A high peritoneal large pore fluid flux causes hypoalbuminaemia and is a risk factor for death in peritoneal dialysis patients

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Abstract

Background. Hypoalbuminaemia is common in peritoneal dialysis (PD) patients and has an associated high mortality. An excess morbidity and mortality has previously been found in patients with high peritoneal transport. A high peritoneal large pore fluid flux (JvL) results in increased peritoneal loss of protein that possibly contributes to patient morbidity. Alternatively, hypoalbuminaemia and high transport status could be just a marker of capillary pathology associated with atherosclerotic comorbidity.

Methods. Peritoneal dialysis capacity computer modelling of peritoneal transport, based on Rippe’s three-pore model, was performed to measure JvL in 155 incident PD patients 2–4 weeks after PD initiation. Patient clinical and biochemical status was determined at 6, 3, 1, and 6 months after PD initiation, and every 6 months thereafter. JvL was redetermined in prevalent patients 2 and 4 years after PD initiation.

Results. JvL was 0.106 ± 0.056 ml/min/1.73 m² (median 0.094, interquartile range 0.068–0.128). It was correlated to age*** (*P < 0.05; **P < 0.01; ***P < 0.001) (20–30 years 0.079 ± 0.04; 70 years 0.121 ± 0.071), but not to gender. No correlation to diabetic or preexisting renal replacement therapy was seen, but patients with atherosclerosis had higher JvL (0.123 ± 0.06 vs 0.100 ± 0.056*) as had patients with other systemic disease (0.121 ± 0.68 vs 0.100 ± 0.051*). JvL was positively correlated to area parameter (r = 0.41***), and negatively correlated to plasma albumin (−0.36***). Patients were divided into three equal groups: group 1, JvL < 0.075 ml/min/1.73 m²; group 2, 0.075–0.11; group 3: >0.11. There was no difference between the groups in p-albumin prior to PD. Immediately after PD start, differences between the three groups appeared (1 month p-albumin: (μmol/l) group 1, 548 ± 83; group 2, 533 ± 86; group 3, 497 ± 78**), and persisted for up to 6 years. No significant change in JvL was seen at 2 and 4 years. Patients with significant albuminuria also had hypoalbuminaemia (<1 g/day: 546 ± 81 μmol/l; >2 g/day: 503 ± 54 μmol/l). Intermittent PD ameliorated the effect of JvL on albumin losses and clearance. Mortality was increased significantly with raised JvL, independently of age (2 year mortality: group 1, 10%, group 3, 32%*). There was no overall effect on technique survival, but hypoalbuminaemic group 3 patients had a higher failure rate*.

Conclusion. JvL is related to hypoalbuminaemia and mortality after PD initiation. A high JvL seems to be a marker of preexisting vascular pathology, and to cause hypoalbuminaemia after PD initiation. It is suggested that peritoneal albumin loss can have an identical pathogenic effect as urinary albumin loss, by causing an iatrogenic ‘nephrotic’ syndrome.

Keywords: hypoalbuminaemia; peritoneal dialysis; peritoneal transport

Introduction

Patients with a high small molecule peritoneal transport rate (HT) have previously been shown to have a paradoxically raised morbidity and mortality in peritoneal dialysis (PD) patients [1,2]. In the CANUSA study [2], three possible explanations were advanced. First, HT patients have a loss of ultrafiltration capacity due to rapid equilibration of glucose across the peritoneal membrane, with consequent overhydration and hypertension. Secondly, HT patients generally also have an increased large pore transport [3], leading to excess loss of protein, with consequent protein malnutrition. Finally, it was noted that HT patients already suffered from hypoalbuminaemia at the time of the first peritoneal equilibration test (PET) 1 month after start of dialysis, and that hypoalbuminaemia was also a powerful predictor of mortality. It has therefore been suggested [4,5] that HT status is just a marker of either
coexisting inflammation or a general capillary morbidity secondary to atherosclerosis, and that PD has no supplementary pathogenic effect. Peritoneal transport occurs through three types of pore [6,7]: aquaporins, which are only permeable to water; small pores, which are responsible for small molecule transport; and large pores through which most albumin and other protein loss occurs. We measured large pore fluid flux ($J_{VL}$) in incident patients, and correlated it with pre-existing comorbidity, temporal changes in plasma albumin and prognosis, in order to elucidate the roles of the differing theories.

