We investigated whether a selective angiotensin II receptor blocker (ARB) would have a regressive effect on left ventricular hypertrophy (LVH) in patients on continuous ambulatory peritoneal dialysis (CAPD). In a double-blind study, 24 CAPD patients with LVH [left ventricular mass index (LVMi) > 110 g/m² for women and LVMi > 137 g/m² for men] were randomized to 12 months' administration of either the ARB valsartan (n = 14) or a placebo (n = 10). The target blood pressure (BP) was 140/90 mmHg or lower in both groups. The following parameters were measured before and at the end of the study: aortic and large-artery compliance and arterial wave reflections [pulse wave velocity (PWV) and augmentation index (AI) application tonometry] and cardiac echocardiography. Periodically recorded were body weight, BP (mercury sphygmomanometer), serum creatinine, electrolytes, complete blood cell counts, urine volume, drainage volume, and weekly creatinine clearance. Two-way analysis of variance for repeated measurements was used for statistical analysis.

Systolic and diastolic BP were both reduced in patients treated with ARB. The LVMi was significantly reduced in patients treated with ARB (to 121 ± 4 from 145 ± 5) but not in those receiving placebo (to 137 ± 3 from 152 ± 3, p < 0.05). The decrease in LVMi was associated with a reduction in PWV and AI. In CAPD patients with LVH, ARB reduced LVMi in association with alterations in arterial hemodynamics.

Key words
Angiotensin II receptor blocker, left ventricular hypertrophy, pulse wave velocity

Introduction
Cardiovascular events and hypertension are among the more frequent causes of death in patients with end-stage renal disease (ESRD) (1) and are the most important factors contributing to the long-term prognosis of continuous ambulatory peritoneal dialysis (CAPD) patients (2). Evidence, documented in many populations, indicates a definite association between adverse cardiovascular outcomes and left ventricular hypertrophy (LVH) (3).

Left ventricular hypertrophy is an adaptive process that occurs in response to long-term increases in myocardial work caused by pressure or volume overload. It results from the interaction between mechanical stimuli and locally generated growth factors and vasoactive substances (4). A large portion of hypertension in dialysis patients is generally considered to be responsive to volume removal, with the remaining portion being attributable to renin-mediated vasoconstriction (5). Cannella et al. (6,7) demonstrated that antihypertensive drugs, including angiotensin-converting enzyme (ACE) inhibitors, prevent the progression of LVH in uremic patients independently of hypotensive effects.

Recently, the results of large clinical trials involving patients with diabetic nephropathy have questioned whether angiotensin II receptor blocker (ARB) can replace ACE inhibitors as the agent of choice in treating hypertension and diabetes (8,9). Data from those...
studies support the view that ARB has hypotensive and renoprotective effects similar to those of ACE inhibitors and that ARB is indicated for patients in whom ACE inhibitors cause intolerable side effects. In the present study, we investigated whether ARB would have a regressive effect on LVH and would attenuate arterial stiffness in hypertensive patients on CAPD.

**Patients and methods**

In a double-blind study, 24 CAPD patients with LVH [left ventricular mass index (LVMi) > 110 g/m² for women and LVMi > 137 g/m² for men] were randomized to 12 months’ administration of either valsartan (n = 14) or a placebo (n = 10). The target blood pressure (BP) was 140/90 mmHg or lower in both groups. The following parameters were measured before and at the end of the study: LVMi (echocardiography), aortic and large-artery compliance and arterial wave reflections [pulse wave velocity (PWV) and augmentation index (AI) application tonometry]. Periodically recorded were body weight, BP (mercury sphygmomanometer), serum creatinine, electrolytes, complete blood cell counts, urine volume, drainage volume, and weekly creatinine clearance.

