The theoretical constructs of, and limited clinical experiments with, continuous flow peritoneal dialysis (CFPD) are very promising. Specifically, removal of small molecular solutes has been shown to approximate that with quotidian hemodialysis. However, progress has been slow because of the lack of an adequate peritoneal access device and the high cost of peritoneal dialysis (PD) solution generation. Several novel designs for CFPD catheters have been introduced during the past year. Those designs may solve some of the problems of fluid mixing and recirculation. This review of the past and latest developments in CFPD identifies the factors that limit the widespread use of this promising therapy.

Key words
Automated peritoneal dialysis, continuous flow peritoneal dialysis, peritoneal access, adequacy

Introduction
Continuous flow peritoneal dialysis (CFPD) has long been considered to have the potential for the highest small-solute clearances and the greatest ultrafiltration of any PD modality (1). A continuous high flow of dialysis solution results both in maximum diffusion gradients and in the elimination of nondialytic transit time. Renewed interest in CFPD is evidenced in the publication of several recent acute experiments with a limited number of patients and in the development of numerous double-lumen catheters. Most of the studies confirm previous experiences that showed markedly increased small-solute clearances, low or negligible ultrafiltration, and poor mixing or streaming of PD solution from one catheter lumen to the other. The latter situation has underlined the need for better catheter designs.

Discussion
Dialysate generation
Large volumes of PD solution can be provided through the use of fresh commercial dialysate, de novo on-line production, or regeneration of spent dialysate with hemodialysis (HD) technology or a sorbent column (1). Most acute experiments have been performed using either commercial dialysate in bags or HD regeneration techniques. The former approach is impractical for clinical use because of its prohibitive cost and enormous storage requirements. Regeneration using HD technology has the advantage of being proven and safe. The solute clearance of a hemodialyzer exceeds peritoneal clearance, rendering the technique very efficient (2). In addition, the process of regeneration transforms the priming PD fluid into a bicarbonate-based solution, because the secondary dialysate is lactate-free and rich in bicarbonate.

Catheters for CFPD
A catheter for CFPD must provide separate conduits for infusing and draining the dialysate into and out of the peritoneal cavity at a high flow rate (100 – 250 mL/min) with good mixing of the peritoneal solution and minimal streaming and recirculation. The catheter should also be cosmetically acceptable (small diameter, minimal bulk), easy to implant and remove, biocompatible, reliable, and safe. The reported clinical experiences have used one of the following access methods:

- Two separate conventional or subcutaneous catheters
- One permanent conventional catheter and an additional temporary catheter
- One catheter and a single-needle HD device
- A dedicated double-lumen catheter.

Figure 1 presents the basic designs for double-lumen CFPD catheters. The simplest devices consist of two straight or curled barrels in a double-D or double-O configuration (3,4). The inflow barrel is shorter, and the drain barrel is longer and located in the most dependent pelvic area. Modifications to this basic design include the addition of discs placed in the distal intraperitoneal segment of the catheter to diffuse the inflow stream of dialysate and to improve mixing (5).
These catheters are simple to manufacture and esthetically acceptable. The external diameter can be markedly reduced by reducing wall thickness. The flow rates have been shown to be adequate for CFPD. The main drawback of the catheters is recirculation, estimated to be in the 40% – 50% range (6). Figure 2 plots peritoneal effluent dextrose concentrations during infusion of a 50 mL bolus of 5% dextrose in a patient undergoing CFPD with 1.0% dextrose solution. The immediate increase in glucose concentration in the effluent strongly suggests streaming and recirculation.

A new, recently introduced design describes a double-lumen catheter with maximum separation of the intraperitoneal limbs to minimize recirculation. The catheter can be implanted peritoneoscopically or laparoscopically (7). It consists of two tubes in a novel

![Diagram of catheter designs](image)

**Figure 1** Catheter designs for continuous-flow peritoneal dialysis. For each catheter, longitudinal views are depicted on the left and cross-sectional views on the right.

