

## Vasodilators in pulmonary hypertension

The pulmonary and systemic circulations differ in two important respects. Firstly, the former is a low pressure system and, secondly, it responds to hypoxia by vasoconstriction rather than vasodilatation. The normal mean pulmonary artery pressure is about 14 mm Hg, a pressure that is maintained even on exercise. Cardiac output can rise up to four fold but, because of vascular recruitment, the pressure remains low. This ensures that the perfusion pressure of the lungs also remains low and that the thin walled right ventricle is not stressed. Hypoxia causes pulmonary vasoconstriction. This mechanism is thought to be responsible for maintaining the closed fetal circulation before birth and for matching perfusion to ventilation after birth. In the face of generalised alveolar hypoxia such as occurs at altitude or with lung disease, however, this adaptive mechanism is malign and the generalised vasoconstriction results in hypertension. Pulmonary hypertension is defined as a mean pulmonary artery pressure >25 mm Hg at rest, or 30 mm Hg on exercise, in the presence of a cardiac output of <5 l/min. The disease occurs most commonly in response to hypoxic lung disease, but can also accompany thromboembolism, left to right cardiac shunts, and living at high altitude. Another rare disease, primary or unexplained pulmonary hypertension, occurs particularly in young women. Until recently the prognosis of this condition was very poor, but the use of vasodilators and lung and heart-lung transplantation have improved this somewhat. There is still no evidence that vasodilators other than oxygen have improved the prognosis of secondary pulmonary hypertension, but there are good theoretical reasons why the morbidity of pulmonary hypertension due to chronic hypoxic lung disease and other forms of secondary pulmonary hypertension might improve if a selective pulmonary vasodilator could be developed.

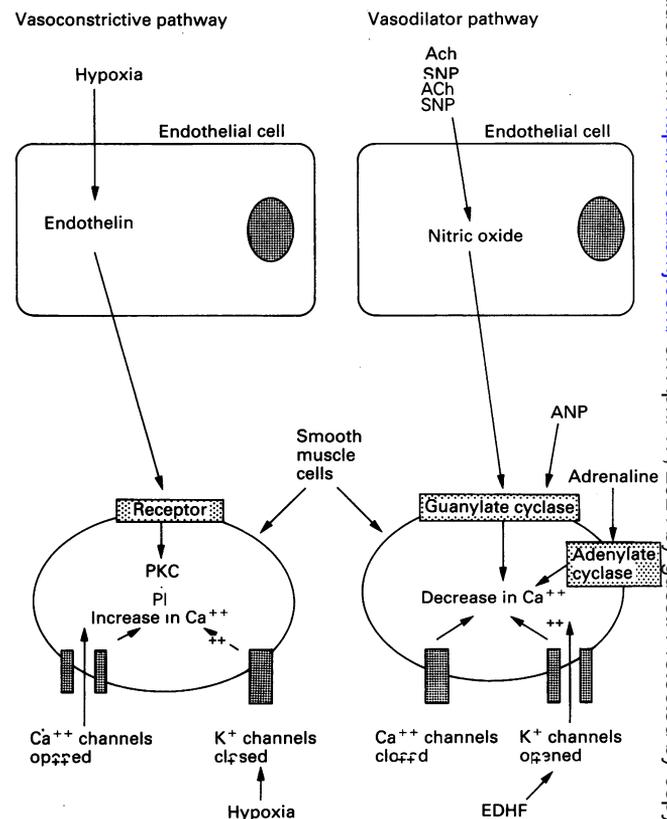
Thus, pulmonary hypertension occurring in association with chronic airflow obstruction is an independent predictor of mortality.<sup>1</sup> The pulmonary artery pressures measured in patients with chronic lung disease are not particularly high (about 40 mm Hg), but this pressure rises on exercise<sup>2</sup> and during sleep when alveolar ventilation is diminished further.<sup>3</sup> The wellbeing of the patient depends on tissue oxygenation, which in turn depends on the heart and lungs working in concert. If the lungs are afflicted by irreversible disease, improving cardiac function is the only way to improve oxygen delivery. This really means that right ventricular function must be favourably influenced, as it has now been shown convincingly that the right ventricle functions poorly in chronic airflow obstruction, even when subjected to modest increases in pressure.