The cause of renal insufficiency was chronic glomerulonephritis in 16 patients and unknown in 8 patients. Patients with diabetic nephropathy were excluded. The previously administered antihypertensive drugs were withheld before the study. Mild hypertension was defined as sitting systolic BP above 140 mmHg and below 160 mmHg after a 2-week run-in period. The most important exclusion criteria were these: presence of overt heart failure; history of heart failure, myocardial infarction, or cerebral accident in the preceding 6 months; pregnancy; illness requiring hospitalization or single episode of peritonitis within the preceding 6 months; and possible existence of malignancy, active infections, and immunologic diseases.

All the patients included in the study gave their informed consent to participation. The study was performed in accordance with the Second Helsinki Declaration and was approved by the local ethical committee (No. 169).

After a run-in period, patients started to receive 40 mg valsartan or placebo once daily. Patients were assessed at 4 and 8 weeks. At 4 weeks, if systolic BP was above 140 mmHg in the valsartan group, the dose of valsartan was increased to 80 mg. If systolic BP was above 140 mmHg in the control group, a calcium antagonist, amlodipine (5 mg once daily), was started and then the dose was increased up to 10 mg. At 8 weeks, if systolic BP was above 140 mmHg in the valsartan group, doxazosin (1 – 4 mg daily) or guanabenz (2 – 4 mg daily) was added. If systolic BP was above 140 mmHg in the control group, the same drugs employed in the valsartan group were added. All patients received at least 40 mg furosemide daily. Systolic and diastolic BP were measured in the sitting position according to World Health Organization guidelines [two measurements in the sitting position after 5 minutes of rest, followed by one measurement in the standing position after at least 2 minutes of equilibration (10)].

The patients’ CAPD treatment consisted of four 2-L exchanges daily using dialysate containing lactate and 1.5 g/dL or 2.5 g/dL dextrose. All patients were treated using a disconnect system. During the study, all subjects were asked to undergo the same dietary and dialysis regimen. Mean daily dietary intake was determined from individual 24-hour food records during a 3-day period. The dietary protein intake was at least 1 g/kg daily, and the energy intake was above 25 kcal/kg daily. Salt intake was restricted to about 9 g daily.

Patients were instructed to visit the outpatient CAPD clinic every 2 weeks. At that time, body weight, urine volume, and dialysate drain volume were checked according to the patients’ own records. Before, and after the start of the study, urine volume and dialysate drain volume were both measured. Additionally, blood samples were taken for measurement of serum chemistry and hemoglobin.

Echocardiograms of the patients were recorded in the week before the start of treatment and at 12 months after the start of drug administration. The measurements included the end-diastole diameter of the left ventricular chamber, the interventricular septum thickness, and the thickness of the left ventricular posterior wall. The LVMi was calculated from the above measurements according to Devereux et al. (11). The cut-off level for defining LVH was LVMi > 110 g/m² for women and LVMi > 137 g/m² for men respectively (11).

The PWV was recorded on the radial artery in the AI form (Nippon Kohlin, Nagoya, Japan). Pulse waves recorded for approximately a 10-second period were
evaluated. From each peripheral pulse wave, a central wave was derived by using a generalized transfer function. Data were collected directly into a portable microcomputer. After 20 sequential waveforms had been acquired, the integral software was used to generate averaged peripheral and central waveforms, which were then subjected to further analysis (determination of either AI or PWV). The AI was defined as the difference between the first and second peaks of the central arterial waveform, expressed as a percentage of the pulse pressure. To determine PWV, pressure waveforms were recorded at the radial artery site for brachial PWV.

Correction of anemia
Recombinant human erythropoietin (rHuEPO) was administered by the subcutaneous route every week or every other week, and doses were adjusted monthly. Patients were given oral iron supplementation if they were diagnosed as iron deficient. Levels of hemoglobin were maintained around 10.0 g/dL in each group.

Biochemical data evaluation
At the beginning of each monthly period, the following parameters were measured: body weight, serum creatinine, blood urea nitrogen, total protein, serum albumin, serum electrolytes, and alkaline phosphatase. During each 6-month period, laboratory values were recorded. Six-month means were calculated for the variables. Parathyroid hormone (PTH) levels (intact molecule assay), serum cholesterol, and triglycerides were measured once every 6 months.