**Subjects and methods**

One hundred and fifty-five incident PD patients from a single centre were included in the study, from 1994–2003. The patients were primarily started on CAPD. Peritoneal dialysis capacity (PDC) measurement [8] was performed as a normal part of the initial patient assessment, usually within 4 weeks of dialysis initiation, and the dialysis regime adjusted accordingly. The PDC test is a computer model based on the Rippe three-pore theory, and measures small solute transport, expressed as the area parameter (peritoneal area/ diffusion distance, A/Dx), the final absorption rate of fluid from the abdominal cavity when the glucose gradient has dissipated ($J_{VAR}$) and large pore fluid flux ($J_{VL}$), corrected for surface area, which is responsible for most protein loss from plasma. The patient performed five dwells with varying concentrations of glucose, with drains after 2, 3, 4, 5 and 8 h. Drain fluid was analysed for volume, creatinine, urea, glucose and albumin. Other variables calculated using standard three-pore formalism, were lymphatic absorption, conductivity, plasma oncotic pressure, ratio of aquaporin number to large pore number (aquaporin number ratio), ratio of aquaporin to large pore area (aquaporin area ratio), ratio of small pore number to large pore number (small pore number ratio) and ratio of small pore area to large pore area (small pore area ratio).

The following patient data was registered at dialysis start: age, gender, primary renal diagnosis, duration of uraemia (creatinine clearance <25 ml/min or plasma creatinine >300 μM) presence of atherosclerotic cardiac disease (previous myocardial infarction, heart failure or angina, but not hypertensive cardiomyopathy), other systemic atherosclerosis (previous cerebrovascular disease, claudication, peripheral ischaemia or pathological arteriography), or other systemic disease (excluding diabetes), and tobacco consumption. The following was measured 1 month after PD start, 6 months after, and every 6 months thereafter, until death or change of therapy: plasma creatinine, urea, albumin, (bromocresol colorimetry, Vitros ALB, Ortho-Clinical), weight, blood pressure, clinical hydration status. Clinical hydration status was classified as dehydrated (reduced skin turgor), normal (no peripheral oedema), overhydrated (peripheral oedema), or very overhydrated (severe oedema or pulmonary oedema). In addition, fluid excess, measured as the difference between body weight and estimated dry weight was registered. A 24 h collection of dialysis effluent and urine was performed, and each collection assessed for volume, creatinine, urea and albumin. $K_i/V$ and creatinine mass transfer area coefficient was measured using the Adequest computer program (Baxter, IL, USA). Retrospective data 1, 3 and 6 months before dialysis initiation was registered. At the same intervals, admission number, admission days, peritonitis number, dialysis treatment and treatment failure (switch to haemodialysis) were registered. Death was registered on an intention-to-treat basis. PDC test was repeated at 2 year intervals.

Dialysis treatment consisted primarily of CAPD (continuous ambulatory peritoneal dialysis) 2–2.5 litres × 4–5. Icodextrin use for the night dwell increased during the period of study, becoming virtually universal after 2001. On the basis of PDC results patients were recommended automated PD (APD) on the following basis: high transport (A/Dx >290 m/1.73 m²), APD; high average (210–290 m) and low average transport (130–210), free choice; low transport (<130), CAPD. The prescription (including supplementary day dwells for APD patients) was adjusted to achieve a $K_i/V >1.7$/week for low and low average patients, and >2.0 for high and high average patients according to the Canadian guidelines [9]. Normohydration was achieved by fluid restriction, hypertonic glucose dialysis and icodextrin use as required, but no specific targets for ultrafiltration were set.

**Statistics**

Categories were compared using Student’s t-test and MANOVA. Correlations were performed using Pearson product-moment correlation. Logarithmic transformation was performed where relevant. Survival was studying using Kaplan–Meier product-limit method and Cox’s proportional hazards model. Significance levels of $P<0.05$, $P<0.01$ and $P<0.001$ were registered. Other probabilities ($P>0.05$) were not significant (NS).

**Results**

Patient data are shown in Table 1. During the period of study, the prevalence of APD rose from 14 to 55%. A total of 18 systemic diseases were registered of which cancer [8], lupus [5], chronic obstructive lung disease [4] and severe hyperparathyroidism [4] were the most common. Details of tobacco consumption were available in 126 patients and uraemia duration in 111.