### Normal pulmonary vascular control

The low pulmonary artery pressure sustained in a normal subject depends on two components: firstly, the high compliance of the major pulmonary blood vessels and, secondly, the state of tone of the peripheral precapillary resistance vessels. As in the systemic circulation, it is likely that systolic pressure is a function of right ventricular stroke volume and major vessel compliance, while diastolic pressure depends on peripheral pulmonary vascular resistance. In pulmonary hypertension there is thickening

of the major vessels and a narrowing of the peripheral vessels. Both features could cause pulmonary hypertension, particularly when cardiac output is raised on exercise. Despite intensive research carried out over many years, the factors that maintain low pulmonary vascular tone and the causes of increased tone in the face of, for example, alveolar hypoxia remain enigmatic. It seems increasingly likely, however, that the state of tone of vascular smooth muscle depends on endothelial factors. Endothelial cell derived vasoconstrictors include endothelin-1, angiotensin II, and platelet derived growth factor. Endothelial cell derived dilators include prostacyclin, endothelium derived relaxing factor (EDRF, now believed to be nitric oxide) and, most recently, endothelium derived hyperpolarising factor (EDHF).<sup>4</sup> The interaction between these mediators in the maintenance of normal low vascular tone, the vasodilatory response to increased cardiac output, and the vasoconstrictive response to hypoxia remain subjects of intense research effort and speculation.

The final common pathway of both vasodilators and vasoconstrictors is considered in the figure. Contraction requires an increase in the concentration of free cytosolic calcium. This may occur either because of the opening of calcium channels permitting calcium to enter the smooth muscle cell, or the release of bound calcium into the cytoplasm. Vasodilators must oppose this system and



Cellular control of pulmonary vascular tone and mechanisms that could be targets for vasoactive agents. ACh—acetylcholine; SNP—sodium nitroprusside; ANP—atrial natriuretic peptide; PI—phosphoinositide; EDHF—endothelium derived hyperpolarising factor.

work either by influencing calcium channels or by other mechanisms to reduce cytosolic calcium. This may include a primary effect on the cellular potassium channels which, in turn, control calcium flux. It is clear that there are several possible mechanisms whereby vasoactive agents could cause contraction or dilatation of pulmonary vessels, either by acting directly on the smooth muscle itself or via the endothelium. Even when they act directly it is likely that the endothelium, if intact, modulates their effects.

### Hypoxic pulmonary vasoconstriction

Hypoxic vasoconstriction is unique to the pulmonary circulation and has remained an object of interest to physiologists and clinicians since it was first described by Von Euler in 1946 in the anaesthetised cat.<sup>5</sup> The continual interest by clinicians in hypoxic pulmonary vasoconstriction results from the role of the reflex in the physiological and pathophysiological control of the circulation, whereby it shunts blood away from the unventilated fetal lung and matches ventilation to perfusion in the adult lung. It is probably significant in the development of pulmonary hypertension in patients with hypoxic lung disease and has provided great interest to physiologists who wish to understand the nature of the oxygen sensor and how low levels of oxygen are transduced to a vasoconstrictive response.<sup>6</sup>

Hypoxic pulmonary vasoconstriction does not depend on the substantial sympathetic innervation of the pulmonary vasculature because it occurs in the isolated lung and in the isolated pulmonary vascular ring. It does seem to depend, however, on endothelial control, and several pieces of evidence point to this conclusion. Firstly, chronic hypoxia impairs the release of EDRF (nitric oxide)<sup>7</sup> and, secondly, nitric oxide reverses acute hypoxic vasoconstriction.<sup>8</sup> Thirdly, inhibitors of nitric oxide synthesis appear to augment hypoxic pulmonary vasoconstriction.<sup>9</sup> These studies have all suggested that a reduction in nitric oxide release, caused either by damage to the endothelium or by inhibition of nitric oxide synthesis, modulates the vascular response to hypoxia. The endothelium could also play a part by secreting a constrictor factor in response to hypoxia. There is some evidence that this is true, since endothelial removal appears to block hypoxic vasoconstriction in human pulmonary vascular rings,<sup>10</sup> and blockade of the receptors for the endothelium derived constricting factor endothelin-1 appears to diminish the hypoxic vascular response (T Stelzner, personal communication). It therefore seems likely that the endothelium at least modulates, if not controls, the vasoconstrictive response to hypoxia.

