Review Article

Pulmonary hypertension in children: perioperative management

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HYPERTENSION PULMONARY: perioperative management

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Pulmonary vascular disease secondary to congenital heart disease (CHD) is well recognized in infants and children. Changes in pulmonary haemodynamics have been well described, as have the high morbidity and mortality associated with acute elevations in pulmonary vascular resistance (PVR) following surgical correction of ventricular septal defects (VSD), transposition of the great arteries (TGA) with VSD or total anomalous pulmonary venous connections.¹

The increase in PVR is a function of structural changes² that decrease the cross-sectional area of the pulmonary vascular bed, and a superimposed

reactive component or active state of contraction of the vascular smooth muscle. Both these features are underlying characteristics of the pulmonary vasculature in children with CHD. Anaesthetic management of these patients cannot change the component of PVR increases related to structure, but they can affect the reactive component and produce corresponding changes in PVR, right ventricular (RV) afterload and, potentially, intracardiac shunting. In this article we describe the consequences of pulmonary hypertension (PH) and the considerations PH necessitates in the perioperative management of affected infants and children.

Sequelae of pulmonary hypertension

Cardiac function

The thin-walled RV compensates poorly for any increased impedance offered by the pulmonary vasculature.³ With gradual chronic elevations of the pulmonary artery pressure (PAP) gradual hypertrophy of the RV occurs, which allows pressures to develop in the ventricle equal to those of the systemic side of the circulation.

Acute rises in PAP initiate a series of abnormalities that depend on the degree of elevation (Figure 1). The effects of such elevations on right and ultimately on left ventricular function, leading to decreased forward cardiac output (CO), are responsible for the high mortality and morbidity associated with PH.³⁻⁸

Right ventricular contractility in response to acute elevations in afterload is restricted by the thinness of the RV.³ therefore, preload must be augmented to assist RV output by the Frank-Sterling principle,³ by increasing venous return.^{9,10} As PAP rises, RV end diastolic volume (RVEDV) and pressure (RVEDP) increase. Coronary blood flow (CBF), which normally occurs during systole and diastole³ in the RV, is limited to diastole, and the volume overload increases wall stress and augments the coronary oxygen demand.^{3,4,6} These changes in CBF and increases in wall stress can cause subendocardial ischaemia and right-sided heart failure. Biochemical evidence of RV ischaemia has been demonstrated in the presence of increased RV afterload.⁵ In addition to injuring the RV free wall, such ischaemia may damage the tricuspid apparatus, producing tricuspid insufficiency, or damage the sino-atrial or atrioventricu-

FIGURE 1 Cardiovascular abnormalities associated with the development of PH culminating in decreased CBF and CO. RVEDP = right ventricular end diastolic pressure. RVEDV = right ventricular end diastolic volume, LV = left ventricle, CBF = coronary blood flow, CO = cardiac output.

lar nodes, resulting in dysrhythmias.¹¹ If CBF to the RV is increased by maintaining coronary perfusion pressure with arterial vasopressors, ischaemia is relieved and function improved.^{4,5,7}

Alterations in RV volume secondary to increases in RV afterload can affect the diastolic mechanical and compliance characteristics of the left ventricle (LV).³ Increased RVEDV produces dramatic shifts in the intraventricular system, increasing LV end diastolic pressure, and decreasing LV filling due to the decreased compliance. Therefore LV end diastolic volume is reduced, CO is decreased and left atrial pressure (LAP) is increased. Thus, the elevated LAP and decreased CO do not reflect decreased LV function but rather altered LV mechanics secondary to RV dysfunction.^{5,7} As in the RV, the decreased compliance of the LV increases LV oxygen demand at a time when blood flow may be limited.

Pulmonary function

Many patients with PH have evidence of both large and small airway obstruction and decreased pulmonary compliance.¹²⁻¹⁴ Extrinsic airway obstruction may result from compression of bronchi by distended pulmonary arteries or an enlarged left atrium, or both.¹² Peripheral airway obstruction is related to perivascular and vascular thickening that compresses small airways and prevents their distention. Such obstruction leads to ventilation/perfusion mismatching and decreased lung compliance,^{13,15}

TABLE I Differentiation of pulmonary vascular occlusive disease

Primary pulmonary artery occlusive disease
Secondary to congenital heart disease
- Acyanotic type
- Cyanotic type
Secondary to chronic airway disease
- Hypertrophied tonsils and adenoids
- Laryngotracheomalacia
- Pulmonary dysfunction (e.g., cystic fibrosis, chronic bronchitis)
Secondary to neuromuscular disorders
- Muscular dystrophies
- Diaphragmatic palsy
- Central (Ondine's curse)

which in turn may result in hypoxaemia and predisposition to respiratory muscle fatigue.^{16,17}

Increased dead space ventilation resulting from decreased effective pulmonary blood flow (PBF) secondary to RV failure, obliteration of the pulmonary vascular bed or precapillary vasoconstriction can occur in children with PH.^{15,18,19} Such increased dead space ventilation can produce hypoxaemia and hypercapnia.

Preoperative assessment of the patient with pulmonary hypertension

It is unlikely that pulmonary vascular obstructive disease (PVOD) will fail to be diagnosed before the patient appears for surgery. The patient will have undergone a cardiac consultation and the results will be available. Therefore, the presence of PH and the basic underlying pathology will be fairly obvious. When a cardiac consultation has not been performed and it is not possible to obtain one, anaesthetic risk is more difficult to determine. In assessing anaesthetic risk for these patients it is important to determine the form of PVOD (Table I).

Primary pulmonary vascular occlusive disease

The most brittle group are the patients with primary PVOD. They have a structurally normal heart, no preceding history of CHD and no intrinsic pulmonary disease.

