

endobronchial involvement in 12 out of 16 patients (75%) with intrathoracic tuberculous lymphadenopathy who underwent bronchoscopy. In our study bronchoscopy yielded the diagnosis in only nine out of 17 patients (53%). This lower success may be explained by the absence of parenchymal disease in all our patients. We found a very high diagnostic yield from mucosal biopsy samples taken from the site of ulcerating granuloma and a 45% success rate from transbronchial or transcarinal aspiration in the presence of tracheal, carinal, or bronchial displacement by enlarged lymph nodes. This high yield may relate to our use of wide bore needles with the rigid bronchoscope.

The presence of mediastinal lymphadenopathy, a positive PPD skin test, and a chest radiograph suggesting a parenchymal lesion are all highly suggestive of the diagnosis of intrathoracic lymphadenitis. However, the absence of any parenchymal lesions and a high population prevalence of PPD skin positivity, such as is found in Turkey, make a

definitive diagnosis of intrathoracic lymphadenitis difficult. Our study indicated that rigid bronchoscopy with appropriate sampling can give the diagnosis in about half of such cases, and direct lymph node biopsy, which may require mediastinoscopy or thoracotomy, diagnosed the remaining patients.

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Impairment of endothelium-dependent pulmonary vasodilation in patients with primary pulmonary hypertension

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Background – Pulmonary vascular tone may be modulated by endothelium-derived vasoactive mediators. Endothelial dysfunction is thought to occur in primary pulmonary hypertension. The aim of this study was to evaluate the vascular responses of patients with severe primary pulmonary hypertension to endothelium-dependent vasodilators (for example, substance P) and non-endothelium-dependent vasodilators (for example, adenosine).

Methods – Six patients with primary pulmonary hypertension (mean (SE) systolic, diastolic, and pulmonary artery pressures 91.1 (7), 45.2 (3), and 62 (4.2) mm Hg, respectively, and baseline total pulmonary vascular resistance (TPVR) 1949 (164) dynes·s·cm⁻⁵) underwent sequential infusions of substance P (5–100 pmol/min) and adenosine (5–50 µg/kg/min) in random order. Pulmonary and systemic haemodynamics were monitored by indwelling radial and pulmonary arterial catheters.

Results – Substance P caused a marked fall in systemic vascular resistance (SVR) but minimal pulmonary vasodilation

(mean maximal percentage change from baseline in TPVR:SVR ratio 27.85 (6.5)%, $p < 0.01$). Adenosine caused TPVR to fall, but resulted in no change in SVR (mean maximum percentage change from baseline in TPVR:SVR ratio –9.85 (3.5)%, $p < 0.05$).

Conclusion – Endothelium-dependent vasodilation is deficient in the pulmonary circulation of patients with primary pulmonary hypertension and may contribute to the abnormalities of pulmonary vascular tone and reactivity seen in that condition.

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Keywords: endothelium, primary pulmonary hypertension.

Primary pulmonary hypertension is rare, occurring most frequently in women in their third and fourth decades, and with a mean survival time after onset of symptoms of only 2–3 years.¹ Early studies speculated that vasoconstriction was a major component of the increase in pulmonary vascular resistance (PVR) that characterises the condition. However, more recently

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interest has focused on the pulmonary vascular endothelium, particularly since the discovery that endothelial cells release various vasoactive factors which may have effects specific to the lung. Thus, the endothelium-derived vasodilator nitric oxide (NO) is known in experimental animals to modulate hypoxic pulmonary vasoconstriction,² and growth factors and cytokines derived from the endothelium can induce the underlying smooth muscle cells to migrate and replicate. Such observations support the hypothesis that pulmonary endothelial dysfunction and abnormal vascular responsiveness may be implicated in the pathogenesis of pulmonary hypertension.³