A further mechanism of vascular control has recently been discovered and is likely to be very important. It has been claimed that potassium channels represent the hypoxia sensor for pulmonary vascular smooth muscle cells by controlling the state of depolarisation of the membrane.<sup>11</sup> It is postulated that hypoxia closes potassium channels causing depolarisation, thereby opening calcium channels and causing increased cytosolic calcium and vasoconstriction. This theory is supported by work with patch clamping on cultured vascular smooth muscle cells from the pulmonary artery and mesentery<sup>12</sup> which showed that hypoxia decreased outward potassium current and increased inward calcium current in the pulmonary artery but not in the mesenteric blood vessels. This effect was independent of internal or external calcium concentrations. Hypoxic contraction of the pulmonary artery was blocked by the potassium channel opener cromakalin and enhanced by the potassium

channel closer glibenclamide. At last it appears that a mechanism has been found to explain why the pulmonary vascular response to hypoxia (vasoconstriction) differs from the systemic vascular response (vasodilatation). Manipulation of potassium channels may provide our best chance of developing a selective pulmonary vasodilator.

### Theoretical aspects of vasodilator therapy in the pulmonary circulation

When they are developed, selective pulmonary vasodilators should represent an enormous therapeutic advance because most forms of cardiorespiratory disease result in pulmonary hypertension, which further compromises cardiac function. At present the only generally available selective pulmonary vasodilator is oxygen. The first priority of any clinician dealing with a patient with pulmonary hypertension should therefore be to ensure that alveolar oxygen concentrations are optimised, if necessary by using domiciliary oxygen therapy. The MRC and NOTT studies<sup>13,14</sup> both showed that patients given continuous oxygen for more than 15 hours per day survived longer than those given oxygen for a shorter period. If the oxygen was given for 24 hours, the prognosis was even better. Whether or not these positive results are attributable to improvements in pulmonary vascular resistance or some other effect of oxygen remains uncertain. The MRC trial, for example, showed that survival improved in those patients receiving oxygen even if pulmonary vascular resistance remained unchanged. This led many clinicians to conclude that the effects of oxygen on the pulmonary circulation were unimportant.

There is, however, more evidence that domiciliary oxygen can lower pulmonary vascular resistance when given on a long term basis<sup>15</sup> by improving cardiac function and oxygen delivery. The provision of domiciliary oxygen should therefore remain a priority for all patients with chronic airflow obstruction and severe hypoxaemia. It would clearly be an advantage if, in addition to oxygen therapy, other selective pulmonary vasodilators were available. Areas of promise include drugs that open potassium channels,<sup>12</sup> adenosine,<sup>16</sup> serotonin antagonists,<sup>17</sup> and nitric oxide. Nitric oxide is not a specific pulmonary vasodilator but, because it is a gas and is therefore inhaled, its first site of action is the pulmonary vasculature. It has a very short circulating half life as it becomes bound to haemoglobin so it does not reach the systemic circulation. Nitric oxide is likely to become much more widely used. In animal models it has been shown to reverse pulmonary vasoconstriction due to heparin protamine or hypoxia.<sup>8</sup> It has also been used in humans with pulmonary hypertension. Studies in adults show that it selectively dilates the pulmonary circulation<sup>18</sup> and in children with neonatal pulmonary hypertension it can reverse pulmonary hypertension and may provide permanent benefit.<sup>19</sup>

When assessing any vasodilator for its effects on the pulmonary circulation strict criteria must be applied, which currently necessitates the insertion of a balloon tipped, flow directed pulmonary artery catheter of the thermodilution type and a radial arterial line for the monitoring of systemic blood pressure and arterial gas tensions. The danger of using vasodilators in pulmonary hypertension is catastrophic circulatory collapse which can only be prevented if there is constant and thorough monitoring of the central circulation during the procedures. A vasodilator can be considered effective if there is a fall in both pulmonary artery pressure and pulmonary vascular resistance (pulmonary artery pressure —

pulmonary artery wedge pressure/cardiac output.)<sup>20</sup> These criteria are very restrictive because they imply no effect of a vasodilator in the more common situation in which cardiac output rises without a fall in pulmonary artery pressure. It is difficult to see how the increased cardiac output could be accommodated in the pulmonary circulation without a rise in pulmonary artery pressure in the absence of pulmonary vasodilatation, but there is no doubt, however, that it is preferable to see a fall in both pulmonary artery pressure and pulmonary vascular resistance. This is because, if pulmonary artery pressure remains the same, the increase in cardiac output must increase right ventricular work. Most workers would regard as successful a trial of vasodilators in patients in whom there was a more than 30% improvement in pulmonary vascular resistance. Nonetheless, survivors have been shown to be those in whom this decrease in resistance was also accompanied by a fall in pulmonary artery pressure.<sup>21</sup>