These patients usually present with exercise intolerance and, frequently, syncope due to their inability to increase cardiac output with exercise. Clinical findings include a loud pulmonic component to the second heart sound, a pulmonic ejection

click, a soft systolic ejection murmur and a soft end-diastolic murmur with pulmonary regurgitation. Radiological findings include right ventricular hypertrophy (RVH). There is an increased main pulmonary artery segment while the pulmonary vascular markings are normal or reduced. The electrocardiogram frequently shows right axis deviation with evidence of RVH or strain.²⁰

Stability during induction of anaesthesia is critical. Any hypoxia can decrease oxygen delivery to the myocardium and even mild hypotension can reduce oxygen supply to the RV. As the oxygen supply-to-demand ratio is already critical (Figure 1), any interference can produce a sudden onset of ventricular fibrillation.

Acyanotic lesions progressing to pulmonary vascular occlusive disease

Acyanotic lesions that progress to PVOD include VSD, patent ductus arteriosus, aortopulmonary window, atrial septal defect (rare in childhood) and atrioventricular septal defect (especially in patients with Down syndrome). The PVOD results from increases in pressure and in PBF in the pulmonary vascular bed.^{21,22} Early in the natural history after PVOD develops, shunting may be very well balanced (i.e., minimal and without cyanosis).^{23,27}

Signs of PVOD usually develop after age two to three years. During the asymptomatic or "well balanced" period clues to the diagnosis include an antecedent history of a heart murmur. The systolic ejection murmur is shortened, with an accentuated P₂ and there is no mid-diastolic murmur. The patient may have a history of being "unwell" in infancy, due to the high PBF at that time.²⁸

These patients with acyanotic lesions are usually reasonably good anaesthetic risks. In the absence of cyanosis and polycythaemia PBF will be adequate. Because of the elevated RV afterload, preload must be maintained to utilize the Frank-Starling principle and systemic vascular resistance must be maintained to prevent right-to-left shunting.

Certainly, by the time such a patient is clinically cyanosed (Eisenmenger complex), PBF is inadequate and any decrease in the mean arterial pressure (MAP) or systemic vascular resistance during anaesthesia increases right-to-left shunting, setting up a vicious cycle. If polycythaemia/hyperviscosity is significant, especially in a very symptomatic

patient, red-cell phoresis before anaesthesia and surgery may increase PBF (primarily by reducing viscosity) and decrease morbidity.²⁹

PVOD develops much earlier in certain complex forms of CHD, such as TGA with VSD, univentricular heart or straddling atrioventricular valve with unobstructed PBF, than in the less complex lesions. However, most patients with complex CHD have a clear-cut history of difficulties in infancy and early childhood because the defects are admixture lesions with obligatory right-to-left intracardiac shunting. Polycythaemia and hyperviscosity appear earlier.³⁰ Guidelines of management are similar to those for PVOD.

Specific considerations

CHRONIC UPPER AIRWAY DISEASE (i.e., hypertrophied tonsils and adenoids) can lead to cor pulmonale with pulmonary artery hypertension in patients without CHD. Clinically, a loud P₂, evidence of tricuspid regurgitation and a soft systolic ejection murmur are apparent. A history of snoring and night time hypoxaemia and hypercarbia, which can be documented by sleep study,^{31–44} are important. Certain patients are susceptible to both upper airway disease and CHD, and the combination may complicate the development of PVOD. This combination is especially common in patients with Down syndrome.

TRUNCUS ARTERIOSUS and PVOD are often associated with significant myocardial ischaemia secondary to decreased aortic (truncal) diastolic pressure. Decreases in MAP or systemic vascular resistance may produce sufficient ischaemia to initiate a sudden onset of ventricular fibrillation.⁴⁵

Perioperative considerations

Anaesthetic management of patients with increased PVR is complicated by the fact that many of the anaesthetic agents and techniques we use have both direct and indirect effects on the PVR, through alterations of CO and PBF. Increased CO into a system with fixed PVR increases PAP, which promotes increased transudation of fluid into the lung interstices. Alternatively, sudden increases in PVR impede RV output sufficiently to also reduce PBF and LV output. Similarly, pulmonary vascular

response to different stimuli depends on the initial state of the pulmonary vasculature. Since the muscle length at which maximum active force develops corresponds to a transmural pressure equal to that normally provided by the systemic circulation, the pulmonary vascular smooth muscle has little potential for activation when PAP and, consequently, pulmonary transmural pressure are normal. In PH, the fiber lengths of the pulmonary vascular smooth muscle are closer to the optimal length for active force development, and stimulation of the vessels to vasoconstrict would produce an exaggerated response compared with the response when PAP is normal.^{46,47}

Therefore, the anaesthetic management of patients with PH is guided by three considerations: the manipulation of factors known to affect PVR, the effect of anaesthetic agents on PVR and the maintenance of CO and coronary perfusion pressure.

Factors that affect pulmonary vascular resistance

Factors that increase PVR and must be avoided in the anaesthetic management of a patient with PH include hypoxia, acidosis, extremes in lung volume, polycythaemia (hyperviscosity) and agitation.⁶

Alveolar hypoxia and hypoxaemia increase PVR.^{48–51} Hypoxaemia, produced by inhalation of low FiO₂, increases PVR only slightly while the PaO₂ decreases from 13.3 kPa (100 mmHg) to 6.7 kPa (50 mmHg). Decreases in PaO₂ below 6.7 kPa (50 mmHg) increase PVR dramatically.^{52–55} A reduced pulmonary artery oxygen content also results in generalised pulmonary vasoconstriction.⁵⁵ Acidosis (both metabolic and respiratory) may induce pulmonary vasoconstriction independently, or greatly enhance the responses identified with hypoxaemia (Figure 2).^{48,54}

The effects of PCO₂ on PVR are not clear at present. In some studies⁵³ increased PCO₂ was associated with increased PVR, but arterial pH was not controlled. Other studies⁵⁴ have not been able to demonstrate an effect of PCO₂ separate from that of pH.

