The lungs in renal failure

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Lee, H. Y. and Stretton, T. B. (1975). Thorax, 30, 46-53. The lungs in renal failure. Pulmonary function was studied in 55 patients with renal failure and no clinical or radiographic evidence of lung disease. A defect of gas transfer was found to be the rule due to a reduction in the diffusing capacity across the alveolar capillary membrane; this abnormality appeared to be related to the severity of the renal impairment. There was also a restrictive ventilatory defect which was more marked in male than in female patients. The significance of these findings is discussed, and attention is drawn to their relevance for patients receiving immunosuppressive therapy or renal transplantation, in whom pulmonary complications are relatively common.

Patients with acute or chronic renal failure not infrequently develop pulmonary complications such as oedema, infection or pleurisy (Merrill and Hampers, 1970). The administration of corticosteroids or cytotoxic drugs as immunosuppressive therapy increases this liability to infection (Hill *et al.*, 1967), and the use of such drugs after renal transplantation may be responsible for the apparent increase among these patients of respiratory infection with uncommon organisms such as *Pneumocystis carinii* and cytomegalic inclusion virus (Hill, Rowlands, and Rifkind, 1964; Craighead, 1971; Doak *et al.*, 1973; Millard *et al.*, 1973). Disturbances of respiratory function have been reported in such circumstances (Rifkind *et al.*, 1964; Slapak, Lee, and Hume, 1968; Doak *et al.*, 1973) though there have been few detailed studies of pulmonary function in uraemic patients in the absence of overt lung disease (Daum, Janota, and Boudik, 1966; Doak *et al.*, 1973).

As a preliminary to a study of lung disease in patients after renal transplantation, we have investigated a group of uraemic subjects whose lungs appeared to be normal by clinical and radiological criteria. The findings of this study are reported.

MATERIALS AND METHODS

Fifty-five patients with various renal diseases were studied. They were selected because of the presence of renal failure and the absence of overt lung disease or pulmonary venous congestion. Renal failure was defined

as an endogenous creatinine clearance of less than 60 ml min⁻¹ and a serum creatinine of more than 1.5 mg 100 ml⁻¹ or a blood urea greater than 45 mg 100 ml⁻¹. Pulmonary disease was 'excluded' by use of a symptom questionnaire, clinical examination, and chest radiography. Patients with a history of cough, sputum production, wheezing, haemoptysis, orthopnoea or paroxysmal nocturnal dyspnoea were not accepted for study. No patients were included if, on examination, they had pulsus alternans, a cardiac triple rhythm, or adventitious sounds on auscultation of the lungs. Nor were patients accepted if they had evident lung disease, including pulmonary oedema, on a plain chest radiograph. Ten patients were being treated by regular haemodialysis. Forty-five were randomly selected from the wards and out-patient clinics. All patients willingly agreed to participate in the investigation.

Respiratory physiological measurements were made with subjects in the sitting position. Smokers desisted from this habit for at least 12 hours before they were studied. Patients being treated by haemodialysis were studied during the inter-dialysis period. Routine measurements of forced expired volume in one second (FEV₁) and vital capacity were carried out with a dry portable spirometer (Vitalograph) and the recorded volumes were converted to BTPS. This instrument was used to facilitate repetition of the measurements on other occasions, when it might not be possible for the patient to visit the laboratory. Arterial PCO₂ was either measured directly on arterial blood (see below) or derived from mixed venous PCO₂. The latter was estimated by a rebreathing procedure (Campbell and Howell, 1962), assuming a difference of 6 mmHg between mixed venous and arterial blood. Residual lung volume (RV) was measured in 11 patients by the helium dilution technique, using a closed-circuit spirometer fitted with a katharometer (Godart expirograph). Duplicate measurements of the transfer factor

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(diffusing capacity) for carbon monoxide (TF) were made by the single-breath method using a modification of the semi-automated apparatus described by Meade *et al.* (1965) (Morgan Resparameter, Mark IV). In 20 patients TF was determined at two different alveolar oxygen tensions (approximately 110 and 600 Torr), and the diffusing capacity of the alveolar-capillary membrane (Dm) and the volume of blood in pulmonary capillaries (Vc) were derived from the equation of Roughton and Forster (1957):

$$\frac{1}{TF} = \frac{1}{Dm} + \frac{1}{\theta Vc} \quad (\text{Equation 1})$$

where θ is the *in vitro* reaction rate of carbon monoxide with haemoglobin.