### Use of vasodilators in primary pulmonary hypertension

There is now convincing evidence that vasodilators improve the long term survival in patients with primary pulmonary hypertension. They may also act as a bridge between diagnosis and heart-lung or lung transplantation. These patients require careful assessment in units specialising in pulmonary circulatory disorders. All causes of secondary pulmonary hypertension such as primary lung disease, thromboembolism, intracardiac shunt, and pulmonary vasculitis are first excluded. Secondly, an acute vasodilator study, usually with intravenous prostacyclin is performed. During this study patients must be monitored as described above. If a positive vasodilator response occurs, either continuous intravenous prostacyclin or, more commonly, high dose calcium antagonists can be administered. Continuous intravenous prostacyclin for primary pulmonary hypertension was first described by Higgenbottam *et al*<sup>22</sup> but there have been several subsequent trials, including a large study, which showed the success of this therapy.<sup>23</sup> Continuous prostacyclin is, however, extremely expensive, costing approximately £200 000 per year and is used rarely. The mainstay of vasodilator therapy is therefore high dose calcium antagonists, titrated carefully to prevent fatal circulatory collapse.<sup>24</sup> Nifedipine (30–120 mg per day) and diltiazem (120–720 mg per day) have both been given successfully. Verapamil is not recommended because of its negative inotropic effects. The major adverse effects of the calcium channel antagonists are decreased cardiac output due to negative inotropic effects, diminished systemic blood pressure, and salt and water retention.

### Use of vasodilators in secondary pulmonary hypertension

#### PULMONARY THROMBOEMBOLISM

It is widely believed that thromboembolism represents a fixed obstruction to the pulmonary circulation, but evidence suggests that pulmonary vascular tone is increased in these patients.<sup>25 26</sup> The optimal treatment is thromboendarterectomy but, if this is impossible, a vasodilator trial may provide benefit. There is evidence that pulmonary vasodilatation can be induced with prostacyclin in pulmonary thromboembolic disease but the effects of long term vasodilator treatment in this condition are unknown. Patients need full assessment and a period of anticoagulation. If this fails and endarterectomy is impossible, a formal acute vasodilator study using prostacyclin can be considered.

#### PULMONARY VASCULAR DISORDERS ASSOCIATED WITH SYSTEMIC DISEASE

The most important disease in which a pulmonary vasculitis seems to dominate is systemic sclerosis. In this condition lung function may remain only minimally disturbed and the patient's breathlessness is due to pulmonary hypertension. It has been shown recently that these patients have a form of Raynaud's phenomenon affecting the pulmonary circulation.<sup>27</sup>

It has also been shown that, in contrast to patients with primary pulmonary hypertension, the vasculature appears to dilate with increases in inspired oxygen.<sup>28</sup> These two findings suggest that the circulation may be labile in systemic sclerosis and work is now being done to determine whether the wellbeing of patients can be improved with vasodilator therapy.

### Chronic hypoxic lung disease

It is well known that chronic hypoxic lung disease, particularly when associated with type II respiratory failure, is accompanied by pulmonary hypertension. There is evidence that this circulatory abnormality is particularly important in those patients in whom fixed airflow obstruction precludes adequate oxygenation. There have consequently been many studies in this condition using a wide variety of vasodilators including nifedipine,<sup>29 30</sup> hydralazine,<sup>31</sup> pirbuterol,<sup>32 33</sup> verapamil,<sup>34</sup> and methyl-dopa.<sup>35</sup> In most of these studies a modest vasodilator effect was observed, sometimes with an improvement in oxygen delivery, but there has been no long term improvement in pulmonary vascular haemodynamics. At present there is therefore no reason to perform further vasodilator studies in this condition using non-specific agents. Until a selective vasodilator is available, clinicians should concentrate on improving lung function and reversing hypoxia.