The mechanisms of these responses are also not clear. There is some evidence to implicate the developing sympathetic nervous system, which would account for the relationship between hypoxic pulmonary vasoconstriction (HPV) and fetal gesta-

FIGURE 2 Change in PVR with oxygenation and H^+ ion concentration. There is a sharp increase in PVR when PaO_2 falls below 6.7 kPa (50 mmHg). Note also the synergistic effect when hypoxaemia is accompanied by acidosis. (Reproduced by permission of the authors⁵⁴ and the Journal of Clinical Investigation.)

tional age.^{56,57} However, other studies show that no significant effect of the sympathetic nervous system on HPV is demonstrated by α -receptor blockade and chemical denervation techniques in neonatal animals.⁵⁸ It is still possible that development of the sympathetic nervous system may play a role.⁵⁹

Currently, it appears that a direct local effect of hypoxaemia or asphyxia is responsible for the pulmonary vascular response, and therefore oxygen is a major factor in controlling the pulmonary circulation. The exact mechanisms are not clear.⁶⁰⁻⁶² Isolated pulmonary artery contracts with acute exposure to hypoxia,⁶³ and histamine has been implicated as a possible mediator in HPV,⁶⁴⁻⁶⁶ but HPV occurs despite H_1 and H_2 histamine receptor blockade.⁶⁷ Angiotensin II augments HPV in isolated rat lungs. Angiotensin-converting enzyme is necessary to convert angiotensin I to angiotensin II, and its activity is enhanced by hypoxaemia. Such enhancement may produce elevated levels of angiotensin II, which could enhance pulmonary vasoconstriction.⁶²

Alkalosis (respiratory or metabolic) decreases PVR and PAP and improves gas exchange in patients with raised PAP.^{48,68-71} Although induced alkalosis initially improves cardiac function and gas exchange,^{72,73} its simultaneous effects on other vascular beds and systems must be recognized. Its use in some patients may be limited by complications related to alkalosis, including systemic hypotension, increased coronary and cerebral vascular resistance, leftward shift of the oxyhaemoglobin dissociation curve, hypocalcaemia, hypokalaemia and dysrhythmias.^{42,45,46}

The degree of lung inflation affects PVR. It is minimal at the lung volume represented by the functional residual capacity (FRC) of the unanaesthetized patient, and both increased and decreased lung volumes are associated with increased resistance to blood flow.^{71,74}

Induction of anaesthesia decreases FRC and changes its relationship to closing volume.⁷⁵⁻⁸³ The decreased FRC is associated with a higher PVR than is present in the unanaesthetized state, due to tortuosity of large extra-alveolar vessels or active hypoxic vasoconstriction.^{84,85} As lung volume returns towards the FRC of the awake state, PVR decreases (Figure 3); above the FRC, the PVR increases again, due to compression of the small, intra-alveolar vessels.

The effects of artificial ventilation on pulmonary haemodynamics have been studied extensively. Positive pressure ventilation, particularly when positive end-expiratory pressure (PEEP) is used, raises mean intrathoracic pressure and reduces stroke volume and CO. Obstruction of venous return, increased PVR, reflex myocardial depression and reduction of LV end diastolic volume by pleural compression and by displacement of the interventricular septum have all been implicated. The relative importance of each factor in decreasing CO and tissue oxygenation remains controversial.⁸⁶⁻⁹⁰

Patients with elevated PVR and decreased RV reserve are likely to tolerate high inflation pressures and PEEP poorly. The benefits of PEEP, increasing FRC towards normal, decreasing PVR somewhat and improving gas exchange, must be balanced against the possibility of decreased CO or increased intracardiac shunting. Hypercarbia must also be avoided because of its effect on PVR related to decreased pH.

FIGURE 3 Changes in PVR with changes in lung volume. The calibre of pulmonary vessels increases with increasing lung volume. PVR is lowest at the lung volume that coincides with FRC. (Reproduced by permission of the author¹⁸³ and Williams and Wilkins.)

Effect of anaesthetic agents on pulmonary resistance

INTRAVENOUS AGENTS

Barbiturates

Few studies have characterised the pulmonary vascular response to barbiturates. In a preparation of pulmonary artery rings thiopentone primarily increased tone but it also diminished the contractile response to exogenous norepinephrine, and the net effect in man could not be established.⁹¹ In an intact dog, thiameylal increased PVR while pentobarbitone had little effect.⁹² Enibomalnatrium, another barbiturate, decreased PAP by decreasing CO,⁹³ but it has little effect on PVR in humans. Since administration of high-dose thiopentone ($10 \text{ mg} \cdot \text{kg}^{-1}$) to healthy adults decreased PAP more than could be accounted for by reduction of CO alone, it was concluded that thiopentone directly affects pulmonary vascular tone and significantly reduces PVR.⁹⁴ The validity of this conclusion when lower doses are used and in other clinical contexts remains to be shown.

Ketamine

The effect of ketamine on PVR is controversial. Increased PVR after the administration of ketamine to adult humans has been documented,⁹⁵⁻⁹⁸ and its

avoidance has been recommended in patients with PH⁹⁶ or reduced ventricular reserve.⁹⁷ In infants and children with normal and elevated PVR, however, studies have shown minimal effects on cardiovascular variables, including the PVR, as long as airway patency and ventilation are maintained.^{99,100} Similarly, under these conditions the hypoxia previously reported⁹⁵⁻⁹⁸ was not seen.⁹⁹⁻¹⁰¹ These studies support the clinical impression that the use of ketamine in infants and children is safe. Use and safety in adults with increased PVR has yet to be confirmed.

Narcotics

The cardiovascular effects of the major narcotics have been studied in dogs.¹⁰² Doses required for deep surgical anaesthesia were administered initially, followed by larger doses to characterize toxicity. Meperidine $2 \text{ mg} \cdot \text{kg}^{-1}$ increased PAP slightly and depressed PVR in a direct ratio to markedly increased heart rate and PBF. Morphine $5 \text{ mg} \cdot \text{kg}^{-1}$ transiently reduced CO and PAP, with no consistent effect on PVR. CO and pulmonary haemodynamics remained stable in response to alfentanil $160 \mu\text{g} \cdot \text{kg}^{-1}$ and fentanyl $50 \mu\text{g} \cdot \text{kg}^{-1}$, while sufentanil $4 \mu\text{g} \cdot \text{kg}^{-1}$ mildly reduced CO and PAP and slightly increased PVR. However, only the effects of meperidine on heart rate and morphine on CO achieved statistical significance, and pulmonary circulatory effects were relatively minor. Cardiovascular toxicity appeared at doses well above the clinical range and was manifest in all cases by sympathetic excitation with acute rises in PAP and PVR. The toxic threshold increased with the potency of the narcotic, fentanyl and sufentanil giving the highest margins of safety.

