

## Results in six patients before and after expansion of plasma volume

Case No	Heart rate (beats/min)		Mean arterial blood pressure (mm Hg)		Pulmonary artery occlusion pressure (mm Hg)		Stroke volume index (ml/m <sup>2</sup> )		Left ventricular stroke work index (g m/m <sup>2</sup> )		Fluid volume* (litres)	Fluid time† (min)
	Before	After	Before	After	Before	After	Before	After	Before	After		
1	177	102	40	85	12	16	8	31	3	29	4-10	50
2	155	90	55	70	1	2	8	30	6	24	4-20	65
3	180	110	45	90	10	15	7	22	3	22	2-25	35
4	147	95	50	75	6	11	12	39	7	34	4-80	75
5	170	115	30	65	2	18	5	27	2	17	3-75	40
6	150	120	65	80	5	14	11	23	9	21	4-30	70

\*Total volume of modified fluid gelatin infused.

†Time taken to achieve controlled plasma volume expansion.

radiography subsequently showed that he had bronchopneumonia. He too developed adult respiratory distress syndrome.

All patients were eventually admitted to the intensive care unit of this hospital. All except the patient in case 3 required mechanical ventilation, and they all continued to suffer from rapid atrial fibrillation after intravenous digitalis had been administered in the form of ouabain 250-500 µg. After hypoxaemia had been corrected pulmonary artery flotation catheters were inserted for measurement of right atrial pressure, pulmonary artery occlusion pressure, and pulmonary artery pressure, and cardiac output was determined by a standard thermodilution technique. Cannulas were inserted into the femoral arteries to measure systemic arterial pressures. The derived variables in the table were calculated by standard formulas. Plasma volume was expanded rapidly with modified fluid gelatin to an optimal pulmonary artery occlusion pressure, above which there were no further falls in heart rate or increases in left ventricular stroke work index.

## Results

The results are shown in the table. Between 2.25 and 4.9 litres of fluid was needed (mean 3.91 litres). All patients developed slowing of the ventricular rate towards normal during transfusion, and the heart rate in all patients reverted to sinus rhythm within 30 minutes of plasma volume expansion. One patient (case 3) was discharged from the intensive care unit 12 hours after admission; the others remained in the unit for two to 12 days. The patients in cases 4 and 5 died. All the others made a good recovery.

## Discussion

The deleterious effects of the sudden onset of atrial fibrillation in critically ill patients have been reviewed and include a rapid ventricular rate and loss of atrial transport.<sup>4</sup> All the patients described above became much worse when the atrial fibrillation developed, but their response to fluids showed that the atrial fibrillation was a complication of an underlying illness rather than the primary cause of their acute deterioration. All patients had

noticeable hypovolaemia, which had not been suspected but was discovered when pulmonary artery occlusion pressures were found to be low or normal. A poor absolute correlation between measured circulating blood volume and pulmonary artery occlusion pressure has been shown.<sup>5</sup> The explanation almost certainly lies in the varying states of left ventricular compliance in critically ill patients.<sup>6</sup> Thus even when pulmonary artery occlusion pressure is not very low (as in cases 1 and 3) a trial of plasma volume expansion is advisable. When filling pressure was normal it did not increase rapidly with transfusion. The usual response to onset of atrial fibrillation in critically ill patients whose circulating blood volume has been well maintained is for the pulmonary artery occlusion pressure to rise quickly to very high levels, and this, combined with falls in cardiac output, may worsen gas exchange and delivery of oxygen to tissues.<sup>2</sup> Unmonitored plasma volume expansion in such patients is therefore not recommended.

The reversion to sinus rhythm after transfusion suggests that hypovolaemia, in addition to the underlying condition, played a major part in the precipitation of atrial fibrillation. We suggest that haemodynamic monitoring is important in the management of hypotensive patients with uncontrollable atrial fibrillation.