In 20 patients resting, expired air was collected into a Douglas bag over a timed period, and the gas volume was measured with a dry gas meter (Parkinson Cowan, Type CD4) and corrected to BTPS or STPD where appropriate. The concentrations of oxygen and carbon dioxide in expired gas were determined respectively with a paramagnetic analyser (Servomex, Mark II) and an infrared analyser (Godart capnograph); both instruments were calibrated with gas mixtures analysed in a Lloyd-Haldane apparatus. During the collection of expired air an arterial blood sample was obtained from the brachial artery. The blood was collected anaerobically in a glass syringe, the dead space of which had been filled with heparin, and was analysed immediately for P_{O_2} with a Radiometer Type E5046 oxygen electrode, for P_{CO_2} using a Radiometer Type E5036 carbon dioxide electrode, and for pH with a glass micro-electrode unit (Radiometer Type 5021). These patients then performed a Valsalva manoeuvre by blowing into a mercury-filled manometer so as to raise the intrathoracic pressure by 40 mmHg while a direct arterial pressure recording was made using a strain gauge pressure transducer (Bell and Howell Type 4-327-L221) and pressure pre-amplifier (Devices DC2, subunit 1) linked to a direct-writing analogue recorder (Mingograf 800).

Physiological dead space (V_D) was calculated from a modification of the Bohr equation:

$$V_D = \left(\frac{P_{aCO_2} - P_{ECO_2}}{P_{aCO_2}} \right) \times V_T - \text{valve dead space} \quad (\text{Equation 2})$$

where P_{aCO_2} and P_{ECO_2} are the carbon dioxide tensions in arterial blood and mixed expired air respectively, and V_T is the tidal volume. The dead space of the valve used in these studies was 47 ml. Alveolar oxygen pressure (P_{AO_2}) was derived by the alveolar air equation of Fenn, Rahn, and Otis (1946):

$$P_{AO_2} = P_{IO_2} - P_{aCO_2} \times \left(F_{IO_2} + \frac{1 - F_{IO_2}}{R} \right) \quad (\text{Equation 3})$$

where F_{IO_2} is the fractional concentration of inspired oxygen (0.2093), P_{IO_2} is the pressure of inspired oxygen (0.2093 $\times$ [barometric pressure - water vapour pressure]) and R is the respiratory exchange ratio. The alveolar to arterial oxygen tension difference ($A - aDO_2$) was obtained by subtracting the measured P_{aO_2} from P_{AO_2} calculated using equation 3.

The methods recommended by Cotes (1968) were used in the calculation of TF, Dm, and Vc. Also since TF is affected by anaemia, all observed values of TF have been standardized for haemoglobin concentration using the equation of Cotes *et al.* (1972):

$$\text{Standardized TF} = \frac{\text{Observed TF} (14.6a + Hb)}{(1 + a) Hb} \quad (\text{Equation 4})$$

where Hb is the patient's haemoglobin concentration in grams per 100 ml and 'a' is the ratio of Dm to Vc. When this ratio has not been calculated, Cotes and his colleagues recommend an assumed value of 0.7. It was possible to check the validity of equation 4 in the 20 patients in whom Dm and Vc had been obtained. In these patients TF, calculated according to the method of Roughton and Forster (1957) (see equation 1), in which the effect of anaemia was taken into account, was compared with the 'standardized TF' of Cotes and his colleagues.

RESULTS

By definition these patients were not troubled by cough, sputum production, wheezing, haemoptysis or paroxysmal nocturnal dyspnoea. Eight of the 55 patients had a just-detectable degree of ankle oedema. Of these, only three had a jugular venous pressure in excess of 4 cm, assessed by eye with reference to the sternal angle. Again by definition, no chest radiograph showed evidence of pulmonary oedema or lung disease. However, in eight there was cardiomegaly and in four of these there was obliteration of the costophrenic angles, but prominence of veins in the upper zones was seen in only one instance.