![Graph of measured dextrose concentration](image)

**Figure 2** Measured dextrose concentration in the peritoneal effluent after infusion of a 50-mL bolus of 5% dextrose. See text for details.
cross-sectional configuration, in which a slightly ovoid tube is nested within a second crescent-shaped tube, providing maximal internal cross-sectional area with minimal external diameter (Figure 1). The external end of the catheter consists of two separate tubes that accept two connectors. The tubes are bonded together as they pass through the abdominal wall and into the peritoneum. Internally, the tubes once again separate intraperitoneally to form a double J. That configuration causes the cranial and caudal limbs to separate by 180 degrees. The cranial segment is shorter than the caudal, and both terminate with a fluted end. The marked physical separation of the limbs (approximately 13 cm) and the functional separation provided by the fluting (which projects fluid away from the lumen) could provide an effective separation of about 20 cm. Preliminary in vitro studies using passive hydrostatic pressure have shown excellent flow rates and good mixing (7). Clinical studies are needed to confirm applicability of this catheter for CFPD.

The latest design consists of a double-lumen catheter with a proximal diffuser for inflow positioned close to the point of entry of the catheter into the peritoneum (8). A long, curled segment—similar to a conventional coiled catheter—is used for drainage. The considerable distance between the inflow component and the drain segment, together with the diffusing effect caused by multiple holes perpendicular to the catheter axis are expected to improve mixing. Limited in vitro recirculation studies suggest low (<3%) recirculation (9).

Clinical experiences

Table I summarizes available clinical data, including system description and results, for most CFPD series reported in the literature (5,6,8,10–19). Slightly more than 100 patients have been studied over the past four decades. Most patients were studied only one to three times over 4 – 6 hours; a few remained on therapy for several weeks. The most common forms of dialysate provision were individual solution bags and regeneration of spent dialysate by HD technology. Peritoneal access was obtained by means of a double-lumen catheter, two separate catheters (various types and configurations), or one catheter and a single-needle device. Glucose concentrations ranged from 0.7% to 1.8%. Exchange volumes varied from 1 L to 4 L. The peritoneal solution flow rates (Qp) ranged widely (20 – 315 mL/min), although most series kept within the 100 – 200 mL/min range.

Small-solute clearances were uniformly higher than those observed with the intermittent technique—in the domain of K_{urea}^T = 30 – 45 mL/min and a similar-magnitude mass transfer coefficient (MTC) for urea. The use of two catheters tended to provide the highest clearances, suggesting superior mixing of the solution. Analysis of the correlation between MTC_{urea} and Q_p showed an initial rapid increase in MTC as a function of Q_p, with an eventual plateau at Q_p > 200 mL/min (20). If those findings are extrapolated to a model of daily CFPD, then an 8-hour session and a Q_p of 250 mL/min predicts a standard Kt/V approximating 3.5. That result is far superior to any other modality of PD and comparable to quotidian HD (2).

Review of the ultrafiltration (UF) observations reveals a curious absence of data and a marked variability in results. Scrutiny of the literature fails, in most cases, to provide enough detail on the methodology used to measure net UF. The areas of concern are several. Whether the bags were weighed before infusion to determine the solution volume is not clear. When UF is calculated by change in patient weight, no detail is provided regarding the methodology used to conduct fluid-balance studies. The theoretical constructs predict a net UF rate of 6 – 7 mL/min with dialysate containing 1.5% glucose (21). Indeed, two rigorous studies of a single patient confirmed that finding (17). However, the reported UF rate varies from negligible to more than 10 mL/min, with most values below 3 mL/min.

Conclusion

Does CFPD have a future?

The potential advantages of CFPD include marked increase in small-solute clearance; convenient provision of bicarbonate-based, biocompatible solutions with variable solute concentrations; lower rates of peritonitis; and reduction in protein losses (1). However, several issues need clarification through further animal models and clinical studies.