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# SHORT REPORTS

## Penetration of pyrazinamide into the cerebrospinal fluid in tuberculous meningitis

Although meningitis is a fairly uncommon form of tuberculosis, its consequences are particularly important as delays in diagnosis and in starting effective treatment can result in serious neurological consequences or even death. Because of the lack of controlled clinical trials evidence for the potential contribution of drugs to the treatment of tuberculous meningitis depends primarily on their efficacy in pulmonary tuberculosis and estimates of their penetration into the cerebrospinal fluid. Pyrazinamide has a key sterilising role in short course chemotherapy for pulmonary tuberculosis<sup>1</sup> but has rarely been used for treating tuberculous meningitis. Before this investigation its penetration into the cerebrospinal fluid had been studied in only two patients.<sup>2,3</sup>

### Patients, methods, and results

We studied 28 Chinese patients with suspected tuberculous meningitis; they were aged 18-71 and weighed 28-80 kg. The diagnosis was confirmed in 25 patients on the basis of clinical symptoms and cerebrospinal fluid evidence. At presentation consciousness was undisturbed in four patients and disturbed in 16, while five patients were comatose or delirious. In addition to daily treatment with pyrazinamide, isoniazid, and rifampicin most patients also received steroids and either ethambutol or streptomycin.

Lumbar punctures were performed only when required clinically to establish the diagnosis and to monitor therapeutic progress. In the first part of the investigation 50 samples of cerebrospinal fluid and blood were obtained about two hours after administration of the drugs. In the second part, 42 pairs of samples of cerebrospinal fluid and blood obtained concomitantly were collected two, five, or eight hours after dosage, the timing on each occasion being by random allocation. Cerebrospinal fluid and serum pyrazinamide concentrations were determined colorimetrically with alkaline nitroprusside after extraction into butanol-toluene and thence into dilute sulphuric acid.<sup>4</sup> Thirty three pairs of samples of cerebrospinal fluid and blood were obtained from patients during the

period in which pyrazinamide was not prescribed and served as controls; they were treated by the same method.

The table shows the mean concentrations of pyrazinamide in the serum and cerebrospinal fluid two, five, and eight hours after dosage. Two hours after dosage the concentrations in the cerebrospinal fluid were about 75% of those in serum, but at five and eight hours cerebrospinal fluid concentrations were about 10% higher than the corresponding serum values. Penetration of pyrazinamide into the cerebrospinal fluid was not influenced by the clinical stage of disease at presentation, the presence or absence of active disease, the concomitant use of steroids, the duration of antituberculosis treatment before the sample of cerebrospinal fluid was obtained, the administration of either ethambutol or streptomycin, or the age or sex of the patient. The extent to which pyrazinamide penetrated into the cerebrospinal fluid was remarkably similar among all the patients, and most of the variability in the calculated ratios of cerebrospinal fluid to serum pyrazinamide concentrations was estimated to be due to errors inherent in the analytical procedure.

Mean (SD) concentrations of pyrazinamide in serum and cerebrospinal fluid

Hours after dosage	No of samples	Pyrazinamide dosage (mg/kg)	Concentration (mg/l)		Ratio of cerebrospinal fluid to serum concentration
			Serum	Cerebrospinal fluid	
2	64	41 (8)	52.0 (14.7)	38.6 (11.1)	0.74 (0.14)
5	14	36 (9)	39.5 (13.1)	44.5 (13.8)	1.15 (0.22)
8	14	34 (6)	28.4 (5.1)	31.0 (6.7)	1.09 (0.11)

### Comment

The excellent penetration of pyrazinamide across the blood-brain barrier was to be expected in view of its physicochemical properties: it is moderately lipophilic, uncharged at body pH, and not bound to serum proteins. In view of its unique bactericidal activity against tubercle bacilli in an acid environment resulting from local inflammation,<sup>2</sup> its important contribution in short course treatment of pulmonary tuberculosis,<sup>1</sup> and its excellent penetration into the cerebrospinal fluid we recommend that pyrazinamide should be included in treatment regimens for tuberculous meningitis.