$J_{VL}$ was $0.106±0.056$ ml/min/1.73 m² (median 0.094, interquartile range 0.068–0.128, range 0.003–0.319). It was correlated to age (Table 2, and Figure 1) but not to gender. No correlation to diabetic or pre-existing renal replacement therapy was seen, but patients with atherosclerosis or other systemic disease, and smokers, had higher $J_{VL}$ (Table 1). $J_{VL}$ was positively correlated to area parameter (Table 2 and Figure 2), and negatively correlated to plasma albumin. On a multiple regression analysis including height, weight, renal creatinine clearance, $K_i/V$, protein nitrogen appearance, age, sex, area parameter, $J_{VAR}$ and $J_{VL}$, only age ($β=−0.22$, $P<0.01$) and $J_{VL}$ ($β=−0.27$, $P<0.01$) were significantly correlated to plasma albumin.

Patients were divided into three approximately equal groups: group 1, $J_{VL}<0.075$ ml/min/1.73 m²; group 2, 0.075–0.11; group 3, >0.11. There was no difference
between the groups in p-albumin prior to PD. Immediately after PD start, differences between the three groups appeared (Figures 3 and 4). The differences tended to disappear after 2 years, but further perusal showed that this was due to a higher treatment failure rate among hypoalbuminaemic patients with high JvL (vide infra). The cohort with long-term treatment survival (>4 years) showed continuing differences between the groups (p-albumin at 4 years: group 1, 554±57 μM/l; group 2: 542±51 μmol/l; group 3: 506±58 μmol/l). Patients with significant albuminuria also had hypoalbuminaemia (<1 g/day: 540±79 μM/l; 1–2 g/day: 522±77 μmol/l; > 2 g/day: 482±85 μmol/l,  P <0.01). No significant change in JvL was seen after 2 years (0.093±0.048 ml/min/1.73 m², 29 patients) and 4 years (0.097±0.039, 11 patients). 16/29 patients who had not suffered peritonitis during the first 2 years had no difference in JvL or change in JvL compared to patients with peritonitis.

Table 1. Categorical patient clinical data and relationship to JvL

| Presence of factor | Number (%) | JvL (ml/min/1.73 m²) | Significance |
|--------------------|------------|----------------------|--------------|
| Male patients      | 89 (57)    | 0.101±0.05           | No           |
| Uraemia duration >2 years | 42 (38)    | 0.111±0.06           | 0.108±0.06   | NS            |
| Previous renal replacement therapy | 17 (11)    | 0.107±0.06           | 0.096±0.05   | NS            |
| Tobacco consumption | 45 (36)    | 0.102±0.05           | 0.101±0.05   | NS            |

Primary renal disease

| Disease                        | Number (%) | JvL (ml/min/1.73 m²) | Significance |
|-------------------------------|------------|----------------------|--------------|
| Shrunken kidneys              | 27 (17)    | 0.107±0.05           | 0.105±0.07   | NS            |
| Glomerulonephritis            | 33 (22)    | 0.109±0.06           | 0.097±0.05   | NS            |
| Chronic interstitial nephropathy | 17 (11)   | 0.105±0.05           | 0.121±0.08   | NS            |
| Polycystic renal disease      | 13 (8)     | 0.108±0.06           | 0.094±0.03   | NS            |
| Diabetic nephropathy          | 27 (17)    | 0.106±0.06           | 0.106±0.06   | NS            |
| Renovascular disease          | 28 (18)    | 0.105±0.06           | 0.114±0.06   | NS            |
| Other                         | 9 (6)      | 0.106±0.06           | 0.121±0.06   | NS            |

Atherosclerotic heart disease

| Disease                        | Number (%) | JvL (ml/min/1.73 m²) | Significance |
|-------------------------------|------------|----------------------|--------------|
| 61 (39)                       | 0.099±0.05 | 0.118±0.07           | P <0.05      |