No significant pulmonary haemodynamic effects were observed in adults with coronary artery disease who were given morphine in doses up to $2 \text{ mg} \cdot \text{kg}^{-1}$.¹⁰³ Similar haemodynamic stability was noted in another group of cardiac patients anaesthetised with high-dose fentanyl in oxygen.¹⁰⁴ Significant but clinically unimportant increases in PAP were seen with high-dose fentanyl and sufentanil at the onset of unconsciousness.¹⁰⁵ However, data on fluctuations in arterial PCO_2 during induction were not provided, and given the well documented sensitivity of the pulmonary vasculature to respiratory acidosis,^{93,106,107} even minor increases in PCO_2 could have accounted for these changes.

Significant reduction in the response of the pulmonary circulation to the stress of endotracheal suctioning after cardiac surgery in infants given fentanyl $25 \mu\text{g}\cdot\text{kg}^{-1}$ has been reported,¹⁰⁸ consistent with previous findings in adults.¹⁰⁹

These data suggest that narcotics as a group, particularly the more potent ones, have little if any direct effect on the pulmonary circulation, although in higher doses blunted reflex responses of the pulmonary vasculature to sympathetic activation are observed. This latter effect may well have clinical benefits in the context of RV overload and right-to-left shunting.¹¹⁰ This can be substantiated, however, only by further clinical trials.

Muscle relaxants

There are no data on the effects of muscle relaxants on pulmonary haemodynamics, apart from those obtained indirectly from studies of other agents. Nevertheless, it appears from many studies involving inhalation anaesthetics and narcotics, in which both depolarizing and non-depolarizing relaxants have been used, that these drugs have little effect on the pulmonary circulation.

Histamine

Many of the drugs we administer (e.g., morphine, thiopentone) have histamine-releasing properties.⁹⁴ Histamine appears to have potent pulmonary vasoconstrictive effects in animals^{111,112} but its effects in man have not been studied. The significance of these effects in animals in relation to the use of histamine-releasing drugs remains speculative. The studies involving morphine and thiopentone suggest that histamine release occurring with these agents has little impact on the pulmonary circulation.⁹⁴

INHALATION AGENTS

Halothane

Numerous studies of the effects of halothane on pulmonary vessels have focused on its influence on HPV and intrapulmonary shunting. HPV may be abolished by clinical concentrations of halothane, which implies a vasodilating effect.^{113,114} This contradicts data obtained in canine preparations,^{115,116} but supports the conclusion of Marshall *et al.*¹¹⁷ that inhalation induction with halothane/oxygen is associated with greater venti-

lation/perfusion mismatch than induction with intravenous thiopentone.

The effects of halothane on haemodynamic parameters have been studied in dogs.¹¹⁸ With 1.5 per cent halothane, PBF and PAP fell while PVR remained unchanged, findings supported by other work in the same species.¹¹⁹ A further study using isolated pulmonary lobes showed that 1.5 per cent halothane given via pump oxygenator induced a small but significant fall in perfusion pressure, while the same concentration given by inhalation had no effect. The authors concluded that halothane acts directly on pulmonary vascular smooth muscle.¹²⁰ This effect may be masked in the intact animal by a concomitant fall in PBF and PAP, since a simultaneous decrease in vascular wall tension and distending pressure may leave vessel diameter and PVR unchanged.

Another study in dogs examined isolated, artificially perfused heart-lung preparations.¹²¹ Under conditions of both normal and increased PBF and PAP, halothane 2.5–3.0 per cent in air/oxygen did not significantly alter pulmonary haemodynamics. Following experimental micro-embolization of the pulmonary vascular tree, however, high PAP was significantly reduced, leading to the conclusion that the effect of the drug on reflex vasoconstriction is more important than any general vasodilating action.

Work in man and other primates has been limited. Studies of macaque monkeys showed no significant changes in PAP or PVR with concentrations of halothane up to twice minimum alveolar concentration (MAC).¹⁰⁶ Healthy young adult volunteers were given halothane 1.5 per cent in oxygen, air/oxygen or nitrous oxide/oxygen under conditions of both spontaneous and controlled respiration, and findings were compared with awake values. Mean PAP, PVR and PBF were affected little by halothane, although the effects of other variables were in some cases significant.¹²² More recently 0.6–1 per cent halothane in air/oxygen administered to adult cardiac patients with normal preoperative values left PAP and PVR within normal limits.¹²³

Thus, the evidence at hand suggests that in normal clinical circumstances halothane has little effect on RV afterload, although gas exchange appears to be impaired by interference with regional hypoxic vasoconstriction. In cases of PH in which reflex vasoconstriction may be important, halothane

may reduce PAP by reflex suppression. However, the effect of this on gas exchange cannot be predicted, nor can effects on PAP when PH is related to fixed pathological changes. Further clinical studies, particularly in patients with right-heart overload, are needed.

Enflurane

The effects of enflurane on pulmonary haemodynamics have not been well documented. In elderly patients anaesthetised with enflurane, PAP increased markedly.¹²⁴ In six healthy paralysed and ventilated young men, administration of two per cent enflurane in nitrous oxide/oxygen was associated with a modest increase in mean PAP (2.9 to 3.5 kPa, 22 to 26 mmHg) as well as the expected depression of PBF.¹²⁴ However, no tests of significance were cited, nor was mention made of such pertinent variables as PCO₂ and the presence or absence of surgical stimulation. Nevertheless, in the absence of additional information it may be safest to avoid enflurane in patients with known PH.