The principal concern is the variable and unpredictable UF rate. The observed disparate UF results are very likely attributable to streaming and recirculation. If that is the case, then perhaps the application of new catheters with better separation of the streams will shed light on the issue. Long-term outcomes—such as the response of the peritoneal membrane and host defense mechanisms to the high flow
TABLE I Summary of clinical data on continuous-flow peritoneal dialysis

| Series                | Pts (n) | Dialysate source       | Catheter type             | Glucose concentration | Time (hours) | Vp (L) | Qp (mL/min) | KpU (mL/min) | KpCr (mL/min) | MTCU (mL/min) | MTCCr (mL/min) | UFR (mL/min) |
|-----------------------|---------|------------------------|---------------------------|-----------------------|--------------|--------|------------|--------------|--------------|---------------|---------------|---------------|-------------|
| Shinaberger et al.    | 7       | HD regeneration        | 2 catheters               | 1.50%                 | 4–8          | 3–4    | 20–315     | 58           | 35           | 70 a          | N/A           | N/A           |             |
| Lange and Treser      | 52      | Single-pass bottles    | Double-lumen              | ?                     | Up to 72     | N/A    | 66         | 29–45        | N/A          | N/A           | N/A           | N/A           |             |
| Stephen et al.        | 10      | HD regeneration        | SC with 2 arms (mouse)    | Variable              | 5            | 1.2–3  | 150–350    | 26–33        | 24.8         | N/A           | N/A           | 4–7          |             |
| Kraus et al.          | 5       | HD regeneration        | 2 catheters               | V                      | 10–13        | N/A    | 80–200     | 53.8         | 40.5         | N/A           | N/A           | N/A           |             |
| Raj et al.            | 8       | HD regeneration        | 1 catheter; single-needle device | 0.73%                 | 8            | 2.5    | 141        | 26.5         | 22.1         | N/A           | N/A           | 2.9          |             |
| Mineshima et al.      | 3       | HD regeneration        | Double-lumen study catheter | 0.8%–1.8%             | 6            | 1      | 100        | 14.1         | N/A          | N/A           | N/A           | 0.6–2.4      |             |
| Cruz et al.           | 4       | Single-pass bags       | 2 Cruz catheters          | 1.5%                  | 4            | 2      | 200        | 40           | 28.2         | 40.4          | 25.2         | 13.4         |             |
| Amerling et al.       | 1       | Single-pass bags       | Double-lumen study catheter | 1.5%                  | 3            | 3      | 200        | 22           | 19           | 26            | 22           | N/A          |             |
|                       | 1       | HD regeneration        | 2 catheters               | 1.5% (?)              | 4            | 3      | 300        | N/A          | N/A          | N/A           | N/A           | N/A          |             |
| Passlick–Deetjen et al. | 4   | HD regeneration        | Dual-lumen modified       | 1.0%                  | 8, 3x/wk     | 2      | 200        | 20.4         | 10.6         | N/A           | N/A           | Nil           |             |
| Freida and Issad      | 5       | Single-pass bags       | 2 catheters               | 1.5% b                | 4            | 2      | 100–150    | 34.9         | 26.1         | 47.9          | 31.8         | 2.44         |             |
| Piraino et al. c      | 5       | Single-pass bags       | Dual-lumen catheter d     | 1.5%                  | 4            | 2      | 100        | 25.5         | 16.1         | N/A           | N/A           | 2            |             |
| Ronco et al.          | 1       | Single-pass bags       | Dual-lumen with diffuser  | N/A                   | N/A          | 0.5–2.0 | 50–150     | 25–49        | 15–28        | N/A           | N/A           | N/A          |             |

a Estimated MTCU at Qp = 200 mL/min.

b +HCO3 5 mEq/L added to each bag.

c Piraino B. CFPD using the dual lumen catheter. Presented at the American Society of Nephrology Renal Week, 2003; 757–61.


Pts = patients; Vp = exchange; Qp = flow rate; KpU = peritoneal urea clearance; KpCr = peritoneal creatinine clearance; MTCU = mass transfer coefficient for urea; MTCCr = mass transfer coefficient for creatinine; UFR = ultrafiltration rate; HD = hemodialysis; N/A = not available; SC = single catheter; 3x/wk = three times weekly.
of CFPD, and to the use of synthetic membranes or sorbents—are equally important and will require longer studies. A simpler but still critical topic is the formulation of optimal solutions for CFPD (21,22). Finally, if CFPD is considered safe and desirable, then the cost must be consistent with reimbursement structures. For now, it is evident that the cost of equipment and disposables for CFPD using HD technology for regeneration of PD effluent should be similar to quotidian HD.