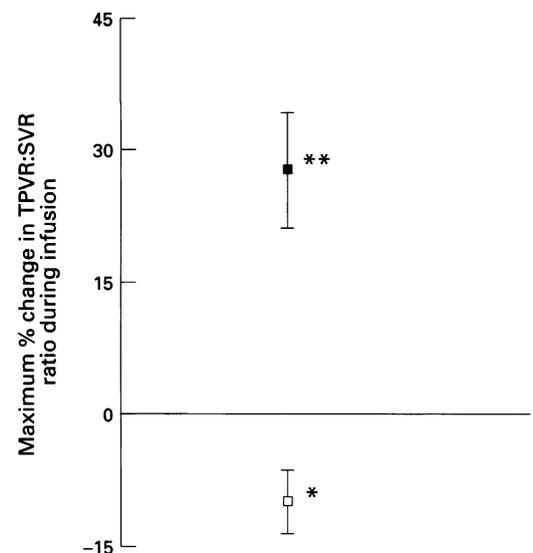
In our institution all cases of primary pulmonary hypertension are subjected to pulmonary vasodilator tests using the non-endothelium-dependent vasodilator adenosine whilst being fully haemodynamically monitored, to assess their suitability for oral vasodilator therapy. We have shown previously that adenosine has effects selective to the pulmonary vasculature.⁴ Substance P is an endothelium-dependent vasodilator that has been shown to induce systemic vasodilation in normal individuals.⁵ The aim of this study was therefore to use substance P and adenosine to see if endothelially-dependent vasodilation was present in patients with advanced primary pulmonary hypertension.

Methods

Six patients with primary pulmonary hypertension were investigated. The diagnosis was made after other cardiac and respiratory causes of pulmonary hypertension had been excluded. A triple lumen, balloon tipped, pulmonary artery catheter of the thermodilution type was positioned in a branch of the pulmonary artery to permit measurements of cardiac output, right atrial, pulmonary artery, and pulmonary arterial occlusion pressures (PAOP). A radial artery catheter was inserted to permit measurement of systemic arterial pressure. Following a one hour period of baseline measurements and a second one hour stabilisation period between infusions, substance P (5, 10, 25, 50, and 100 pmol/min)⁵ or adenosine (5, 10, 30, 50 µg/kg/min)⁴ were infused directly into the pulmonary artery in random order. Each dose increment lasted 15 minutes. During the last five minutes of each dose measurements were taken of pulmonary and systemic haemodynamics and cardiac output (by thermodilution in triplicate).

ANALYSIS OF DATA

Total pulmonary vascular resistance (TPVR) and systemic vascular resistance (SVR) were calculated using standard formulae. TPVR was used as PAOP measurements were not obtainable in all patients (as is frequently the case in primary pulmonary hypertension). In view of the wide variation in baseline measurements data were analysed as the percentage change from baseline, expressed as the maximal percentage change from baseline in TPVR:SVR



Mean (SE) maximal percentage change from baseline in TPVR:SVR ratio during infusion of substance P (■) or adenosine (□). * $p < 0.05$, ** $p < 0.01$ compared with baseline.

ratio, and compared using the Student's paired t test. The TPVR:SVR ratio is regarded as an accurate index of the selectivity of a vasodilator to the pulmonary circulation.⁶

Results

All patients had severe primary pulmonary hypertension (mean (SE) systolic, diastolic, and pulmonary artery pressures of 91.1 (7), 45.2 (3), and 62 (4.2) mm Hg, baseline TPVR during initial control period 1949 (164) dynes \cdot s⁻⁵, baseline cardiac output 2.68 (0.18) l/min, baseline systemic vascular resistance 2410 (333) dynes \cdot s \cdot cm⁻⁵, baseline TPVR:SVR ratio 0.88 (0.11)). The mean maximal percentage change in TPVR:SVR ratio was 27.85 (6.5)% for substance P and -9.85 (3.5)% for adenosine (figure).