Isoflurane

Administration of isoflurane in animals during controlled ventilation produced either no change or a small dose-related decrease in PAP.^{125–131} PVR either did not change or slightly increased.^{125–128,130,131} Pulmonary capillary wedge pressure (PCWP) was not altered.¹²⁶ In spontaneously breathing dogs receiving 1 to 2.5 MAC isoflurane, PAP, PVR and PCWP did not change.¹³² In humans, measurements made during controlled ventilation with nitrous oxide and constant PaCO₂ demonstrated no change in PAP, PCWP or PVR after the administration of isoflurane 0.75 to 1.5 per cent.^{133,134} Thus, it appears that isoflurane has little effect on the pulmonary circulation.

Nitrous oxide

Evidence of myocardial depression and peripheral vasoconstriction due to alpha-adrenergic stimulation by nitrous oxide has been reported.^{133,136–142} Fewer studies have been performed evaluating the effects of nitrous oxide on the pulmonary circulation, but they suggest that PVR increases significantly in patients with pre-existing PH, irrespective of the anaesthetic technique employed.^{123,143} As in other studies,^{46,47} the response of pulmonary vasculature was directly related to the pre-existing

increase in PVR. These studies indicate that nitrous oxide must be used with caution in patients with elevated PVR, particularly when RV dysfunction is present.

Maintenance of cardiac output and coronary perfusion pressure

When PH is complicated by RV failure, anaesthetic techniques that will not further impair RV function must be used. Many of the anaesthetic drugs mentioned above are contraindicated because of their negative inotropic effects on the RV. The problem is to maintain CO in the presence of an elevated afterload. Agents that provide such stability in infants and children include ketamine, fentanyl and sufentanil.^{108–110}

Further anaesthetic management is similar to that for patients with decreased LV reserve. Preload can be assessed by central venous pressure measurement. Normally the RV has a relatively high diastolic compliance. Because of this, changes in RV volume are associated with only modest increases in right atrial pressure (RAP). In the presence of an elevated RV afterload produced by PH, the RAP increases and the mean pressure in the systemic vasculature must be elevated slightly to maintain adequate venous return and preload.⁹ Fluid management, therefore, is critical in these patients because initiation of positive pressure ventilation can reduce right ventricular preload.¹⁴⁴

If the RAP increases sufficiently because of a greatly increased RV afterload, the increase in mean systemic vascular pressure necessary to maintain normal venous return, and therefore CO, may lead to signs of RV failure with no change in the slope of the heart function curves.⁹ If PVR is increased, such volume expansion may increase RV oxygen requirements so that the RV oxygen supply/demand ratio is significantly reduced, leading to RV ischaemia and deterioration of RV performance.^{7,9,145} Such evidence of subendocardial ischaemia and performance has been demonstrated in postmortem specimens from children dying of CHD.^{146–152}

Inotropic support is required in these settings. The choice of agent is important because the pulmonary effects are a major consideration. Isoproterenol, although a pulmonary vasodilator, also reduces systemic vascular resistance and may decrease blood pressure (BP). Such a reduction in BP also

decreases RV perfusion pressure and, with PH, results in RV ischaemia and a fall in CO.⁷ Recent studies on the effects of dopamine and norepinephrine suggest that maintenance or elevation of systemic vascular resistance and MAP may be important in the improvement of RV performance. The reason is that increased contractility, whether due to direct effects of the inotropic agents on the myocardium or secondary to increased BP and improved RV function, can decrease RVEDP and RVEDV and increase CO.^{153,154}

RV function may also be improved by afterload reduction. Children with cyanotic congenital lesions may be polycythaemic. Reduction in haematocrit can reduce PVR and increase CO without demonstrable effect on the PAP. In severely polycythaemic infants and children, benefit may be derived by haemodilution before anaesthesia and surgery.¹⁵⁵⁻¹⁵⁷ In the presence of a reactive component to the increased PVR, a pulmonary vasodilator may be useful. After oxygenation and acid/base status are optimal, sodium nitroprusside¹⁵⁸⁻¹⁶⁰ or nitroglycerin¹⁶¹⁻¹⁶³ can be useful. However, they may decrease preload because of vasodilatation.

Postoperative management of pulmonary hypertension

Postoperative changes in PAP and PVR are relatively common in children with certain types of CHD. Acute rises in PAP in the immediate postoperative period can lead to life-threatening hypoxia secondary to failure of the RV to maintain an adequate output in the face of an acute rise in RV afterload. The sudden onset of cyanosis, hypotension and an abrupt fall in lung compliance are probably secondary to a PH crisis; urgent attempts should be made to influence the reactivity of the pulmonary vascular bed either by changes in ventilation or by the use of vasodilator therapy. Reports on the management of acute rises in PAP concentrate on pharmacological manipulation of the pulmonary vascular bed^{1,67,68,164} with so-called pulmonary vasodilator therapy. However, the tendency has been to consider the pulmonary circulation as a separate entity and overlook the fact that any change in the systemic circulation is automatically reflected in the pulmonary vascular bed.

Our approach emphasizes respiratory management, since the most important influence on PVR is oxygenation. First we identify patients at risk, from preoperative catheterisation, pulmonary

wedge angiography and lung biopsy data.¹⁶⁵ Postoperative management is based on four principles: (1) continuously monitoring and recording PAP; (2) anticipating and, by adjusting positive pressure ventilation, avoiding respiratory events that might trigger PH; (3) ensuring optimum CO by use of volume loading together with inotropes and vasodilator therapy; (4) using pulmonary vasodilator therapy.

Pulmonary artery pressure monitoring

PAP is monitored via a PA line that is placed, under direct vision, into the pulmonary artery and passed directly through the chest wall after weaning from cardiopulmonary bypass. PAP is continuously displayed and stored in the computerized data management system together with systemic pressure values. Thus, we can analyse events and therapeutic manoeuvres that change PAP both prospectively and retrospectively. The measurement of dye dilution CO enables us to derive the PVR

$$\left[\text{PVR} = \frac{(\overline{\text{PAP}} - \text{LA})}{\text{CO}} \times 80 \text{ dynes/cm}^2 \right].$$

If a direct pulmonary artery line has not been placed, bedside catheterisation of the artery in the Intensive Care Unit (ICU) using a Swan-Ganz catheter is feasible,^{166,167} although it carries a much higher incidence of complications in children than in adults. A recent report¹⁶⁸ of Swan-Ganz catheter insertions in 19 paediatric ICU patients showed serious catheter related problems in 23 per cent and significant problems associated with gaining vascular access in 16 per cent of patients.