Calcium metabolism
Patients whose PTH levels were higher than 200 pg/mL were treated with 1,25-(OH)₂ D₃ and CaCO₃ supplements, and patients whose levels were lower than 70 pg/mL were treated with CaCO₃ to reduce hyperphosphatemia. The doses were adjusted by the value of the calcium–phosphate product below 70.

Lipid metabolism control
Lipid-lowering drugs (mainly statin derivatives) were administered if serum cholesterol levels were above 240 mg/dL.

Statistical analysis
All data are presented as mean ± standard deviation. Multiple comparisons were analyzed by analysis of variance (ANOVA) with the Kruskal–Wallis test and subsequent Dunn test. A simple regression analysis was performed for corrections among the variables. A value of $p < 0.05$ was required for statistical significance.

Results

Characteristics of the patients
The average age was 56 ± 3 years in the valsartan group and 57 ± 2 years in the control group. The mean duration of CAPD was 9.4 ± 2.2 months in the valsartan group and 8.9 ± 3.2 months in the control group.

Effects of valsartan on blood pressure
Oral administration of valsartan had significantly reduced both systolic and diastolic BP at the end of the study (to 129/80 ± 4/2 mmHg from 155/91 ± 4/2, Figure 1). In the control group, systolic and diastolic BP were both significantly reduced at the end of the study (to 131/79 ± 3/2 mmHg from 158/88 ± 2/5 mmHg). There was no significant difference between the two groups.

Effects of valsartan on urine volume and serum creatinine
No significant changes in urine volume or serum creatinine were observed throughout the study; however, levels of serum creatinine in the valsartan group gradually increased (Figures 2 and 3).

Effects of valsartan on cardiothoracic ratio
In both groups, a significant reduction in cardiothoracic ratio was observed 12 months after the start of treatment (Figure 4, $p < 0.05$). Moreover, a significant difference was seen between the patients treated with and without ARB ($p < 0.05$).

Changes in echocardiographic variables
Table I presents data from the echocardiographic records taken before the start of the study and after 12 months of treatment. The echocardiographic dimensions of the left ventricle were almost the same in the two groups at the start of the study. In the valsartan group, the LVMi decreased significantly by the end of the study as compared with the LVMi at the start ($p < 0.05$); it also decreased significantly as compared with LVMi in the control group ($p < 0.05$, Figure 5).
During treatment with valsartan, the significant reductions in LVMi were attributable mostly to significant reductions in both the septal and the posterior wall thicknesses and, to a lesser extent, to a reduced diastolic left ventricular width.

Changes in augmentation index and pulse wave velocity
In both groups, AI and PWV were significantly reduced at the end of the study as compared with basal values \((p < 0.05)\). No significant difference was seen between the two groups (Figure 6). Moreover, a significant correlation was observed between systolic BP and PWV in the control group, but not in the valsartan group \((p < 0.05, \text{Figure 7})\).

Adverse effects
During the study period, the patients had no significant intercurrent illnesses (such as infection, surgery, or blood loss). No serious side effects were reported.
Discussion

Despite the many advantages of CAPD in maintaining hemodynamic stability, approximately 50% – 60% of CAPD patients experience hypertension and require antihypertensive treatment. Currently, the drugs most commonly used to treat hypertension in dialysis patients (12) are calcium channel blockers (52%), ACE inhibitors (24%), and beta adrenergic blockers (17%). The ACE inhibitors have been shown to reduce mortality in patients with heart failure and to reduce morbidity in those with coronary disease or LVH. Recently, Favazza et al. (13) noted increased peritoneal transport of creatinine and dextrose, and reduced ultrafiltration volume in patients taking enalapril or nifedipine. Recent data support the view that an ARB (indicated for patients in whom ACE inhibitors cause intolerable side effects) may obviate those symptoms. Moreover, the ACE inhibitors most frequently used are eliminated by renal clearance and are therefore likely to accumulate in the presence of renal dysfunction (14). In contrast, ARB is typically eliminated by hepatic clearance (15), and peritoneal clearance of losartan (the most frequently used ARB worldwide) and its metabolites is reported to be negligible (16).