References

Corresponding author:
Jose A. Diaz-Buxo, MD FACP, 1051 East Morehead Street, Suite 250, Charlotte, North Carolina 28204 U.S.A.
E-mail: jose.diaz-buxo@fmc-na.com
The peritoneal mesothelium is a barrier to ion transport in peritoneal dialysis. In the present study, we investigated, by means of Ussing chamber experiments, the effect of adrenaline on the electrical transepithelial resistance ($R_{TE}$) of isolated visceral sheep peritoneum.

Peritoneal samples from the omentum of adult sheep were isolated within 30 minutes of the animal’s death and were transferred to the laboratory in a cooled Krebs–Ringer bicarbonate solution (4°C, pH 7.5) bubbled with 95% O$_2$/5% CO$_2$. A visceral peritoneal planar sheet was mounted in an Ussing-type chamber and adrenaline ($10^{-7}$ mol/L) was added to the apical and the basolateral side in turn. We measured $R_{TE}$ before and serially for 30 minutes after addition of the adrenaline. Because active ion transport is temperature-dependent, all experiments were performed at 37°C. All results are presented as mean and standard error ($\bar{x} \pm SE$) of 6 experiments.

The control $R_{TE}$ (before adrenaline) was 20.05 ± 0.61 Ω·cm$^2$. Within 1 minute after the addition of adrenaline to the basolateral side of the membrane, $R_{TE}$ increased to 21.8 Ω·cm$^2$, a rate that thereafter progressively decayed, returning to the control value. Adrenaline action on the apical side of the membrane was similar, with a rapid rise of $R_{TE}$ to 22.5 Ω·cm$^2$ and a subsequent decrease ($p < 0.05$).

Previous studies provide evidence for a clear association between $R_{TE}$ and active ion transport. The results of the present study indicate rapid action of adrenaline on the permeability of the visceral peritoneum.

Key words
Peritoneum, adrenergic, permeability, Ussing chamber, transepithelial resistance

Effect of Adrenaline on the Electrophysiologic Profile of Isolated Visceral Sheep Peritoneum

Introduction
The peritoneal mesothelium is one of the main barriers to water and ion transport from the peritoneal cavity to the peritoneal capillary bed (1). Physiologic solute transport across the peritoneal mesothelium is essential for effective peritoneal dialysis treatment. One of the major problems associated with peritoneal dialysis is ultrafiltration failure, which affects up to 50% of patients treated for more than 6 years with peritoneal dialysis (2,3). Peritoneal permeability for small solutes has been proven to increase with time on peritoneal dialysis, eventually leading to ultrafiltration failure and failure of the treatment modality (2,3).

Several studies have shown a clear association between transepithelial electrical resistance ($R_{TE}$) measured in Ussing-type chamber experiments and transcellular active ion transport in serosal membranes such as the peritoneum (4–7) or the pleura (8–10). Those studies were investigating alterations in the permeability of serosal membranes in relation to the action of certain substances—for example, sex hormones, insulin, channel blockers, NO inhibitors, and antibiotics and their metabolites.

In the present study, we investigated the electrophysiologic properties of visceral sheep peritoneum, and especially the effect of adrenaline on transepithelial resistance ($R_{TE}$). To our knowledge, the influence of adrenergic substances on the transepithelial resistance ($R_{TE}$) of the peritoneal membrane has not been previously investigated.

Materials and methods
Intact sheets of visceral sheep peritoneum were obtained from the omentum of adult animals. The samples were collected from a slaughterhouse within 30 minutes of the death of the animals and were transferred to the laboratory in oxygenated Krebs–Ringer solution at 4°C. Immediately after the peritoneal
tissue was removed from the animals, it was placed in the Krebs–Ringer bicarbonate solution. The solution was balanced at pH 7.4 and bubbled with 95% O₂/5% CO₂. The solution contained 117.5 mmol/L NaCl, 1.15 mmol/L NaH₂PO₄, 24.99 mmol/L NaHCO₃, 5.65 mmol/L KCl, 1.18 mmol/L MgSO₄, 2.52 mmol/L CaCl₂, and 5.55 mmol/L glucose.

