmonary vascular bed.

This technique is carried out at the time of cardiac catheterization by directing a balloon catheter into the axial artery of the posterior basal segment of the right lower lobe. Subsequent injection of contrast material outlines the arteries and enables evaluation of the rate of tapering of the arteries. This tapering has been correlated with the degree of maldevelopment of the pulmonary vascular bed (Table V).^{28,47}

A second technique, recently introduced into practice in borderline cases, is the use of lung biopsy with frozen section at the time of surgery. It is the previously mentioned fact that the abnormalities determined by the morphometric technique are generalized throughout the lung and not regionally different, as are the changes described by Heath

and Edwards that enable an accurate assessment of the pulmonary vascular bed to be made, and of the potential for reversal of elevations in PVR and PAP from the microscopic features as will be discussed.^{27,29,48}

Treatment

Changes in pulmonary blood flow, increases in pulmonary artery pressure, and/or level of haematocrit or decreases in oxygen saturation, likely contribute to the development of pulmonary vascular disease.⁷ Current treatment is surgical treatment, to correct the underlying cardiac defect, combined with medical treatment for the management of persistent pulmonary hypertension, if necessary.

Surgical correction of certain congenital heart lesions is now possible at very early ages,^{49,51} and it is hoped that such early repair will result in improved prognosis of pulmonary vascular disease. It appears that the earlier a patient with a congenital lesion, predisposing to the development of PVOD, undergoes surgical correction, the greater is the likelihood of the PVR decreasing to normal levels^{8,10,46,52} after surgery.

In older patients, in whom PVR has become elevated prior to repair, it is the degree to which the PVR is elevated prior to surgery that is the determining factor in operability and prognosis. If PVR is one-third or less than systemic levels, then progression after operation is unlikely. Greater than this, no regression and even progression of PVOD may occur postoperatively.^{8,10,46,52,53} Borderline cases for surgery may be assessed more completely, as discussed previously. The presence of increased pulmonary vascular resistance places a patient at greatly increased risk for mortality and morbidity^{10,46,52-54} and if operated on, they require careful postoperative management. Proper treatment then requires prevention rather than treatment of pulmonary vascular disease.

Although vasodilator therapy has been used with some success in patients with idiopathic pulmonary hypertension and pulmonary hypertension resulting from chronic obstructive pulmonary disease,⁵⁵ few trials have been instituted in the treatment of children with persistent pulmonary hypertension secondary to congenital heart defects. There is some evidence to suggest that anti-platelet therapy may be of value in polycythemic patients, but

caution is necessary in these patients, since they are at risk for haemoptysis.⁵⁶ However, the use of prophylactic heparin does not appear to alter the high mortality in the immediate postpartum period in women with Eisenmenger's syndrome.^{57,58}

Recently information regarding the reversibility of the impaired growth and alteration in structure of the pulmonary vascular bed, present at the time of surgery, has become available. Infants whose conditions were corrected surgically before nine months of age, regardless of the severity of the pulmonary vascular changes, demonstrated normal mean pulmonary artery pressure and/or pulmonary vascular resistance one year after repair. If repair was delayed past nine months of age, results were less successful. Increasing age therefore, is associated with the persistence of elevated pulmonary artery pressure and pulmonary vascular resistance postoperatively with less severe morphometric and Heath-Edwards grades. In this older group of patients, the utilization of both the morphometric and the Heath-Edwards grades, as well as the age of the patient at the time of surgical repair enables determination as to whether pulmonary artery pressure will return to normal or remain elevated.⁵⁹

Postoperative considerations

The postoperative features seen in patients with persistent or progressive PVOD are indistinguishable from those of patients who have not undergone corrective procedures. Symptoms include increasing effort intolerance, angina pectoris, syncope, hemoptysis, pulmonary infarction and cor pulmonale. Cardiac arrhythmias and sudden death are common.⁶⁰ Such patients with persistent PVOD demonstrate an impaired response to exercise.^{53,61-63} It is unclear what the influence of prior ventriculotomy, presence of myocardial dysfunction, pathological changes in the pulmonary vascular bed or altered pulmonary reactivity singly or in combination is on the response to exercise. Haemodynamic measurements carried out in patients' post-ventricular septal defect repair with residual pulmonary hypertension subjected to intense upright exercise demonstrates that some of these patients respond with a decrease in cardiac output in the face of elevating pulmonary artery pressures. The left side of the heart is variably involved with left ventricular filling pressures rising in some patients only. The implication at present is that vigorous physical exercise and isometric exer-

cise is best avoided in these patients.^{10,63} With increasing sensitivity of techniques of evaluating cardiovascular function, further information on cardiovascular responses to exercise and stress should soon be available.