In the present study, systolic and diastolic BP were both reduced after chronic treatment with valsartan. Those data accord well with previous data from Pedro et al. (16). Those authors reported that losartan is very effective in decreasing BP to 120/74 mmHg from 166/97 mmHg in 1 week and that the drug is well tolerated by CAPD patients. It therefore appears that ARB is useful for treatment of mild-to-moderate hypertension in patients on CAPD.

In general, in CAPD patients, activity of the renin–angiotensin system is suppressed, and ACE inhibitors and ARB seem to play lesser roles. However, BP was markedly reduced with ARB, indicating the
possibility that the renin–angiotensin system in tissue was activated instead of circulating angiotensin II.

The question of whether blockade of the renin–angiotensin system has regressive effects on LVH (with or without BP control in hypertensive and diabetic patients as well as in patients receiving dialysis therapy) is controversial (17). Cannella et al. (18) proposed that prolonged antihypertensive therapy with strict BP control (systolic BP below 140 mmHg and diastolic BP below 85 mmHg) was effective in considerably reducing LVH in chronically hemodialyzed patients. On the other hand, the same group demonstrated that giving ACE inhibitors in doses that did not affect BP was able to reverse LVH (7). However, in both studies, ACE inhibitors were included in the antihypertensive regimen. Based on those studies, the effects of ACE inhibitors cannot be denied.

In the present study, we expanded that notion to use ARB in diabetic patients with LVH. Compared with the efficacy of ACE inhibitors on regression of LVH in diabetic patients with nephropathy who are on dialysis therapy, the beneficial effects of ARB has been less frequently documented. In the ELHE (Evaluation of Losartan in Hemodialysis) study (19), losartan was demonstrated to be a well-tolerated antihypertensive in hemodialysis patients, with a low incidence of adverse reactions. But in that study, the percentage of patients achieving good BP control was low, which is probably due to the fact that antihypertensive regimens in dialyzed patients typically provide only mild BP reduction. The results of the present study clearly demonstrate that valsartan (but not other antihypertensive drug regimens without ARB) regress LVH with reduction of BP.

Pulse wave velocity, a marker of aortic stiffness, has been shown to be a strong independent predictor of cardiovascular and all-cause mortality in patients with ESRD on hemodialysis (20). The cause of reduced arterial compliance and distensibility is probably multifactorial (21). Structural changes (related to atherosclerosis and evidenced by increased arterial wall thickness) contribute to the arterial stiffening. Functional abnormalities, such as angiotensin II–induced vasoconstriction and volume overload play an important role. Recently, Tycho Vuurmans et al.
(22) showed that, in hemodialysis patients, volume reduction without inhibition of the renin–angiotensin system had no significant effect on PWV and AI. In comparison, ACE inhibition reduced PWV with increment of AI and produced further volume reduction. From those data, they concluded that volume correction and ACE inhibition both improve arterial compliance and increase AI in hemodialysis patients.

Volume status in CAPD patients is completely different from volume status in hemodialysis patients. In CAPD patients, BP may be less dependent on volume overload because of the continuous removal of volume. It is therefore likely that, in CAPD patients, BP per se plays an important role in the determination of PWV.

Perhaps the most striking findings in our study were the positive correlation between systolic BP and PWV in patients treated without ARB, and the lack of a significant correlation between systolic BP and PWV in patients treated with ARB. Moreover, no regression of LVH was observed in the patients treated without ARB despite a BP reduction similar to that seen in the patients treated with ARB. The PWV correlated with LVH, and those two variables are known to depend on aortic compliance. There was dissociation between regression of LVH and attenuation of PWV in response to BP reduction. A reduction in BP with ARB had a regressive effect on LVH and attenuation of PWV; on the other hand, reduction of BP without ARB did not affect LVH despite attenuation of PWV. Moreover, we found no significant correlation between LVH and PWV in the patients enrolled in our study, indicating lack of a direct relationship between LVH and PWV. Development and regression of LVH are determined by various factors (23), but PWV correlates to increased distention from BP rather than to structural changes because the brachial artery (used for determination of PWV in this study) is considered to remain free of atherosclerosis.