The angiotensin converting enzyme inhibitors may be of greater interest because there is considerable evidence that the fluid retention that characterises hypoxic lung disease is due in part to renal dysfunction. Since angiotensin converting enzyme inhibitors reverse the effect of the renin angiotensin system and are also vasodilators, they may be of value, but this remains unproven.<sup>36</sup>

### Conclusion

In primary pulmonary hypertension there is now good evidence that vasodilator therapy can improve prognosis and act as a bridge to heart-lung or lung transplantation. Despite considerable evidence that pulmonary hypertension and right ventricular dysfunction are important in the morbidity associated with chronic hypoxic lung disease, there is currently no means of improving these haemodynamic variables. If selective pulmonary vasodilators become available in the future they are likely to have widespread use in both cardiac and respiratory medicine.

ANDREW PEACOCK  
Pulmonary Vascular Unit,  
Department of Respiratory Medicine,  
Western Infirmary,  
Glasgow G11 6NT

Reprint requests to: Dr A Peacock

- Cooper R, Ghali J, Simmons BE, Castaner A. Elevated pulmonary artery pressure—an independent predictor of mortality. *Chest* 1991;**99**: 112–20.
- Light RW, Mintz HM, Linden GS, Brown SE. Haemodynamics of patients with severe chronic obstructive pulmonary disease during progressive upright exercise. *Am Rev Respir Dis* 1984;**130**:391–5.
- Fletcher EC, Levin DC. Cardiopulmonary haemodynamics during sleep