Table 2. Parametric clinical data, peritoneal physiology and correlations to JvL

| Value                                | Correlation | Significance |
|--------------------------------------|-------------|--------------|
| Age (years ± SD)                     | 56.2±14.3   | 0.22         | <0.001       |
| Weight (kg ± SD)                     | 71.5±14.7   | NS           |              |
| Height (cm ± SD)                     | 171±9.3     | NS           |              |
| Body mass (kg/m²)                    | 24.4±4.5    | NS           |              |
| Renal creatinine clearance (ml/min)  | 2.5 (0.5–3.7) | 0.27       | <0.01        |
| Diuresis (ml/day)                    | 851±722     | 0.27         | <0.01        |
| Plasma albumin (μmol/l)              | 525±79      | -0.36        | <0.001       |
| Kₖ/V (per week)                      | 2.07±0.68   | 0.24         | <0.01        |
| PNA (g/kg/day)                       | 1.07±0.37   | 0.27         | <0.01        |
| Total creatinine clearance (ml/min)  | 6.9±2.3     | 0.28         | <0.001       |
| Peritoneal creatinine clearance (ml/min) | 4.3±1.2 | NS           |              |
| Area parameter (m²/1.73 m²)          | 200.3±8.06  | 0.41         | <0.001       |
| Final reabsorption rate (Jᵥ⁾ᵛ⁾        | 2.16±1.02   | 0.26         | <0.01        |
| Lymphatic drainage (ml/min/1.73 m²)  | 1.05±0.76   | 0.29         | <0.001       |
| Plasma oncotic pressure (mmHg)       | 24.8±2.9    | -0.31        | <0.001       |
| Aquaporin number ratio (×10³)        | 1224±969    | -0.66        | <0.001       |
| Aquaporin area ratio                 | 930 (666–1459) | -0.67   | <0.001       |
| Small pore number ratio              | 313±248     | -0.67        | <0.001       |
| Small pore area ratio                | 238 (173–372) | -0.65       | <0.001       |

First PDC only. Mean±SD, plus median (interquartile range) where appropriate.

Fig. 1. Relationship of JvL to age.

perusal showed that this was due to a higher treatment failure rate among hypoalbuminaemic patients with high JvL (vide infra). The cohort with long-term treatment survival (>4 years) showed continuing differences between the groups (p-albumin at 4 years: group 1, 554±57 μM/l; group 2: 542±51 μmol/l; group 3: 506±58 μmol/l). Patients with significant albuminuria also had hypoalbuminaemia (<1 g/day: 540±79 μM/l; 1–2 g/day: 522±77 μmol/l; > 2 g/day: 482±85 μmol/l,  P <0.01). No significant change in JvL was seen after 2 years (0.093±0.048 ml/min/1.73 m², 29 patients) and 4 years (0.097±0.039, 11 patients). 16/29 patients who had not suffered peritonitis during the first 2 years had no difference in JvL, or change in JvL compared to patients with peritonitis.

Group 3 patients were preferentially referred to APD due to their generally higher small solute transport. Thus, after 1 year, APD prevalence was 17% for group 1, 29% for group 2 and 51% for group 3. Prevalence rates for APD with dry day were 6, 21 and 37%, respectively. APD with dry day reduced albumin loss and albumin peritoneal clearance for
all groups, compared to continuous dialysis forms (Table 3). Group 3 patients on intermittent therapy had a smaller fall in p-albumin than those on continuous therapy (−49 ± 66 µM/l vs −73 ± 74 µmol/l, P < 0.05). There was no effect of JvL on p-albumin or change in albumin in the subgroup of patients treated with APD with dry day.

No relationship was seen to plasma calcium ion, phosphate, PTH, bicarbonate or to use of antihypertensive therapy, erythropoietin, calcium carbonate or alfacalcidol. Other follow-up details are shown in Table 4. There were no significant differences in admission frequency, admission days or peritonitis frequency. Patients with a high JvL had a higher
residual renal function at start of dialysis, and this difference was preserved, leading to a higher $K_t/V$ and lower plasma creatinine. Despite this, they were characterized by a lower creatinine generation rate. There was no difference in prevalence of overhydration or use of hypertonic glucose bags.