During such monitoring the object of therapy is not necessarily to achieve normal PAP, as it obviously takes considerable time for the changes in these abnormal pulmonary vessels to regress, but rather to maintain mean PAP at less than 50 per cent of mean systemic artery pressure (SAP).

Respiratory management

GAS EXCHANGE AND PULMONARY HYPERTENSION

Changes in blood gases play a major role in alterations in PVR. The classic studies of Rudolph and Yuan⁵⁴ firmly established the fact that hypoxia ($\text{PaO}_2 < 6.7 \text{ kPa}$, 50 mmHg) caused rapid increases in PVR, an effect that was enhanced by increases in the presence of a hydrogen ion concentration

(pH < 7.4) (Figure 2). While there is little doubt that alveolar hypoxia triggers the pulmonary vasoconstrictor response,^{48,168,169} the exact mechanism remains to be elucidated, although activation of products of arachidonic acid metabolism, in particular the leukotrienes, are currently favoured.^{170,171} The vasoconstrictor response is at the level of the small pulmonary arterioles or alveolar vessels,⁴⁸ but it has not been resolved whether hypoxia causes vasoconstriction by direct effect on pulmonary vessel smooth muscle or indirectly via release of vasodilator or inhibition of vasoconstrictor substances.

The other variable that may profoundly influence pulmonary vascular tone in patients with PH is manipulation of H^+ concentration indirectly by changes in arterial PCO_2 . The effect of hyperventilation and respiratory alkalosis on infants with persistent pulmonary hypertension (PPH) and right-to-left shunting is well documented and is an established method of treatment of PH crises in newborns.^{65,71,172,173} Hyperventilation ($PaCO_2 < 4.0$ kPa, 30 mmHg) accompanied by an appropriate rise in pH (> 7.6) increases PaO_2 and decreases shunting in infants with PPH.⁷¹ The predominant factor in reducing PVR in this instance is the reduction in H^+ rather than in $PaCO_2$, as there is no evidence that CO_2 per se has any direct effect on the pulmonary microvasculature.^{174,175}

INFLUENCE OF LUNG VOLUME AND FUNCTION ON PULMONARY VASCULAR RESISTANCE

The changes in morphometric configuration of the pulmonary vessels in children with CHD^{2,176–181} and infants with PPH^{182,183} have been well documented. The contribution of the lung parenchyma itself in reference to the effects of elevated PAP and increased PBF on lung structure and function has received less emphasis. There is little doubt that diseases associated with increased PBF may have important effects on lung function and mechanics that contribute significantly to hypoxaemia and increased PVR. Hordof *et al.*¹⁴ has described reversible airway obstruction in infants with VSD, which rapidly regressed after closure of the VSD. In infants with CHD there was no difference in lung volumes but lung compliance was significantly lower in infants with increased PBF than those with decreased PBE.¹³ The decrease in compliance was significantly correlated with mean PAP. Where

PBF was increased but PAP was normal, pulmonary compliance was not decreased, suggesting that the pressure level rather than increased blood flow within the lung is responsible for the often dramatic changes in lung compliance seen during PH crises. This is usually accompanied by acute bronchoconstriction, indicated by a sudden increase in airway pressures in mechanically ventilated patients.

There may be an element of peripheral airway obstruction in patients with PH; indeed Fernandez-Bonetti *et al.*¹⁵ documented increased airway resistance in adults with primary PH. It seems likely that this bronchoconstrictor response may be mediated by the leukotrienes C_4 and D_4 , products of the lipoxygenase pathway of arachidonic acid metabolism. These substances, previously known as the slow-reacting substances of anaphylaxis (SRS-A) cause pulmonary oedema. In a recent study of newborn infants, increased levels of leukotrienes were found in the lung lavage fluids of infants with PPH.¹⁸⁴

In addition to changes in lung mechanics, the actual structure and development of the lung parenchyma may be abnormal in children with cardiac defects associated with increased PBF. The specimens from lung biopsies of 39 infants with PH who had undergone surgical correction of a variety of congenital heart defects showed thickening and lymphoid infiltration of alveolar septae, which was referred to as "septitis."¹⁸⁵ This septitis was closely related to the degree of PH, and the investigators concluded that this finding had an important role in the prognosis.

There is also a substantial body of evidence to show that infants with Down syndrome have underlying pulmonary hypoplasia, irrespective of whether they have CHD.¹⁸⁶ Lung biopsy specimens from infants with Down syndrome and CHD compared with those from otherwise normal children with similar congenital heart lesions associated with increased PBF confirmed the alveolar hypoplasia previously reported in infants with Down syndrome. In addition, comparison of the mechanically ventilated patients from the two groups showed the lung tissue from infants with Down syndrome was characterised by interstitial emphysema and distention of peripheral air spaces.¹⁸⁷ Although no information was available on the presence of PH, there can be little doubt that this degree of pulmonary parenchymal disruption would have a significant effect on PVR.

The precise response of patients with pulmonary vascular disease to mechanical ventilation and PEEP is difficult to determine. Hyperventilation reduces PAP, acting via CO_2 and H^+ , especially in the newborn period. However, two other mechanisms may be involved. First, cyclical stretching of the lung results in the release of prostaglandin E_2 , a well known pulmonary vasodilator.^{188,189} also, increased lung volume may decrease PVR. The effect of positive pressure ventilation on the pulmonary vascular bed depends on whether the vessels are juxtaposed to the alveolus or are extra-alveolar.