Conclusion

In CAPD patients with LVH, ARB reduced LVMi in association with alterations in arterial hemodynamics.

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15 Valsartan-Produced Regression of LVH


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Our aim in the present study was to simultaneously determine, in peritoneal dialysis (PD) patients, interleukin-15 (IL-15) concentrations in serum and dialysate, peritoneal transport parameters, and ultrafiltration (UF). The study was performed in 42 patients who had been treated with PD for 24.5 ± 20.1 months. Concentration of IL-15 was measured (ELISA: IBL, Hamburg, Germany) during a peritoneal equilibration test. Of 42 patients, 69% had serum IL-15 concentrations above normal values (<13.0 pg/mL). The mean dialysate-to-plasma ratio (D/P) for IL-15 exceeded 1. We observed a negative relationship between dialysate IL-15 and effluent volume. Patients with UF ≤ 200 mL or < 100 mL had higher dialysate IL-15 concentration, higher D/P for IL-15, higher mass transfer area coefficient (K_BD) for creatinine, and higher dialysate creatinine concentration than patients with more UF. The K_BD for creatinine correlated negatively with dialysate effluent volume. We conclude that, in PD patients, elevated serum and dialysate IL-15 concentrations confirm the existence of systemic and local inflammation; the source of IL-15 in dialysate is not only serum, but also local generation in the peritoneum; and dialysate IL-15 concentration may be a marker of UF capacity.

Key words
Interleukin-15, peritoneal equilibration test, ultrafiltration, peritoneal transfer

Introduction
Hausmann et al. (1), in studying the role of human peritoneal mesothelial cells (HPMCs) in the generation of an immune response during peritonitis, found during in vitro studies that HPMCs produce and secrete interleukin-15 (IL-15). Those authors also detected IL-15 in effluent of patients treated with continuous ambulatory peritoneal dialysis (CAPD). However, they could not exclude other peritoneal cells, including macrophages, as additional sources of IL-15.

Interleukin-15 is a 14-kDa to 15-kDa glycoprotein whose mature form consists of 114 amino acids (2). In humans, the IL-15 gene is coded by chromosome 4q31 (3). Interleukin-15 is a member of the 4 α-helix bundle cytokine family, which includes such cytokines as IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, and IL-9 (2). Vascular endothelial growth factor (VEGF) upregulated IL-15 mRNA levels in isolated uterine natural killer cells (4) and in human colon cancer (Colo320) cells (5). It also affected NO production by mouse brain microglia (6) and induced expression of hyaluronan on primary endothelial cells and microvascular endothelial cell lines (7). All of those factors influence the function of the peritoneum as a filtration membrane.

In uremic patients, endothelial NO synthase activity correlated positively with peritoneal dialysis (PD) duration. That finding reflects the significant increase in endothelial area in long-term PD patients (8). The data suggest that release of NO secondary to endothelial NO synthase upregulation might be a major regulator of ultrafiltration (UF) in long-term PD patients.

Expression of VEGF is clearly upregulated in peritoneal membrane retrieved from long-term PD patients (8). Also, VEGF has been detected in the dialysate of PD patients, in which its abundance correlates with permeability for small solutes and loss of UF (9). By analogy to other vascular diseases, upregulation of
VEGF might trigger vascular proliferation in the peritoneal membrane in long-term PD.

Intraperitoneal hyaluronan production increased with a more highly permeable membrane and with length of time on CAPD. Monitoring of hyaluronan in the dialysate effluent may be useful as a marker to assess functional and morphologic changes in the peritoneum in long-term CAPD patients (10).

Taking into account the aforementioned facts, our aim in the present study was to determine, in PD patients, the source (blood, peritoneal membrane) of IL-15 in dialysate and the relationships between concentrations of IL-15 in serum and dialysate and parameters of peritoneal transport and UF.