Discussion

The results of this study indicate that substance P causes more systemic than pulmonary vasodilation and adenosine has the reverse effect in this patient population. Examination of the raw data revealed that all patients showed a marked, dose-dependent fall in mean systemic arterial pressure during infusion of substance P to a similar extent as has been described previously in normal individuals,⁵ an effect that was absent with adenosine. By contrast, substance P caused no change in mean pulmonary arterial pressure which fell during adenosine infusion. Cardiac output rose markedly in a dose-dependent fashion during infusion of substance P and showed a small rise following adenosine. This suggests that only the systemic vascular endothelium was responsive to substance P, a result similar to that reported by others following infusion of substance P in two patients with primary pulmonary hypertension over a more limited dose range.⁷ The non-endothelium-dependent vasodilator adenosine

caused a 9% fall in the TPVR:SVR ratio from baseline values, indicating an effect selective to the pulmonary vasculature. This fall was similar in extent to that which we have previously reported using this drug,⁴ although the patients in the current study had more severe disease as indicated by a higher baseline TPVR.

The pulmonary vascular selectivity of adenosine is attributable to its short half life in vivo, some 80% of the drug being first-pass metabolised in the lung.⁴ The lack of effect of the drug on systemic vascular resistance was therefore expected. By contrast, substance P has a longer half life in vivo and has been shown to induce systemic vasodilation in normal individuals,⁵ although (invasive) measurements of PVR were not performed. The results of the current study imply, however, that either substance P has no effect on pulmonary vascular tone because the pulmonary vascular endothelium is selectively insensitive to the drug, or that in patients with primary pulmonary hypertension endothelial cells in the pulmonary circulation are unresponsive to the drug. There is ample indirect evidence to support the latter contention. Thus, the possibility that patients with primary pulmonary hypertension may have abnormal endothelial cell function has considerable experimental support³ to which our clinical data may now be added. Furthermore, histological evidence of injury to the endothelium has been shown to occur before the development of both pulmonary hypertension and increased vascular reactivity following administration of monochrothaline to rats. Fibrinopeptide A (reflecting thrombin activity) levels are raised and those of a stable metabolite of prostacyclin are reduced in patients with primary pulmonary hypertension.⁸ Increased immunofluorescence staining for von Willebrand factor has been demonstrated in the pulmonary arterial endothelium of patients with pulmonary hypertension secondary to congenital heart disease. Finally, others have shown impaired endothelium-dependent vasorelaxation in response to acetylcholine in isolated human pulmonary vascular rings from patients with a wide variety of chronic lung diseases leading to increased PVR.

The importance of a functioning endothelium in regulating pulmonary vascular tone is likely to be considerable. Thus, endothelium-derived vasoactive factors modulate pulmonary vascular tone both in experimental animals and clinically. We have reported previously that nitric oxide modulates hypoxic pulmonary vasoconstriction in the isolated, blood perfused

rat lung preparation,³ and others have demonstrated that the endothelium-dependent vasodilator acetylcholine produces dose-dependent vasodilation in the intact rabbit lung preparation when vascular tone is raised above baseline. Furthermore, in isolated porcine pulmonary artery rings, endothelium-dependent vasodilation by acetylcholine is greater in smaller than in larger vessels. Lastly, administration of nitric oxide by inhalation causes dose-dependent selective pulmonary vasodilation in patients with primary pulmonary hypertension.⁹

The clinical relevance of our findings may prove to be considerable. Specifically, patients with primary pulmonary hypertension who respond to high dose calcium channel blockade by showing a reduction in PVR and who take warfarin survive longer than those who do not.¹⁰ It may be that a dysfunctional endothelium with deficient intrinsic antithrombotic properties necessitates the use of anticoagulants, thereby improving prognosis; and vasodilators that provide a reduction in smooth muscle tone via non-endothelium-dependent pathways will similarly prove more clinically effective than those working through the release of nitric oxide. Whether or not a functionally intact endothelium is important in preventing the changes in pulmonary vascular remodelling that characterise primary pulmonary hypertension, or whether this determines the disease process itself, remains unknown. Nevertheless, evidence presented in the current study suggests that endothelial cell dysfunction does occur in such cases.

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