Pieces of visceral peritoneum were carefully isolated from underlying adipose tissue by removing the fat with a scalpel. The tissues were then visually examined for evidence of holes or adherent tissue. The surfaces was touched as little as possible. The peritoneum was mounted as a planar sheet between two acrylic Ussing-type chambers filled with Krebs–Ringer bicarbonate solution.

Each Ussing chamber was conical in shape and was attached to a glass reservoir of 20 mL total volume (including the chamber volume). The cross-sectional area of the exposed tissue between the reservoirs was 1.43 cm². Because active transport of ions is influenced by temperature, all measurements of transepithelial potential difference were taken at 37°C.

We used 3 mol/L KCl 3% agar bridges placed 3 mm on either side of the membrane to measure the transepithelial potential difference across the visceral peritoneum. The bridges were connected on either side to Ag / AgCl electrodes and a preamplifier (DVC-3: World Precision Instruments, Berlin, Germany) with input impedance of 10¹² Ω. Output was amplified. To determine the voltage response to an external current, direct current provided by a voltage-clamp apparatus (DVC-1000: World Precision Instruments) was passed through the tissue via 3 mol/L KCl agar bridges placed in the reservoirs connected to each hemi-chamber.

The voltage response to applied current (range: −400 to 400 µA) was measured. The transepithelial resistance (Rₜₑ) was calculated according to the Ohm law, from the voltage deflections produced in response to constant current pulses, which were applied across the tissue (the resistance of the solution having been deducted).

The mesothelial cell membranes facing the peritoneal fluid or the blood side in vivo are cited as the apical or basolateral membranes, respectively. The experimental solution bathing the apical side is here called the serosal solution, and the solution bathing the basolateral side is called the mucosal solution.

After addition of adrenaline to each bathing solution (mucosal and serosal consecutively) measurements were taken over a period of 30 minutes (at minutes 1, 3, 5, 10, 15, 20, 25, and 30). The concentration of the adrenaline solution was 10⁻⁷ mol/L in all experiments. All solutions were freshly prepared before each experiment, heated to 37°C and continuously bubbled with a 95% O₂/5% CO₂ gas mixture.

We conducted 6 experiments. All data are expressed as mean and standard error (x ± SE) of those 6 experiments. The probability of error for comparison of the mean values was calculated using the t-test for paired data. Values of p < 0.05 were regarded as significant.

### Results

The spontaneous electrical potential difference across the visceral peritoneum was not significantly different from zero (0.4 ± 0.1 mV). Before the addition of adrenaline, the Rₜₑ of the visceral peritoneum was found to be 20.05 ± 0.61 Ω · cm².

Within 1 minute after the addition of adrenaline (10⁻⁷ mol/L) to the apical membrane side, the Rₜₑ rose significantly to 22.5 ± 0.66 Ω · cm² (p < 0.05). After the 1st minute, the Rₜₑ progressively declined, but remained significantly higher than the control value throughout the observation period of 30 minutes (Figure 1). After addition of adrenaline (10⁻⁷ mol/L) to the basolateral membrane side, the Rₜₑ also increased significantly to 21.8 ± 0.45 Ω · cm² (p < 0.05) in the 1st min and declined progressively thereafter to return to control values at the end of the experiment (Figure 2).

### Discussion

Our data show very low ohmic resistance and no measurable spontaneous potential difference across visceral sheep peritoneum. The Rₜₑ values (20.05 ± 0.61 Ω · cm²) measured in this study are comparable to those previously reported for “leaky” epithelial tissues such as the proximal renal tubule and sheep pleura (9).

One minute after the addition of adrenaline (10⁻⁷ mol/L), the ohmic resistance of the visceral sheep peritoneum rose significantly. According to our own unpublished data, adrenaline produces similar effects on the Rₜₑ of isolated sheep pleura. Our observations indicate the existence of an adrenergic influence on the ionic permeability of the peritoneal membrane,
which becomes less permeable to ionic currents after the action of adrenaline.