Conclusions

Pulmonary vascular occlusive disease is a serious complication in a significant number of patients with congenital heart defects.⁸ Surgical correction of congenital heart defects is now possible during the first two years of life with low mortality and this has been demonstrated to produce regression of the pulmonary vascular disease.^{8,59} Various studies have demonstrated the defects in which pulmonary vascular lesions occur and those lesions in which progression of changes is likely to occur.⁸⁻²¹ Continuing development of diagnostic techniques may soon allow us to detect individuals at particular risk to develop pulmonary vascular disease.

References

- 1 Moore KL. The Developing Human. Toronto: W. B. Saunders Company, 1973, pp. 239-80.
- 2 Boyden EA. The developing bronchial arteries in a fetus of the twelfth week. *Am J Anat* 1970; 129: 357-68.
- 3 Auer J. The development of the human pulmonary vein and its major variations. *Anat Rec* 1948; 101: 581-94.
- 4 Elliot FM, Reid LM. Some new facts about the pulmonary artery and its branching pattern. *Clin Radiol* 1965; 16: 193-8.
- 5 Reid LM. The pulmonary circulation: remodelling in growth and disease. *Am Rev Respir Dis* 1979; 119: 531-46.
- 6 Hislop A, Reid L. Pulmonary arterial development during childhood: branching pattern and structure. *Thorax* 1973; 28: 129-35.
- 7 Nadas AS, Fyler DF. Pediatric Cardiology. Philadelphia: WB Saunders Company, 1972, pp. 684.
- 8 Friedli B, Kidd BS, Mustard WT, Keith JD. Ventricular septal defect with increased pulmonary vascular resistance. *Am J Cardiol* 1974; 33: 403-9.
- 9 DuShane JW, Krongrad E, Ritter DG, McGoon DC. The fate of raised pulmonary vascular resistance after surgery in ventricular septal defect. In: Rowe RD, Kidd BSL, eds. *The Child with Congenital Heart Disease after Surgery*. Mount Kisco, New York: Futura, 1976 p. 299-314.
- 10 Hallidie-Smith KA, Hollman A, Cleland WP, Bentall HH, Goodwin JF. Effects of surgical closure of ventricular septal defects upon pulmonary vascular disease. *Br Heart J* 1966; 31: 246-60.
- 11 Hoffman JIE, Rudolph AM. The natural history of ventricular septal defects in infancy. *Am J Cardiol* 1965; 16: 634-53.
- 12 Castaneda AR, Zamora R, Nicoloff DM et al. High pressure, high resistance ventricular septal defect: surgical results of closure through right atrium. *Ann Thorac Surg* 1971; 12: 29-38.
- 13 Maron BJ, Redwood DR, Hirschfield FW Jr et al. Postoperative assessment of patients with ventricular septal defect and pulmonary hypertension. Response to intense upright exercise. *Circulation* 1973; 48: 864-74.
- 14 Reid LM, Stevenson JG, Coleman EN et al. Moderate to severe pulmonary hypertension accompanying patent ductus arteriosus. *Br Heart J* 1964; 26: 60-5.
- 15 Newfield EA, Sher M, Paul MH, Higashi N. Pulmonary vascular disease in complete atrio-ventricular canal defect. *Am J Cardiol* 1977; 39: 721-6.
- 16 Marcelletti C, McCoon DC, Mair DD. The natural history of truncus arteriosus. *Circulation* 1976; 54: 108-11.
- 17 Besterman E. Atrial septal defect with pulmonary hypertension. *Br Heart J* 1961; 23: 587-98.
- 18 Viles PM, Ongley PA, Titus JL. The spectrum of pulmonary vascular disease in transposition of the great arteries. *Circulation* 1969; 40: 31-41.
- 19 Newfield EA, Paul MH, Muster AJ, Idriss FS. Pulmonary vascular disease in complete transposition of the great arteries. A study of 200 patients. *Am J Cardiol* 1974; 34: 75-82.
- 20 Waldman JD, Paul MH, Newfield EA, Muster AJ, Idriss FF. Transposition of the great arteries with intact ventricular septum and patent ductus arteriosus. *Am J Cardiol* 1977; 39: 232-8.
- 21 Berman W Jr, Whitman V, Pierce WS, Waldhausen JA. The development of pulmonary vascular obstructive disease after successful Mustard operative in early infancy. *Circulation* 1978; 58: 181-5.
- 22 Paul MH, Miller RA, Potts WJ. Long-term results of aortic pulmonary anastomosis in tetralogy of Fallot: an analysis of the first 100 cases 11 to 13 years after operation. *Circulation* 1961; 23: 525-33.
- 23 Heath D, Edwards JE. The pathology of hypertensive pulmonary vascular disease. *Circulation* 1958; 18: 533-47.