Extra-alveolar vessels, which include the microvasculature within the lung parenchyma, are directly affected by changes in lung volume, since lung expansion exerts traction on the vessel wall, tending to increase the calibre. Alveolar vessels located in the corner of alveolar walls are exposed directly to changes in alveolar pressure associated with either spontaneous or positive pressure ventilation.¹⁹⁰ With large negative intrapleural pressure, associated with deep inspiration, vascular pressures fall and alveolar pressures can exceed capillary pressures, compressing the vessels and increasing PVR. Similarly, with positive pressure ventilation, alveolar pressure may exceed capillary pressures, causing increased PVR. However, taking into account the differing effects on alveolar and extra-alveolar vessels, it is generally accepted that the net balance of the changes in lung volume causes the PVR to be lowest when lung volume is at or near FRC¹⁹⁰ (Figure 3). The importance of not allowing lung volumes to fall below FRC in patients with pulmonary vascular disease was illustrated by the study of Jenkins *et al.*¹⁹¹ In children who had been on mechanical ventilation after surgical repair of congenital heart defects, PVR rose significantly following weaning from mechanical to spontaneous respiration when FRC fell. This finding was most marked in children whose PVR was already elevated due to their CHD.

The effect of PEEP on PVR seems to be somewhat variable. PEEP enhances prostaglandin generation in the lung, an effect that can be blocked with indomethacin.¹⁹² But no significant increase in PVR was seen when PEEP was applied to the lungs of adults with mitral valve disease and PH.¹⁹³ The routine use of PEEP levels $>5 \text{ cm H}_2\text{O}$ with mechanical ventilation is probably not advisable in patients with pulmonary vascular disease where PH

is compounded by hypoxaemia due to low lung compliance. However, theoretical considerations of the possible adverse effects of PEEP on pulmonary vessels take second place to the positive benefits that PEEP may have in recruiting lost lung volume and correcting hypoxaemia.

Cardiac output and pulmonary hypertension

The pulmonary circulation cannot be considered without reference to the systemic circulation, as changes in CO and LV performance have important effects on PAP and PVR. Any vasodilator used to reduce systemic afterload and improve LV performance will affect the pulmonary circulation either directly through the pulmonary microvasculature or indirectly by reducing RV afterload. Similarly, inotropic drugs used to augment LV contractility also have an inotropic effect on the RV.

Certain misconceptions exist about the effect of vasoactive drugs, particularly inotropes, in PH. concern centres around the potential for these drugs to further constrict the already abnormal pulmonary vessels. The pulmonary microcirculation is invested with both α and β receptors¹⁹⁴ and obviously it would be foolhardy to use an inotrope with pronounced α -agonist properties to augment CO. However, there is a mistaken belief that dopamine is contraindicated in PH because it may increase PVR. This misconception is based on an animal study, performed with an isolated pulmonary circulation, that examined the effect of this drug on pulmonary haemodynamics without reference to its effect on the systemic circulation.¹⁹⁵

It is axiomatic that the normal response to inotropic support of the failing LV is a rise in CO and systemic pressure, with PAP rising in tandem. More important is the question of whether the ratios between the pressures remain the same. In our experience the PVR actually falls when CO improves even in patients with PH, since a slight increase in PAP in the normal pulmonary vascular bed decreases PVR (Figure 4). Even patients with significant narrowing of the pulmonary vessels retain the capacity to either recruit vessels in areas of the lung that had been underperfused or increase PBF by distending abnormal vessels. Also, since PVR is derived from the formula

$$\text{PVR} = \frac{(\overline{\text{PAP}} - \text{LAP})}{\text{CO}} \times 80,$$

FIGURE 4 The effect of increasing PAP and pulmonary venous pressure on PVR. Note that with a rise in PAP, PVR actually falls as non-perfused vessels are recruited. (Reproduced by permission of the author¹⁸³ and Williams and Wilkins.)

any drug that increases CO will reduce PVR, unless its α -agonist properties cause active pulmonary vasoconstriction. A study of dopamine in adult patients with PH showed increases in CO and both SAP and PAP, but at the same time there was no change in PVR.¹⁹⁶

There is limited published information of the effect of dopamine in children with PH. A study of the effect of dopamine and nitroprusside on haemodynamics in 28 children after repair of CHD found that CO increased but PVR did not change with a dose of $8 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ of dopamine.¹⁹⁷ Five patients with postoperative PH showed no increase in PVR while CO increased. A combination of dopamine and nitroprusside gave an even more favourable outcome. This benign effect of dopamine on the pulmonary vascular bed has been confirmed elsewhere.^{198,199}

Vasodilators

The value of "pulmonary" vasodilators in PH is debatable. Most of our information about these drugs comes from the treatment of adults with primary PH and infants with PPH. Most of the adult studies consist of small series with limited haemo-

dynamic data and little information regarding potential long-term benefit. Vasodilators that have been useful are hydralazine,^{200–205} isoproterenol,^{201,206–208} nifedipine,^{204,205,209,210} nitroprusside and nitroglycerin.²⁰³ The number of vasodilators that have been tried attests to the fact that there is no genuine pulmonary vasodilator (i.e., a drug that consistently dilates the pulmonary vascular bed in preference to the systemic circulation), except oxygen.

Of the drugs most commonly used to treat PH in children, tolazoline is perhaps best known. Although claims have been advanced for its selective action on the pulmonary vascular bed, particularly in infants with PPH, it also has a pronounced systemic effect. As well as being a vasodilator, tolazoline has sympathomimetic properties,²¹¹ which frequently result in increased CO. For these reasons its effect as a selective pulmonary vasodilator is often variable. The only reports of its use in infants with PPH are small series with unpredictable responses. Both Peckham and Fox⁶⁸ and Drummond *et al.*⁷¹ report small numbers of favourable responders in their series, as well as infants whose condition deteriorated with the use of the drug. This, together with the concern that the drug causes gastrointestinal haemorrhage, cautions against its overenthusiastic use.