The physiologic basis of the $R_{\text{TE}}$ elevation is probably inhibition of transcellular sodium transport. In previous studies, adrenaline was shown to inhibit in vitro active sodium transport in rat cortical collecting ducts and in canine tracheal epithelia (11,12). The concentration of adrenaline used in the present study ($10^{-7}$ mol/L) is far below that used in previous studies ($1 \times 10^{-6}$ to $5 \times 10^{-5}$ mol/L). We selected this low adrenaline concentration because it is similar to that observed in vivo during biologically stressful conditions (13).

Addition of adrenaline raises the $R_{\text{TE}}$ of visceral peritoneum within 1 minute. This rapidity of action indicates that the effect is mediated by adrenergic receptors. The change in $R_{\text{TE}}$ induced by adding adrenaline on the apical side of the visceral peritoneum is more prolonged than that occurring on the basolateral side. We hypothesize that our finding may be attributable to a difference in the concentration and subtype composition of the adrenergic receptors found on the apical and basolateral sides of the peritoneum.

Conclusion

The results of the present study indicate that adrenaline has a rapid effect on the ionic permeability of the visceral peritoneum. The effect of adrenaline on the apical side of the mesothelial membrane is more prolonged than that on the basolateral side. More studies are needed to elucidate the physiologic role represented by these findings.

References


Corresponding author:
Ioannis Stefanidis, MD, Division of Nephrology, University Hospital of Larissa, Larissa 41110 Greece.
E-mail: stefanid@med.uth.gr
Angiotensin II receptor blockers (ARBs) are effective in controlling blood pressure and have been shown to reduce proteinuria with fewer adverse effects than angiotensin converting enzyme inhibitors. In the present prospective study, we evaluated the action of irbesartan, an ARB with a long half-life, on proteinuria, peritoneal protein losses, and peritoneal transport in patients with chronic renal failure (CRF) undergoing peritoneal dialysis (PD).

We enrolled 15 stable patients (11 with diuresis of more than 500 mL/day; 40% women; 40% with diabetes) into the study. Mean age of the patients was 65 ± 15 years, and mean time on PD was 33 ± 21 months. The study was performed in two stages. In stage I, patients received no irbesartan. In stage II, patients received 30 days of treatment with irbesartan (145 ± 72 mg/day).

After treatment with irbesartan, and no changes in blood pressure level as compared with baseline, we observed a reduction in proteinuria ($r = 0.690$, $p < 0.05$), decreased peritoneal protein losses at 4 hours’ and 24 hours’ dwell time ($r = 0.910$ and $r = 0.930$, $p < 0.001$), decreased peritoneal $K_t/V$ ($r = 0.586$, $p < 0.05$), and increased peritoneal creatinine clearance ($r = 0.943$, $p < 0.001$). Levels of serum albumin ($r = 0.630$, $p < 0.05$), prealbumin ($r = 0.810$, $p < 0.001$), and transferrin ($r = 0.551$, $p < 0.05$) increased after treatment with irbesartan.

We conclude that treatment with irbesartan in patients with CRF undergoing PD modifies peritoneal transport and reduces peritoneal and urinary protein loss. This effect probably has a positive impact on nutritional parameters. Further studies are required to elucidate the mechanisms involved.

Key words
Peritoneal transport, angiotensin receptor blockers, irbesartan, nutrition

Introduction
Ever since peritoneal dialysis (PD) has been used in the treatment of chronic renal failure (CRF), high peritoneal protein losses (PPL) have been observed after each PD exchange. In adult patients, the losses have been estimated to be between 6 g and 13 g daily (1,2). Losses are usually higher during episodes of peritonitis. No differences in PPL have been found between patients on continuous ambulatory peritoneal dialysis (CAPD) and those on continuous cycling peritoneal dialysis (CCPD). An even higher PPL has been reported in diabetic patients (3). Continuous PPL in patients undergoing long-term PD may contribute to malnutrition (1).