- 24 *Wagenvoort CA*. Lung biopsy specimens in the evaluation of pulmonary vascular disease. *Chest* 1980; 77: 614–25.
- 25 *Short DS*. Postmortem pulmonary arteriography with special reference to the study of pulmonary hypertension. *J Fac Radiol (Lond)* 1956; 8: 118–31.
- 26 *Davies G, Reid L*. Growth of the alveoli and pulmonary arteries in children. *Thorax* 1970; 25: 669–81.
- 27 *Haworth SG, Reid L*. A morphometric study of regional variation in infants with pulmonary hypertension and congenital heart defect. A justification of lung biopsy. *Br Heart J* 1978; 40: 825–31.
- 28 *Rabinovitch M, Keane JF, Fellows KE, Castaneda AR, Reid L*. Quantitative analysis of the pulmonary wedge angiogram in congenital heart defects. Correlation with hemodynamic data and morphometric findings in lung biopsy tissue. *Circulation* 1981; 63: 152–64.
- 29 *Rabinovitch M, Sanders SP, Castaneda AR, Reid L*. Morphometric analysis of lung biopsy tissue in candidates for Fontan-type surgical procedures. *Am J Cardiol* 1981; 47: 447 (Abst).
- 30 *Hislop A, Haworth SG, Shinebourne EA et al*. Quantitative structural analysis of pulmonary vessels in isolated ventricular septal defect in infancy. *Br Heart J* 1975; 37: 1014–21.
- 31 *Haworth SG, Sauer U, Buhlmeier K, Reid L*. Development of the pulmonary circulation in ventricular septal defect: a quantitative structural study. *Am J Cardiol* 1977; 40: 781–8.
- 32 *Johnson JB, Felter ML, West JR, Cournand A*. The relationship between electrocardiographic existence of right ventricular hypertrophy and pulmonary arterial pressure in patients with chronic pulmonary disease. *Circulation* 1950; 1: 536–50.
- 33 *Chou T, Masangkay MP, Young R, Conway GF, Helm RA*. Simple quantitative vector cardiographic criteria for the diagnosis of right ventricular hypertrophy. *Circulation* 1973; 48: 1262–7.
- 34 *Weidman WH, DuShane JW, Kincaid OW*. Observations concerning progressive pulmonary vascular obstruction in children with ventricular septal defects. *Am Heart J* 1963; 65: 148–54.
- 35 *Iverson RE, Linde LM, Kegel S*. The diagnosis of progressive pulmonary vascular disease in children with ventricular septal defects. *J Pediatr* 1966; 68: 594–600.
- 36 *Silverman NH, Snider AR, Rudolph AM*. Evaluation of pulmonary hypertension by M-mode echocardiography in children with ventricular septal defect. *Circulation* 1980; 61: 1125–32.
- 37 *Rabinovitch M, Fisher KC, Treves S*. Quantitative thallium-201 myocardial imaging in assessing right ventricular pressure in patients with congenital heart defects. *Br Heart J* 1981; 45: 198–205.
- 38 *Stevenson G, Kawabori I, Guntheroth WG*. Non-invasive detection of pulmonary hypertension in patent ductus arteriosus by pulsed Doppler echocardiography. *Circulation* 1979; 60: 355–9.
- 39 *Stocker FP, Wilhoss OS, Nadas AS*. Oxygen consumption in infants with heart disease. *J Pediatr* 1972; 80: 43–51.
- 40 *Tarnow J, Hess W*. Pulmonary hypertension and pulmonary oedema caused by intravenous ketamine. *Anesthetist* 1978; 27: 486–7.
- 41 *Rosenthal A, Nathan DG, Marty AT et al*. Acute hemodynamic effects of red cell volume reduction in polycythemia of cyanotic congenital heart disease. *Circulation* 1970; 42: 297–307.
- 42 *Vogel JH, McNamara DC, Blount SG Jr*. Role of hypoxia in determining pulmonary vascular resistance in infants with ventricular septal defect. *Am J Cardiol* 1967; 20: 346–9.
- 43 *Keane JF, Ellison RC, Rudd M, Nadas AS*. Pulmonary blood flow and left ventricular volumes with transposition of the great arteries and intact ventricular septum. *Br Heart J* 1973; 35: 521–6.
- 44 *Jones ODH, Shore DF, Rigby ML et al*. The use of tolazoline hydrochloride as a pulmonary vasodilator in potentially fatal episodes of pulmonary vasoconstriction after cardiac surgery in children. *Circulation* 1981; 64: 134–9.
- 45 *Mair DP, Ritter DG, Ongley PA, Helmholtz HF Jr*. Hemodynamics and evaluation for surgery of patients with complete transposition of the great arteries and ventricular septal defect. *Am J Cardiol* 1971; 28: 632–40.
- 46 *Vogel JHK, Grover RF, Jamieson G, Blount SG Jr*. Long-term physiological observation in patients with ventricular septal defect and increased pulmonary vascular resistance. *Adv Cardiol* 1974; 11: 108–21.
- 47 *Nihill MR, McNamara DG*. Magnification of pulmonary wedge angiography in the evaluation of children with congenital heart disease and pulmonary hypertension. *Circulation* 1978; 58: 1094–1106.
- 48 *Rabinovitch M, Castaneda AR, Reid L*. Lung biopsy with frozen section as a diagnostic aid in pa-