**Patients and methods**

The study was performed in 42 stable PD patients [age: 52.3 ± 14.4 years; PD duration 24.5 ± 20.1 months (range: 0.4 – 72.4 months)] without any clinical signs of infection during the preceding 2 months. In all patients, PD was started 2 weeks after insertion of a standard Tenckhoff catheter. Of the 42 patients, 34 were being treated with CAPD; the others were being treated with automated PD. All patients used standard peritoneal dialysis solutions (Dianeal PD1, Dianeal PD4: Baxter Healthcare SA, Castlebar, Ireland; CAPD/DPCA 17, 18, 19: Fresenius Medical Care, Bad Homburg, Germany). Causes of end-stage renal disease were chronic glomerulonephritis (12 cases), chronic pyelonephritis (8 cases), diabetic nephropathy (8 cases), hypertensive nephropathy (5 cases), polycystic kidney disease (3 cases), and Schönlein–Henoch syndrome (1 case). In 5 cases, the cause of end-stage renal disease remained unknown.

Serum and dialysate IL-15 concentrations were measured during a peritoneal equilibration test (PET) performed with 2.27% glucose dialysis solution according to the method described by Twardowski et al. (11). The PET was carried out after a preceding overnight exchange with 2 L of 2.27% glucose dialysis solution. Drainage of the dialysate from the overnight exchange was individually prolonged in every case to empty the peritoneal cavity as much as possible. (The drain bag was weighed on an electronic scale during dialysate outflow, and drainage was stopped when 3 consecutive weighings, taken at 5-minute intervals, yielded the identical value.)

During the PET, dialysate samples (5 mL each) were collected at 0, 2, and 4 hours’ equilibration time after infusion, and blood samples were drawn at 2 hours after dialysate infusion. At the end of the 4-hour dwell, the dialysate was collected, and dialysate volume was measured.

The dialysate-to-plasma ratio (D/P) creatinine was calculated at 0, 2, and 4 hours of the PET. The D/P IL-15 was calculated at 4 hours. We used the Waniweski model (12) to calculate the mass transfer area coefficient (K_{BD}) for creatinine. For the K_{BD} calculation, we assumed that the blood solute level was stable for the entire 4-hour dwell and that linear increments in dialysate volume occurred up to 2 hours of the dwell. The instilled volume of dialysis solution (2 L at time 0) and the measured effluent volume after the 4-hour dwell plus 15 mL (3 ≈ 5 mL removed for analysis) were used for interpolation. Inflow and outflow times were not used in the calculations; the K_{BD} values represent peritoneal transfer during the dwell (not during the entire exchange).

Values of K_{BD} creatinine were calculated for these PET dwell periods: between time 0 and 2 hours of the dwell, between 2 hours and 4 hours of the dwell, and between time 0 and 4 hours of the dwell. The IL-15 concentration in serum and dialysate was determined by ELISA (IBL, Hamburg, Germany). Creatinine and glucose were estimated using reagents from Cormay Reagents (Lublin, Poland).

The patients were divided into four peritoneal transport groups (H = high; HA = high average; LA = low average; L = low) on the basis of their D/P creatinine at the 4th hour of the PET. Two limit values (200 mL and 100 mL) were taken as indicators of UF deterioration or failure (13,14). Based on those limits, the patients were divided into several subgroups: group I, UF volume > 200 mL; group II, UF volume ≤ 200 mL; group A, UF volume ⊕ 100 mL; group B, UF volume < 100 mL.

Data are presented as mean ± standard deviation (in the case of normal distribution) or median (percentiles: 25% – 75%) and range (in the case of other than normal distribution). Comparisons between results obtained by peritoneal transport type were performed by one-way analysis of variance. Differences between groups based on UF volume were checked by the Mann–Whitney test. Correlations between variables were analyzed using the Pearson or Spearman test, as appropriate. A significance level of p < 0.05 was accepted.
Results
For all 42 patients, the median serum IL-15 concentration was 25.0 pg/mL (range: 0.0 – 857.1 pg/mL). Serum IL-15 concentration was above the accepted normal value (<13.0 pg/mL) in 29 patients (69%). Median dialysate IL-15 level (64.3 pg/mL; range: 14.3 – 142.9 pg/mL) was higher than the median concentration in serum, and the D/P for IL-15 exceeded 1 (1.7; range: 0.1 – 41.7).