Mortality was increased significantly with raised $J_{VL}$ (Figure 5). The trend was also present on an as-treated analysis (3 year mortality: group 1, 14%; group 2, 28%; group 3, 43%) but this was not significant. The causes of death are shown in Table 5. The cause of the increased death risk in group 3 patients seemed

![Fig. 4. Changes in plasma albumin from baseline (average of months -6, -3 and -1). Cohort survival >3.5 years.](image-url)
to be due to an excess risk of infection. Sixteen deaths due to infection occurred while on PD therapy; of these, eight were due to peritonitis, giving an overall mortality risk for peritonitis of 3%. On a multiple regression analysis, including age and JvL, the effect of JvL on mortality was independent of age; the increased risk per 10 μl/min/1.73 m² increase in JvL was 4.2% (confidence limit 0.4–8.3, P < 0.05). If comorbidity and/or

### Table 4. Relationship of JvL to selected follow-up results, dialysis variables and clinical biochemistry

| JvL (ml/min/1.73 m²) | <0.075 | 0.075–0.11 | >0.11 | Significance |
|----------------------|--------|------------|-------|--------------|
| **Clinical Variables** |        |            |       |              |
| Admission no. (/year) | 1.94 ± 2.7 | 1.95 ± 3.0 | 1.92 ± 2.6 | NS |
| Admission days (no./year) | 16.9 ± 23.2 | 15.7 ± 25.3 | 17.4 ± 25.0 | NS |
| Peritonitis no. (/year) | 0.62 ± 1.1 | 0.67 ± 1.3 | 0.70 ± 1.1 | NS |
| Dry weight (kg) | 75.1 ± 14.2 | 71.6 ± 12.9 | 69.0 ± 13.9 | NS |
| Change in dry weight (kg) | 0.71 ± 3.6 | 2.8 ± 5.6 | 1.5 ± 3.8 | NS |
| Poor clinical state (prevalence, %) | 11 | 16 | 20 | NS |
| Overhydration (prevalence, %) | 21 | 26 | 20 | NS |
| Fluid excess (kg) | 1.3 ± 2.2 | 1.4 ± 2.2 | 1.0 ± 2.3 | NS |
| Urine volume (ml/day) | 490 ± 624 | 517 ± 644 | 752 ± 724 | NS |
| Statin use (%) | 21 | 28 | 40 | <0.05 |
| **Biochemical variables** |        |            |       |              |
| Sodium (mM) | 138.5 ± 3.9 | 138.8 ± 3.6 | 137.0 ± 3.9 | <0.05 |
| Creatinine (μM) | 890 ± 229 | 892 ± 232 | 718 ± 231 | <0.01 |
| Urea (mM) | 18.8 ± 6.0 | 19.5 ± 6.6 | 18.3 ± 6.8 | NS |
| Renal creatinine clearance (ml/min) | 2.87 ± 3.4 | 2.81 ± 3.2 | 3.45 ± 3.1 | P < 0.05 |
| **Dialysis variables** |        |            |       |              |
| Kt/V (/week) | 1.80 ± 0.5 | 1.94 ± 0.4 | 2.24 ± 0.5 | P < 0.01 |
| Total creatinine clearance (ml/min) | 6.09 ± 2.5 | 6.45 ± 1.5 | 7.00 ± 1.39 | P < 0.05 |
| PNA (g/kg/day) | 0.86 ± 0.25 | 0.91 ± 0.25 | 1.03 ± 0.31 | P < 0.05 |
| Ultrafiltration (ml/day) | 1153 ± 78 | 1159 ± 752 | 851 ± 695 | NS |
| Dialysis glucose (mg%) | 1.88 ± 0.46 | 1.93 ± 0.49 | 1.86 ± 0.43 | NS |
| Creatinine generation rate (μmol/min) | 6.36 ± 1.8 | 4.80 ± 1.6 | 4.45 ± 2.5 | P < 0.05 |

Average values.

**Fig. 5.** Relationship of JvL to patient survival.
ately after initiation, patients with a high \( J_vL \) are at increased risk of technique failure, two patient desire, one ultrafiltration failure and peritonitis, six mechanical problems, four social causes, four insufficient dialysis, two abdominal operations, two patient desire, one ultrafiltration failure and one sclerosing peritonitis.