- tients with congenital heart defects. *Am J Cardiol* 1981; 47: 77-84.
- 49 *Castaneda AR, Lamberti J, Sade RM, Williams RG, Nadas AS.* Open heart surgery during the first three months of life. *J Thorac Cardiovasc Surg* 1974; 68: 719-31.
- 50 *Mair DD, McGoon DC.* Surgical correction of atrio-ventricular canal during the first year of life. *Am J Cardiol* 1977; 40: 66-9.
- 51 *Stark J, DeLeval MR, Waterston DJ, Graham GR, Bonham-Carter RE.* Corrective surgery of transposition of the great arteries in the first years of life. Results in 63 infants. *J Thorac Cardiovasc Surg* 1974; 67: 673-81.
- 52 *Whitman V, Ellis NG.* Pulmonary hemodynamics after repair of left-to-right shunts associated with pulmonary artery hypertension. In: Rosenthal A, Sonnenblick EH, Lesch M, eds. *Postoperative Congenital Heart Disease*, New York: Grune & Stratton, 1975: 111-8.
- 53 *Cartmill TB, Dushne JW, McGoon DC et al.* Results of repair of ventricular septal defect. *J Thorac Cardiovasc Surg* 1966; 52: 486-99.
- 54 *Wheeler J, George BL, Mulder DG, Jarmakani JM.* Diagnosis and management of postoperative pulmonary hypertensive crisis. *Circulation* 1979; 60: 1640-3.
- 55 *Rubin LJ, Peter RH.* Hemodynamics at rest and during exercise after oral hydralazine in patients with cor pulmonale. *Am J Cardiol* 1981; 47: 116-22.
- 56 *Fuster V, Giuliani ER, Brandenburg RO, Weidman WH, Edwards ED.* The natural history of idiopathic pulmonary hypertension. *Am J Cardiol* 1981; 47: 422 (Abst.)
- 57 *Jones AM, Howitt G.* Eisenmenger syndrome in pregnancy. *Br Med J* 1965; 1: 1627-31.
- 58 *Pitts JA, Crosby WM, Basta LL.* Eisenmenger's syndrome in pregnancy. Does heparin prophylaxis improve maternal mortality rate? *Am Heart J* 1977; 93: 321-6.
- 59 *Rabinovitch M, Keane JF, Norwood WI, Castaneda AR, Reid L.* Vascular structure in lung tissue obtained at biopsy correlated with pulmonary hemodynamic findings after repair of congenital heart defects. *Circulation* 1984; 69: 655-67.
- 60 *Wood P.* The Eisenmenger syndrome or pulmonary hypertension with reversed central shunt. *Br Med J* 1958; 2: 701-9, 755-62.
- 61 *Gotsman MS, Beck W, Barnard CN, Schriber V.* Haemodynamic studies after repair of ventricular septal defect. *Br Heart J* 1969; 31: 63-8.
- 62 *Lillehei CW, Anderson RC, Wang Y.* Clinical and hemodynamic changes after closure of ventricular septal defects. *JAMA* 1968; 205: 822-7.
- 63 *Friedman WF, Heiferman MF.* Clinical problems of postoperative pulmonary vascular disease. *Am J Cardiol* 1982; 50: 631-6.