No statistically significant differences were observed in serum IL-15 level, dialysate IL-15 level, or D/P IL-15 between the various peritoneal transport types. In all groups, the D/P ratio for IL-15 exceeded 1 (Table I).

Correlations between serum and dialysate IL-15 concentration or between D/P ratio for IL-15 and other estimated parameters were not statistically significant, with one exception. A negative correlation was observed between dialysate IL-15 level and effluent volume in the PET (Figure 1).

Comparative analysis of patients grouped according to UF volume showed that group II had a significantly higher dialysate IL-15 concentration than did group I [78.6 pg/mL (50.0 – 142.9 pg/mL) vs. 57.1 pg/mL (14.3 – 103.6 pg/mL), Figure 2], and group B had a significantly higher D/P IL-15 than did group A [6.67 (0.69 – 41.67) vs. 1.42 (0.06 – 14.85), Figure 3]. Group II also showed a higher K_D creatinine during the first 2 hours of the PET than did group I (5.3 ± 3.5 mL/min vs. 2.9 ± 2.6 mL/min, p = 0.08). The K_D creatinine obtained during the first 2 hours of the dwell correlated negatively with effluent volume (r = –0.495, p = 0.004). Moreover, group B had a higher dialysate creatinine concentration at 4 hours of the dwell than did group A (12.3 ± 8.7 mg/dL vs. 6.9 ± 2.5 mg/dL, p = 0.016).

Discussion
Systemic activation of monocytes in the absence of peritonitis or other apparent causes of inflammation (15) and elevated levels of C-reactive protein and pro-inflammatory cytokines present in serum of PD patients (16) indicate the existence of systemic inflammation in that group of patients. Chronic inflammation is also confirmed by our study, in which we observed elevated serum concentrations of such

![Figure 1](image_url)  
**FIGURE 1** Relationship between dialysate interleukin-15 (IL-15) concentration and effluent volume from a 4-hour peritoneal equilibration test.

TABLE I  Concentration of interleukin-15 (IL-15) in serum and dialysate, and dialysate-to-plasma ratio (D/P) for IL-15 [median, range (mean ± standard deviation)] in groups of patients selected by peritoneal transport type

<table>
<thead>
<tr>
<th>Transport type</th>
<th>Patients (n)</th>
<th>Serum IL-15 (pg/mL)</th>
<th>Dialysate IL-15 (pg/mL)</th>
<th>D/P IL-15</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>6</td>
<td>30.4, 0.0–128.6</td>
<td>67.9, 14.3–100.0</td>
<td>1.3, 0.4–8.0</td>
</tr>
<tr>
<td>HA</td>
<td>14</td>
<td>21.5, 0.0–635.7</td>
<td>64.3, 39.3–103.6</td>
<td>3.0, 0.1–27.8</td>
</tr>
<tr>
<td>LA</td>
<td>14</td>
<td>30.4, 0.0–857.1</td>
<td>76.8, 50.0–142.9</td>
<td>1.8, 0.1–41.7</td>
</tr>
<tr>
<td>L</td>
<td>8</td>
<td>16.1, 0.0–128.6</td>
<td>55.4, 39.3–100.0</td>
<td>3.4, 0.4–14.9</td>
</tr>
</tbody>
</table>

H = high; HA = high-average; LA = low-average; L = low.
pro-inflammatory cytokines as IL-15 (almost 70% of examined stable PD patients) in the absence of clinical signs of infection.