Fifteen patients, selected at random from the whole group, had direct arterial pressure recordings while performing a Valsalva manoeuvre. None exhibited the square-wave pattern of cardiac failure (Sharpey-Schafer, 1955). Two patients had a completely normal response. Thirteen demonstrated normal pulse pressure changes during the phase of raised intrathoracic pressure but there was no 'overshoot' in pressure after the Valsalva manoeuvre was terminated; instead, the systolic, diastolic, and mean pressures rose progressively to the resting level, and no rate-changes occurred.

A summary of the age, degree of renal impairment, haemoglobin concentration, and smoking habits of the 55 patients is given in Table I. The duration of renal failure could not often be assessed with confidence, but the shortest history of acute renal failure was two days and, at the other extreme, one patient had documented renal failure for over 20 years.

The diseases held to be responsible for the renal failure are listed in Table II. The group with renal tract malformations includes five patients with

TABLE I

SUMMARY OF AGE, SMOKING HABITS, HAEMOGLOBIN AND RENAL FUNCTION IN 55 PATIENTS STUDIED

	Male	Female
No. of patients	29	26
No. of cigarette smokers	11	7
Age (years)	36.6 (14.2)	39.8 (12.8)
Haemoglobin (g 100ml ⁻¹)	10.0 (3.6)	8.8 (3.0)
Creatinine clearance (ml min ⁻¹)	22.2 (24.4)	16.7 (18.8)
Blood urea (mg 100ml ⁻¹)	147 (83)	154 (93)

(Mean values and standard deviations are given where appropriate.)

TABLE II

SUMMARY OF VARIOUS 'CAUSES' OF RENAL FAILURE IN 55 PATIENTS

	No. of Patients
Glomerulonephritis	11
Pyelonephritis	8
Renal tract malformation	14
Hypertension	8
Hypovolaemia	3
Pre-eclamptic toxemia	3
Nephrotic syndrome	3
Miscellaneous	5
Total	55

polycystic kidneys. Malignant hypertension was the presenting feature of eight patients listed under 'hypertension' and remained the dominant clinical problem; this appeared to be of the 'essential' variety. The three patients with hypovolaemic renal failure were women who had severe haemorrhage associated with childbirth. In the 'miscellaneous' group were included two patients with Cushing's syndrome, two with diabetic nephropathy, and one with gout.

Table III summarizes the results of the pulmonary tests. The values for FEV₁ and vital capacity were

both reduced when compared with normal values derived from Cotes (1968) for subjects of the same sex, age, height, and ethnic group. The reductions in FEV₁ and vital capacity were both of significance in the male patients ($p < 0.001$); in the women, only the reduction in FEV₁ reached a significant level ($p < 0.01$). The ventilatory defect is restrictive, and airways obstruction is absent as judged by the ratio of FEV₁ to vital capacity. Residual volume, measured in 11 patients, was within normal limits.

The measurement of transfer factor for carbon monoxide in our laboratory has a coefficient of variation of 7% and the standard error of a single estimate is 1.002 ml min⁻¹ mmHg⁻¹. Transfer factor in these patients was consistently reduced (Fig. 1) due to a reduction in Dm (Fig. 2) rather than to any consistent change in Vc (Fig. 3). The ratio of Dm/Vc for the 20 patients in whom these measures

FIG. 1. Carbon monoxide transfer factor (TF) in 55 patients with renal failure; observed values compared with predicted normal values.

TABLE III
RESULTS OF PULMONARY FUNCTION TESTS

	Sex	No.	Mean	±SD	Mean of Individual Predicted Values	P
FEV ₁ (l. BTPS)	M	29	3.05	0.87	3.75	<0.001
	F	26	2.20	0.50	2.50	<0.01
VC (l. BTPS)	M	29	3.86	0.86	4.63	<0.001
	F	26	2.75	0.62	2.95	NS
FEV ₁ /VC	M	29	0.78	0.10	0.76	NS
	F	26	0.81	0.10	0.82	NS
TF (ml min ⁻¹ mmHg ⁻¹)	M	29	19.20	4.80	31.50	<0.001
	F	26	14.50	3.10	25.10	<0.001
Dm (ml min ⁻¹ mmHg ⁻¹)	M	13	31.60	10.40	62.80	<0.001
	F	7	19.80	5.20	41.80	<0.001
Vc (ml)	M	13	62.80	19.50	76.80	<0.05
	F	7	63.40	30.10	59.40	NS

Predicted normal values for forced expiratory volume in one second (FEV₁), vital capacity (VC) and ratio of FEV₁ to VC were derived from Cotes (1968); those for carbon monoxide transfer factor (TF) were taken from Cotes and Hall (1970); predicted values for diffusing capacity of the alveolar capillary membrane (Dm) and volume of blood in the pulmonary capillaries (Vc) were from three sources: Cotes and Hall (1970), Francis (1970), and Bucci, Cook and Barrie (1961); P values for the differences between observed and predicted measurements were derived by the method of paired comparisons.