**Discussion**

The finding that a high \( J_vL \) is related to high age, smoking, and the presence of atherosclerosis and other systemic disease at the start of dialysis supports the theory that increasing large pore permeability is a marker of generalized capillary disease. Previous studies have shown that increased vascular permeability, as measured by transcapillary escape rate of albumin, is found in hypertension, atherosclerosis, diabetes and smokers. However, this is not the explanation of the hypoalbuminaemia seen in patients in this study. Plasma albumin gradually fell in the months up to dialysis, secondary to increasing anorexia. There was no apparent effect of \( J_vL \) on plasma albumin prior to PD, but immediately after initiation, patients with a high \( J_vL \) (>0.11 ml/min/1.73 m²) experienced a dramatic and sustained fall in plasma albumin. In contrast, a gradual increase was seen in patients with a low \( J_vL \) (<0.75 ml/min/1.73 m²), presumably secondary to increased appetite. Patients with ongoing urinary albumin loss also had lower albumin levels. The most likely explanation for these findings is a ‘bathtub’ model. Albumin synthesis, while it is stimulated in the peritoneal dialysis model, the ultrafiltration coefficient \( L_pS \), which is a marker of generalized capillary disease. Previous studies have shown that there appears to be an upper limit to the clinical gains that can be achieved by increasing small solute clearance, and that attention should be shifted to other parameters of dialysis quality. PD can perhaps be optimized by minimizing peritoneal protein losses. PD with dry day is an attractive possibility, which reduces protein loss compared with CAPD. The present study also lends support to this treatment modality, although the effect was not so great as expected. The potential benefit of reducing dialysis exposure time may be limited by the fact that even small amounts of residual dialysate in the peritoneum during the day can lead to appreciable protein losses, since virtually total equilibration with blood plasma can be expected in this situation. Another promising possibility is the recent demonstration that intraperitoneal heparin reduces albumin result in an equilibration of plasma albumin at a lower level. Thus the hypoalbuminaemia at the initial PET in CANUSA [2] was due to the effects of 1 month’s PD rather than predialytic disease. This suggests that peritoneal albumin loss can have an identical pathogenic effect to urinary albumin loss, by causing an iatrogenic ‘nephrotic’ syndrome. In particular, hypoalbuminaemia induces hypercoagulation and endothelial dysfunction in PD patients and contributes to the malnutrition-inflammation-atherosclerosis syndrome [12–14]. The fact that no apparent excess prevalence of overhydration was seen in these patients may be due to the fact that dialysis treatment, in particular use of APD, was continually adjusted to achieve and maintain normal fluid status. In accordance with this theory, patients with high \( J_vL \) had a lower creatinine generation rate and a mortality double that of patients with low values, and initially hypoalbuminaemic high \( J_vL \) patients had an increased technique failure rate. This effect was independent of age but not both age and comorbidity. This study does not therefore have the power to differentiate whether \( J_vL \) is just a marker of increased mortality or a direct cause secondary to increased protein loss. It is, however, interesting to note that the excess death rate in high \( J_vL \) patients was mainly due to increased infection rather than atherosclerotic disease; it may be that peritoneal immunoglobulin loss is contributing to their morbidity.

While this study suggests that \( J_vL \) is a major cause of hypoalbuminaemia, other possibilities cannot be excluded. Significant amounts of albumin are also lost through the small pores by convection. Area parameter and \( J_vL \) were correlated to each other. This may be real (bigger membranes have more of both types of pore) or a result of mathematical coupling. In the PDC model, the ultrafiltration coefficient \( L_pS \), which affects the calculation of \( J_vL \), is mainly determined from the area parameter. Although \( J_vL \) was more closely correlated to plasma albumin than area parameter, the PDC model can therefore not determine exactly the relative roles of area parameter and \( J_vL \) in the determination of plasma albumin.

The HEMO [15] and ADEMEX [16] studies have shown that there appears to be an upper limit to the clinical gains that can be achieved by increasing small solute clearance, and that attention should be shifted to other parameters of dialysis quality. PD can perhaps be optimized by minimizing peritoneal protein losses. APD with dry day is an attractive possibility, which reduces protein loss compared with CAPD. The present study also lends support to this treatment modality, although the effect was not so great as expected. The potential benefit of reducing dialysis exposure time may be limited by the fact that even small amounts of residual dialysate in the peritoneum during the day can lead to appreciable protein losses, since virtually total equilibration with blood plasma can be expected in this situation. Another promising possibility is the recent demonstration that intraperitoneal heparin reduces albumin.
permeability [19] possibly due to its anti-inflammatory properties.

Conflict of interest statement. None declared.

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