Studies in CAPD patients also have demonstrated the presence of chronic sterile inflammation at the level of the peritoneum (17). Inflammatory status in CAPD patients becomes aggravated with time on PD. Dialysate concentrations of IL-1β, tumor necrosis factor α, IL-6, IL-8, interferon γ, and transforming growth factor β1 were observed to increase in the course of 5 months of CAPD treatment without infection (18,19). Interleukin-15, detected in dialysate by Hausmann et al. (1) and also in our study, may contribute to the generation of that local inflammation.

In our entire study population, and in the subgroups based on peritoneal transport, the median value for D/P IL-15 exceeded 1. That finding suggests local generation of the cytokine. The main source of IL-15 in the dialysate is probably HPMCs, but peritoneal macrophages cannot be excluded as an additional source (1). Dialysate and serum IL-15 concentrations seem to be independent of parameters of peritoneal permeability, because we observed no statistically significant differences between the various peritoneal transport groups.

Persistent systemic and local inflammatory response may be a consequence of clinically unrecognized dialysis-related or non-dialysis-related infections (20). Additionally, the repeated use of bioincompatible dialysis solutions causes a deteriorating effect on the peritoneal membrane (21). Conventional acidic, lactate-buffered, glucose-containing dialysis solutions and the glucose degradation products generated during heat sterilization are widely believed to contribute to structural and functional changes in the dialyzed peritoneal membrane (22–25). Thickening of the submesothelial space owing to collagen deposition and alterations in the morphology of small blood vessels is involved in changes to the peritoneal structure (24). Functional disturbances concern mainly the tendency toward an increased small-solute transport rate with reduced UF (22,24). The relationship between the structural and the functional changes have not been fully defined (22,24); however, VEGF, NO, and hyaluronan (among other factors) are postulated to play roles in that relationship (8–10). Interleukin-15 influences expression of all of those factors in various types of cells (4–7). Therefore, IL-15 may play a role in the function of the peritoneum as a dialyzing membrane.

In our study, we observed a statistically significant negative correlation between dialysate IL-15 level and effluent volume in a PET. Also, in the patient subgroups characterized by a UF volume suggesting UF deterioration, we observed a significantly higher dialysate IL-15 concentration and D/P IL-15 than we observed in patient subgroups with a greater UF volume. Those data suggest a link between IL-15 and UF.

Several mechanisms have been suggested for UF capacity loss. The most common explanation is in-
creased diffusive transport resulting in rapid glucose absorption and thus rapid loss of the osmotic driving force (26). Such a mechanism may be associated with IL-15, because the subgroup of patients with a higher dialysate IL-15 level and a UF volume ≤ 200 mL simultaneously showed a greater $K_{BD}$ creatinine, which indicates higher peritoneal transport (27). Moreover, the patient subgroup with a higher D/P IL-15 and a UF volume < 100 mL showed a greater dialysate creatinine concentration, which also might indicate increased diffusive transport.

Loss of peritoneal function is a major factor leading to PD failure (22). Peritoneal UF capacity and small-solute transport characteristics seem to be relatively stable in most patients treated with PD for up to 3 years (26). Garred et al. (28) demonstrated relatively constant $K_{BD}$ urea and creatinine up to 3.5 years of PD. However, in patients treated for a longer period, tendencies toward increasing diffusive transport for small solutes and a decreasing net UF were observed (26). Passlick–Deetjen et al. (29) reported that, in PD patients, PET values for creatinine changed significantly after 24 months and values for urea and glucose changed significantly after 36 months. Other studies also indicated increments in peritoneal permeability during the course of PD, usually after several years of treatment (30,31). The risk for loss of UF capacity may even be as high as 50% after 6 years on PD (9). Therefore, dialysate IL-15 concentration as a marker of UF capacity in PD patients may be a useful tool for detecting UF deterioration during PD treatment.

Conclusions
Elevated serum and dialysate IL-15 concentrations confirm the existence of systemic and local inflammation in PD patients. The source of IL-15 in dialysate is not only serum, but also local generation in the peritoneum. Dialysate IL-15 concentration may be a marker of UF capacity in PD patients.

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