FIG. 2. Observed diffusing capacity of the alveolar capillary membrane compared with predicted values in 20 patients.

FIG. 3. Observed pulmonary capillary blood volume compared with predicted normal values.

ments were made had a mean value of $0.511 \pm \text{SD } 0.278$. TF derived in these 20 patients using the equation of Roughton and Forster (Equation 1) showed a highly significant correlation ($r = 0.97$) with TF values calculated using Equation 4 and an assumed ratio of D_m/V_c of 0.7, as recommended by Cotes *et al.* (1972). TF showed a negative correlation ($P < 0.001$) with the blood urea concentration (Fig. 4) and a positive correlation ($P < 0.05$) with the creatinine clearance (Fig. 5) though there was no apparent association between TF and haemoglobin concentration in our 55 patients (Fig. 6). Mean values for the transfer coefficient, K_{CO} , that is the transfer factor per unit of alveolar volume, were

FIG. 4. Relationship between the carbon monoxide transfer factor (TF) as a percentage of normal and the blood urea level.

FIG. 5. Relationship between TF as a percentage of normal and creatinine clearance.

FIG. 6. Relationship between TF as a percentage of normal and the haemoglobin concentration.

3.3 ± 1.1 for males and 3.5 ± 1.1 for females. Expected values, derived from Cotes and Hall (1970), were 5.3 for both sexes. Twenty-two paired comparisons of alveolar volume were made using the two techniques of measurement: (a) the closed-circuit equilibration of helium, and (b) the dilution of the single breath containing helium taken at the time of measurement of the transfer factor. There was close correlation between the values obtained ($r = 0.95$).

Blood gas data, the ratio of physiological dead space to tidal volume, and alveolar to arterial oxygen tension difference in 20 patients are shown in Table IV. They were all normal.

TABLE IV

RESULTS OF ARTERIAL BLOOD GAS STUDIES, pH, ALVEOLAR TO ARTERIAL OXYGEN TENSION DIFFERENCE ($A-aDO_2$), RATIO OF PHYSIOLOGICAL DEAD SPACE TO TIDAL VOLUME (V_D/V_T), HAEMOGLOBIN, BLOOD UREA, AND RATIO OF OBSERVED TO PREDICTED TRANSFER FACTOR IN 20 PATIENTS

PaO_2 (mmHg)	90.9 (6.6)
$PaCO_2$ (mmHg)	37.2 (4.8)
H^+ concentration (nEq l^{-1})	42.1 (6.4)
pH	7.38
$A-aDO_2$ (mmHg)	16.7 (11.7)
V_D/V_T	0.35 (0.06)
Hb (g 100 ml^{-1})	10.8 (2.9)
Urea (mg 100 ml^{-1})	112.3 (79.7)
TF/predicted TF	0.6 (0.12)

DISCUSSION

The presence of lung disease was excluded as far as possible in this group of 55 patients by clinical and radiological criteria. Certainly no patient with chronic bronchitis, asthma, emphysema or evident infection or oedema of the lungs was accepted for investigation. Many patients complained of exertional dyspnoea though little importance could be attached to this symptom in view of the frequent presence of anaemia. Slightly under one-third of the patients smoked cigarettes and this factor did not appear to influence the physiological findings. The demonstrated abnormality in gas transfer across the alveolar-capillary membrane appears, therefore, to be a characteristic of renal failure; so does the restrictive ventilatory defect seen predominantly in the male patients. The reduction in TF is evidently both a feature of renal failure and related to the degree of renal insufficiency, as judged by the blood urea concentration (Fig. 4) or the creatinine clearance (Fig. 5).