- in subjects with chronic obstructive pulmonary disease. *Chest* 1984; **85**:6-14.
- 4 Chen G, Suzuki H, Weston AH. Acetylcholine releases endothelium-derived hyperpolarising factor and EDRF from rat blood vessels. *Br J Pharmacol* 1988; **95**:1165-74.
  - 5 Von Euler US, Liljestrand G. Observation on the pulmonary arterial blood pressure in the cat. *Acta Physiol Scand* 1946; **12**:301-20.
  - 6 Voelkel NF. Mechanisms of hypoxic pulmonary vasoconstriction. *Am Rev Respir Dis* 1986; **133**:1186-95.
  - 7 Adnot S, Raffestin B, Eddahibi S, Braquet P, Chabrier PE. Loss of endothelin-dependent relaxant activity in the pulmonary circulation of rats exposed to chronic hypoxia. *J Clin Invest* 1991; **87**:155-62.
  - 8 Frostell C, Fratacci MD, Wain JC, Jones R, Zapol WM. Inhaled nitric oxide, a selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. *Circulation* 1991; **83**:2038-47.
  - 9 Robertson BE, Warm JB, Nye PC. Inhibition of nitric oxide synthesis potentiates hypoxic vasoconstriction in isolated rat lungs. *Exp Physiol* 1990; **75**:255-7.
  - 10 Demiryrek T, Wadsworth RM, Kane AK, Peacock AJ. The role of endothelin in hypoxic constriction of human pulmonary artery rings. *Am Rev Respir Dis* 1993; **147**:283-90.
  - 11 Albarwani S, Xia N, Nye PCG. Excitation of small isolated pulmonary blood vessels from the rat by 4-aminopyridine and hypoxia. *J Physiol* 1993; **467**:46P.
  - 12 Yuan XJ, Goldman WF, Tod ML, Rubin LJ, Blaustein MP. Contrasting effects of hypoxia and potassium currents in cultured pulmonary and mesenteric artery cells. *Am Rev Respir Dis* 1992; **145**:A227.
  - 13 Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet* 1981; **i**:681-6.
  - 14 Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxaemic chronic obstructive lung disease. *Ann Intern Med* 1980; **93**:391-8.
  - 15 Weitzenblum E, Sautegau A, Ehrhart M, Mammosser M, Pelletier A. Long-term oxygen therapy can reverse the progression of pulmonary hypertension in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1985; **131**:493-8.
  - 16 Morgan JM, McCormack DG, Griffiths MJ, Morgan CJ, Barnes PJ, Evans TW. Adenosine as a vasodilator in primary pulmonary hypertension. *Circulation* 1991; **84**:1145-9.
  - 17 Templeton AGB, Clayton RA, Macyn tyre PD, Hillis WS, Peacock AJ. Selective effect of sumatriptan on bovine pulmonary arteries. *Br J Pharmacol* 1993; **108**:249P.
  - 18 Pepke-Zaba J, Higgenbottam TW, Dink-Xuan AT, Stone D, Wallwork J. Inhaled nitric oxide as a cause of selective pulmonary vasodilation in pulmonary hypertension. *Lancet* 1991; **338**:1173-4.
  - 19 Kinsella JO, Neish SR, Shaffer E, Abman SH. Low dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn. *Lancet* 1992; **340**:819-20.
  - 20 Rich S, Martinez J, Lam W, Levy PS, Rosen KM. Reassessment of the effects of vasodilator drugs in primary pulmonary hypertension: guidelines for determining a pulmonary vasodilator response. *Am Heart J* 1983; **105**:119-27.
  - 21 Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992; **327**:76-81.
  - 22 Higgenbottam TW, Wells F, Wheeldon D, Wallwork J. Long-term treatment of primary pulmonary hypertension with continuous intravenous epoprostenol (prostacyclin). *Lancet* 1984; **ii**:1046-7.
  - 23 Rubin LJ, Mendoza J, Hood M, McGoon M, Barst R, William WR, et al. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol): results of a randomized trial. *Ann Intern Med* 1990; **112**:485-91.
  - 24 Rich S, Kaufmann E. High dose titration of calcium channel blocking agents for primary pulmonary hypertension: guidelines for short-term drug testing. *J Am Coll Cardiol* 1991; **18**:1323-7.
  - 25 Widimsky J. Pressure, flow and volume changes of the lesser circulation during pulmonary artery occlusion in healthy subjects and patients with pulmonary hypertension. *Prog Resp Res* 1970; **5**:224-36.
  - 26 Dantzker DR, Bower JS. Partial reversibility of chronic pulmonary hypertension caused by pulmonary thromboembolic disease. *Am Rev Respir Dis* 1981; **124**:129-31.
  - 27 Vergnon J, Barthelemy J, Riffat J, Boissier C, Claudy A, Emonot A. Raynaud's phenomenon of the lung. A reality both in primary and secondary Raynaud syndrome. *Chest* 1992; **101**:1312-7.
  - 28 Morgan J, Griffiths M, du Bois RM, Evans TW. Hypoxic pulmonary vasoconstriction in systemic sclerosis and primary pulmonary hypertension. *Chest* 1991; **99**:551-6.
  - 29 Simonneau G, Escourou P, Duroux P, Lockhart A. Inhibition of hypoxic pulmonary vasoconstriction by nifedipine. *N Engl J Med* 1981; **304**:1582-5.
  - 30 Muramoto A, Caldwell J, Albert RK, Lakshminarayan S, Butler J. Nifedipine dilates the pulmonary vasculature without producing symptomatic systemic hypotension in upright resting and exercising patients with pulmonary hypertension secondary to chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1985; **132**:963-6.
  - 31 Keller CA, Shepard JW, Chun DS, Dolan GF, Vasquez P, Minh V. Effects of hydralazine on haemodynamics, ventilation and gas exchange in patients with chronic obstructive pulmonary disease and pulmonary hypertension. *Am Rev Respir Dis* 1984; **130**:606-11.
  - 32 Peacock AJ, Busst C, Dawkins K, Denison DM. Response of pulmonary circulation to oral pirbuterol in chronic airflow obstruction. *BMJ* 1983; **287**:1178-80.
  - 33 Winter RJD, Langford JA, Rudd RM. Effects of oral and inhaled salbutamol and oral pirbuterol on right and left ventricular function in chronic bronchitis. *BMJ* 1984; **288**:824-5.
  - 34 Brown SE, Linden GS, King RR, Blair GP, Stansbury DW, Light RW. Effects of verapamil on pulmonary haemodynamics during hypoxaemia, at rest and during exercise in patients with chronic obstructive pulmonary disease. *Thorax* 1983; **38**:840-4.
  - 35 Evans TW, Waterhouse J, Finlay M, Suggett AJ, Howard P. The effects of long term methylodopa in patients with hypoxic cor pulmonale. *Br J Dis Chest* 1988; **82**:405-13.
  - 36 Peacock AJ, Matthews A. Transpulmonary angiotensin II formation and pulmonary haemodynamics in stable hypoxic lung disease: the effect of captopril. *Respir Med* 1992; **86**:21-6.