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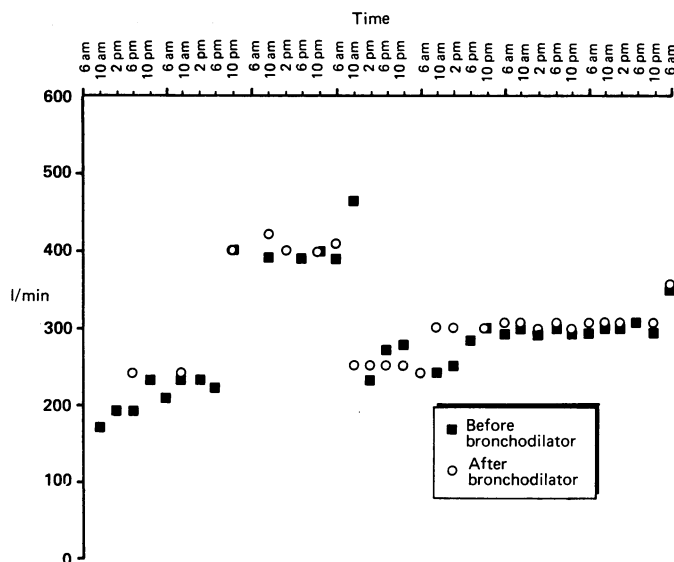
## Falsely high peak expiratory flow readings due to acceleration in the mouth

Asthma is a major cause of morbidity and mortality, which might be reduced by a more aggressive approach to diagnosis and management.<sup>1</sup> Peak flow rate is often used particularly in continuous monitoring, to diagnose and assess the response to treatment of asthma and other forms of airway obstruction<sup>2</sup> and may be the most satisfactory method of assessing the response in chronic partially reversible airway obstruction.<sup>3</sup> Though the normal range is wide (about a third of the normal mean measurement) repeated measurements usually give consistent results in normal subjects and many patients with persistent obstruction. Some subjects, however, cannot produce consistent results, while others produce falsely high figures by accelerating the air flow from the mouth with a spitting action.

I report such a case.

### Case report

A man aged 64 with a long history of increasing breathlessness and wheeze and previous doubtful response to bronchodilators was admitted for a formal assessment of his response to maximal doses of bronchodilators and corticosteroids. The peak expiratory flow rate was recorded every four hours. He was treated with nebulised salbutamol, and after three days the peak flow rate suddenly increased without apparent immediate response to a bronchodilator (figure). When asked to show how he used the peak flow meter, the patient performed a spitting action, using the tongue and buccal musculature to accelerate the air through the mouth. When he used the simple maximal blow the peak flow rate fell to previous levels. Further recordings showed a slow rise, compatible with gradual clinical improvement.



Four hourly peak flow chart showing the different measurements achieved by the patient with the correct technique and the trick manoeuvre.

### Comment

The ability to accelerate the peak flow rate has been seen in several patients. In this case a mini peak flow meter with a mouthpiece circular in cross section was used. The patient put the mouthpiece just inside his lips, but when asked to put it further back into the mouth so that it overlay the anterior part of the tongue, he could not perform the trick manoeuvre. The peak flow rate could not be accelerated beyond that obtained with the mouthpiece forward in the mouth using a simple blow. Though this patient was using the mini meter, the phenomenon has also been seen in patients using a standard instrument. This may, however, be slightly more difficult to manipulate—for example, another patient with peak flow rates of about 250 l/min produced readings of 295, 375, and 305 l/min with a standard instrument and 390, 410, and 420 l/min with the mini meter. This patient could also produce falsely high readings only with a mouthpiece of elliptical rather than circular cross section. Six attempts in random order produced readings of 250, 250, 270 l/min with a circular mouthpiece and 400, 420, and 420 l/min with the mouthpiece of elliptical section. The patient stated that he could not manipulate his tongue into the orifice of the circular mouthpiece.

This phenomenon has not been seen in patients during standard spirometry, presumably because of the emphasis on full expiration. The problem can usually be avoided if the mouthpiece is well inside the mouth, overlying the tongue, and is less likely to occur if a mouthpiece of circular rather than elliptical cross section is used. The standard peak flow meter may be slightly less susceptible to this manipulation than the mini meter.

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