Anaemia was usual in the patients we studied though this was not profound; the mean haemoglobin concentration in male patients was 10.0 ± 3.6 and in females 8.8 ± 3.0 g 100 ml^{-1} . The amount of

haemoglobin in pulmonary capillaries influences the rate of uptake of carbon monoxide in the lungs (Roughton and Forster, 1957) so that TF is reduced in anaemia (Rankin, McNeill, and Forster, 1961; Dinakara *et al.*, 1970; Guleria *et al.*, 1971; Cotes *et al.*, 1972). If the impairment of gas transfer in our patients were solely due to anaemia, the measures taken to correct for the effects of this (Cotes *et al.*, 1972) should have produced TF values close to predicted normal. This was not the case (Fig. 1), suggesting that other factors were responsible for the reduction in TF.

Anaemia has other important cardiorespiratory consequences (Bishop, Donald, and Wade, 1955; Roy *et al.*, 1963; Duke and Abelman, 1969; Guleria *et al.*, 1971) which include a rise in cardiac output, peripheral vasodilatation, shortened circulation time, and increased tissue oxygen extraction from the blood. Cotes *et al.* (1972) found little evidence of any change in exercise ventilation or in cardiac frequency and output in a group of women with iron deficiency anaemia though there was a significant reduction in TF which was related to the anaemia. The severity of anaemia in their women was of an order similar to that in our patients with renal failure, but the reduction in TF was less marked and was not due to a reduction in D_m such as we have found. It does appear, therefore, that our findings are unlikely to be due to the associated anaemia, unless in renal failure this is accompanied by an alteration in the value of θ_{CO} . We have been unable to find any relevant data on this point. However, it is noteworthy that we have recorded impairment in TF as long as three years after successful renal transplantation despite normal renal function and a normal blood count.

A common feature of severe anaemia is widening of the $A-aDO_2$, and arterial desaturation has been observed by some (Roy *et al.*, 1963; Guleria *et al.*, 1971) though not by others (Whitaker, 1956; Housley, 1967). Desaturation of arterial blood will occur if there is a marked reduction in arterial PO_2 or if there is a shift to the right in the oxygen dissociation curve. While our patients had a normal PO_2 we have found a small rightward shift in the dissociation curve in a few subjects (unpublished observations) due, presumably, to an increased erythrocyte 2,3 diphosphoglycerate concentration (Hurt and Chanutin, 1964) but insufficient to lead to arterial unsaturation.

Daum *et al.* (1966), using the steady-state method, found a reduction in TF in 14 out of 16 uraemic patients. Although measurement of D_m and V_D produced variable results, Daum and his colleagues concluded that, in general, both values were reduced.

However, at least eight of their patients appeared to be in left-sided heart failure at the time of study, and this could account for the physiological findings, including their low observed values for P_{ao_2} . Doak *et al.* (1973), also using the steady-state technique, found impairment of TF in five uraemic patients who were awaiting renal transplantation. None had overt left ventricular failure at the time they were investigated but all had had pulmonary oedema in the past.

It appears that in neither of these two groups of patients was the effect of anaemia on gas transfer taken into account. However, as we have shown, even when adjustment is made for the influence of anaemia, TF is constantly abnormal. Also, a reduction in the transfer factor, as measured by the steady-state technique, could in part be attributable to a widening of the normal range of ventilation-perfusion ratios in the patients' lungs during tidal breathing. Measurement of TF by the single-breath technique is less susceptible to this kind of disturbance (Cadigan *et al.*, 1961) and our data provide additional and independent evidence to suggest that there were no gross ventilation-perfusion abnormalities in these patients. Thus the mean arterial P_{O_2} for the group was 90.9 ± 6.6 mmHg with a mean alveolar to arterial oxygen pressure difference of 16.7 ± 11.7 mmHg, and the ratio of physiological dead space to tidal volume was 0.35 ± 0.06 .

The presence of pulmonary oedema could be responsible for defective gas transfer and this is a common complication of renal failure (Merrill and Hampers, 1970). We took care to exclude from this study any patient with radiological evidence of pulmonary oedema or clinical features of left ventricular failure such as pulsus alternans or a gallop rhythm. Also, of the 15 randomly selected patients whose arterial pressure was recorded during a Valsalva manoeuvre, none showed the square-wave response attributed to heart failure (Sharpey-Schafer, 1955). The abnormal heart rate and arterial pressure changes after the Valsalva procedure seen in 13 patients suggests that they had impaired baroreflex sensitivity (Pickering, Gribbin, and Oliver, 1972). However, it does seem probable that patients with cardiac failure were successfully excluded from the study. This is also supported by the demonstration in 20 patients of pulmonary capillary blood volumes (Table III) that were either normal or even slightly reduced.