Of the more time-honoured pulmonary vasodilators, substantial claims were advanced for the benefit of hydralazine for primary PH,²⁰⁰ which subsequently proved to be unwarranted.²⁰² Nitroprusside and nitroglycerin have substantial effects on the systemic circulation and the response of the pulmonary vasculature is very variable.²⁰³

Considerable recent interest has centred on the calcium channel blocker nifedipine, since some encouraging reports of its use in the treatment of primary PH.^{204,209,210,212,213} As with other vasodilators, response to its use in primary PH is somewhat variable, but the drug may be of more benefit in patients with PH and cor pulmonale secondary to chronic lung disease.^{214,215} The patients in both these studies showed significant improvement in exercise tolerance and increased CO without much change in PAP and PVR. Although in both studies nifedipine had little or no effect on the pulmonary vascular bed the vasodilator properties of the drug did bring about an overall improvement in cardiac performance and symptoms.

FIGURE 5 Protocol for the management of patients at risk for developing postoperative PH following correction of CHD. IPPV = intermittent positive pressure ventilation, $\overline{PAP}$ = mean pulmonary artery pressure, CPAP = continuous positive airway pressure, N = normal.

Protocol for intensive care unit management of postoperative pulmonary hypertension

Patients at risk for the development of postoperative PH are identified on the basis of preoperative haemodynamics. A pulmonary artery line is placed at the completion of bypass and management is designed to maintain $\overline{PAP} \leq 50$ per cent of SAP. The patient is paralysed with metocurine and electively hyperventilated so that PaCO_2 is 4.0–4.7 kPa (30–35 mmHg) for the first 12 hours. If $\overline{PAP}$ remains <50 per cent of SAP at the end of this period, the muscle relaxant is discontinued and the patient is weaned gradually to continuous positive airway pressure (CPAP) using intermittent mandatory ventilation (IMV), as long as PaO_2 and PaCO_2 are normal (Figure 5). If there is persistent elevation in $\overline{PAP}$ during this period, as distinct from the normal brief rises seen with coughing, suction, etc., muscle paralysis and hyperventilation are re-intro-

duced for a further 12 hours before weaning is attempted again. If this mild degree of hyperventilation fails to control $\overline{PAP}$, the PaCO_2 is reduced further to 3.3–4.0 kPa (25–30 mmHg) for the next 12 hours. We adopt this approach since manipulation of PaCO_2 and H^+ ion is the simplest and most consistent method of reducing $\overline{PAP}$ while at the same time causing the least change in haemodynamics. If this strategy proves successful in controlling $\overline{PAP}$, the patient is weaned in steps, first by allowing the PaCO_2 to rise to 4.0–4.7 kPa (30–35 mmHg) and then by progressing to IMV and CPAP.

In the rare instances where the adjustments in positive pressure ventilation and CO fail to maintain $\overline{PAP} < 50$ per cent of SAP, we resort to pharmacological agents in an attempt to reduce $\overline{PAP}$. The drugs we have tried in this situation are listed in Table II. The length of the list testifies to the somewhat unpredictable response.

TABLE II Pharmacologic agents used to reduce pulmonary artery pressure

Drug	Dosage	Comments
Tolazoline	1 ml·kg ⁻¹ by i.v. bolus 1 mg·kg ⁻¹ ·hour ⁻¹ by infusion	Antacid therapy is required because of gastrointestinal haemorrhage.
Isoproterenol	0.05–0.1 µg·kg ⁻¹ ·min ⁻¹	Marked effect on B ₁ receptors may cause unacceptable tachycardia. May cause a drop in systemic pressure by effect on B ₂ receptors.
Salbutamol	0.1–1.0 µg·kg ⁻¹ ·min ⁻¹	More B ₂ selective than isoproterenol but tachycardia may still be a problem. May also cause hypokalaemia.
Nifedipine	0.1–0.5 µg·kg ⁻¹ ·min ⁻¹	The IV preparation is light sensitive. Marked effects on systemic circulation.
Nitroglycerin	0.5–1.0 µg·kg ⁻¹ ·min ⁻¹	Major effects on preload to LV and RV.
Nitroprusside	0.5–8.0 µg·kg ⁻¹ ·min ⁻¹	Acts mainly as an afterload reducer with some effect on preload.
Hydralazine	0.2–0.5 mg·kg ⁻¹ by i.v. bolus	Not used as an IV infusion; therefore, dose is difficult to titrate.
Phenoxybenzamine	1 mg·kg ⁻¹ by i.v. loading dose 0.5–2 mg·kg ⁻¹ ·day ⁻¹ maintenance	Potent vasodilator useful in situations where vasodilator therapy is to continue for some time.

FIGURE 6 The effect of hyperventilation on PAP and MAP in a 6-year-old child with postoperative PH. With a reduction of PaCO₂ from 5.3–3.9 kPa (40–29 mmHg) and an appropriate rise in pH, PAP falls in relation to SAP. PAP rises again when PaCO₂ is allowed to return to normal.

The principal problem with all these drugs is the lack of specificity, since all have pronounced systemic effects. No one drug has proved to be consistently superior in all circumstances and the only approach that can be advocated is to try each in turn with the expectation of identifying the vasodilator that will reduce PAP more than SAP without reducing CO in each patient.

Perhaps the best method to control PAP is a combination of mild hyperventilation and vasodilatory therapy, as was demonstrated in a child who developed postoperative PH. Initially the PAP fell in response to hyperventilation, but it then in-

FIGURE 7 When the manoeuvre shown in Figure 6 is repeated after a loading dose of phenoxybenzamine 0.5 mg·kg⁻¹, the rebound rise in PAP is blunted when PaCO₂ and pH return to normal (data from Dr. P. Swan).

creased when hyperventilation was discontinued (Figure 6). When the manoeuvre was repeated after loading with phenoxybenzamine, the rebound rise in PAP after discontinuing hyperventilation was blunted (Figure 7).

Conclusion

Acute rises in PAP are increasingly recognised as a cause of deteriorating condition and even death in

children with abnormally reactive pulmonary vasculature secondary to CHD. With increased awareness of the problem, we can identify patients at risk preoperatively so that with careful monitoring and management these rises may be prevented or at least kept at reasonable levels.

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