These observations do not exclude the possibility that there was some degree of pulmonary oedema due to overhydration (Allwall, Lunderquist, and Olsson, 1953) or to increased capillary permeability (Bass and Singer, 1950; Robin, Carroll, and Zelis,

1973), though we believe the former was most unlikely in this carefully screened group of patients. Evidence of increased pulmonary capillary permeability was adduced by Gibson (1966), who found the pulmonary arterial pressure to be normal or only slightly raised in six out of seven patients with acute pulmonary oedema complicating renal failure. Also, Crosbie, Snowdon, and Parsons (1972), using an isotopic technique, obtained evidence of increased permeability to the sodium ion in similar patients. Such findings are consistent with the demonstration of normal pulmonary capillary blood volumes, even in patients with evident pulmonary oedema (Daum *et al.*, 1966). The situation may be analogous to that found in alloxan-induced pulmonary oedema in dogs (Staub, Nagano, and Pearce, 1967). Staub and his colleagues found normal values for pulmonary capillary volume and they also showed that oedema fluid appeared first in the loose connective tissue around extra-alveolar vessels and airways before there was any significant change in alveolar wall thickness. Peribronchiolar oedema might permit these airways to close prematurely, that is, at a higher lung volume than normal. This possibility was considered by Zidulka, Despas, Milic-Emili, and Anthonisen (1973), who measured 'closing capacity' of the lungs along with other indices of pulmonary function in six uraemic patients before and after haemodialysis. Using radioactive xenon as a marker gas according to the technique of Dollfuss, Milic-Emili, and Bates (1967), they found evidence of premature closure of the dependent airways in four patients. After haemodialysis there was a reduction in the 'closing capacity' towards the mean predicted value, consistent with the view that excess liquid in the lungs had been responsible for this physiological abnormality. It is also of interest that the six patients of Zidulka *et al.* (1973) had a reduced TF which was not improved by haemodialysis. However, Zidulka and colleagues did observe that some of their patients had concomitant clinical heart failure. By contrast, measurements of 'closing capacity' in a group of patients examined after renal transplantation (Barnes, Lee, and Stretton, unpublished observations) have produced normal results despite a persisting abnormality of pulmonary gas transfer. This supports the view that excess liquid in the lungs was not responsible for the reduced transfer factor found in the patients we studied.

Although it appears that pulmonary oedema at the time of study was not responsible for the reduced transfer factor, the possibility remains that this was the legacy of previous episodes of pulmonary oedema. Oedema fluid due to a 'capillary leak syndrome' (Robin *et al.*, 1972) contains much

protein, including fibrinogen. The lungs of patients dying in uraemia have long been known to contain large amounts of fibrin (Doniach, 1947; Hopps and Wissler, 1955). This could be the result of abnormal protein leakage coupled with a reduced fibrinolytic activity (MacLeod, Stalker, and Ogston, 1962). Thus, the reduced gas transfer and the restrictive ventilatory defect may well both be the consequence of deposition of fibrin within the alveoli of these patients. Unfortunately we do not have histological data to correlate with our physiological findings.

Our initial hypothesis, on which the present study was based, was that immunological damage to lung capillaries in certain renal diseases might impair gas transfer. However, the discovery that TF is regularly reduced in renal failure, irrespective of the underlying aetiology of the kidney disease, makes this improbable. We have been unable to relate the abnormality to respiratory infection, to drug therapy or to the duration of renal failure, though it does appear to be related to the severity of the latter. The precise cause remains uncertain. Nevertheless we suggest that documentation of pulmonary function is important in patients with renal failure, especially if immunosuppressive therapy or renal transplantation is contemplated. Then, if respiratory problems do arise, it may be possible to distinguish the additional physiological disturbances due to the complications from those associated with renal failure. Otherwise abnormalities of lung function observed after the onset of pulmonary complications need to be interpreted with caution.

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