Leakage of proteins through the peritoneal membrane resembles the nephrotic syndrome with high proteinuria, although the causes and anatomic structures are not the same. The use of angiotensin converting enzyme inhibitors (ACEIs) in nondiabetic renal disease, particularly diabetic nephropathy, has been demonstrated to be effective in reducing proteinuria and slowing the progression of kidney disease (4,5). The main mechanism of the antiproteinuric action of ACEIs is a reduction in the negative effects of angiotensin II on kidney hemodynamics. However, that mechanism may not be the only factor.

In a study carried out in 1989, we described how captopril, an ACEI, reduced proteinuria and also significantly decreased PPL in a group of diabetic patients undergoing CAPD (6). Based on those results, we conducted a study in PD patients treated with irbesartan, an angiotensin II antagonist (ARB). Angiotensin II antagonists have been demonstrated to have an antiproteinuric action similar to that of ACEIs.
(7), even in patients with CRF (8), and a good response–tolerability in patients undergoing PD (9). In the present study, we determined the effect of irbesartan on proteinuria, PPL, and other peritoneal function parameters.

**Patients and methods**

For this prospective study, we enrolled 15 PD patients (9 men, 6 women) with a mean age of 64.9 ± 15.0 years (range: 41 – 88 years) and an average PD duration of 33.3 ± 20.9 months (9 on CAPD, 6 on CCPD). Of the 15 patients, 6 had diabetes.

The study was divided into two consecutive stages. In stage I, the patients received no ARB. (Patients with high blood pressure were treated with other non ACEI anti-hypertensive drugs.) In stage II, patients were treated with irbesartan for 30 days. The mean dose of irbesartan was 145 ± 72 mg daily. (In stage II, no patient was treated with ACEIs.)

Irbesartan is an ARB with a prolonged half life and is eliminated mainly by the biliary pathway. Titration is not necessary, because the drug is not dialyzable (10). Irbesartan has not been demonstrated to worsen anemia or to elevate serum potassium levels in PD patients (9).

During the two stages of the study, the dialysis regime remained the same. In both stages, we analyzed blood, peritoneal effluent fluid at 4 hours’ and 24 hours’ dwell time, and 24-hour urine (in patients with residual diuresis >500 mL daily). Blood was used to determine urea, creatinine, albumin, pre-albumin, and transferrin levels. Peritoneal effluent fluid at 4 hours’ and 24 hours’ dwell time was used to determine proteins, and at 24 hours’ dwell time to determine urea and creatinine. Based on the results, and using the PD Adequest 2.0 kinetic modeling software (Baxter Healthcare Corporation, Deerfield, IL, U.S.A.), we calculated the weekly peritoneal Kt/V urea and the weekly peritoneal creatinine clearance (CCr).

None of the patients used bicarbonate dialysate during the study. Patients who had had peritonitis in the 3 months preceding the study were excluded. Statistical analysis was carried out using the SPSS 11.0 software package (SPSS Inc., Chicago, IL, U.S.A.). The Student t-test, variance, correlations, and multivariate linear regression were calculated. Differences were considered significant at \( p < 0.05 \).

**Results**

During treatment with irbesartan, adequate blood pressure control was achieved. Blood pressure was not different from that obtained in stage I of the study, during which treatment consisted of non ACEI/non ARBs antihypertensive drugs. Adverse effects were not observed in any of the patients, and the irbesartan was well tolerated.

After the irbesartan had been added to the treatment of the PD patients, proteinuria was reduced in 11 patients who maintained residual diuresis (500 – 2350 mL daily), decreasing to 0.63 ± 0.31 g/L from 0.71 ± 0.43 g/L (\( r = 0.690, p < 0.05 \)). Table I shows the amount of protein leakage into the peritoneal effluent. In the table, treatment with irbesartan can be seen to significantly reduce peritoneal protein losses in the tests carried out after 4 hours and 24 hours of fluid residence in the peritoneal cavity.

Figure 1 shows the correlation between PPL at 24 hours’ dwell with and without irbesartan treatment. Peritoneal Kt/V urea decreased to 1.36 ± 0.4 from 1.46 ± 0.5 (\( r = 0.586, p < 0.05 \)), and peritoneal CCr increased to 40.6 ± 14.9 L weekly from 39.5 ± 14.9 L weekly (\( r = 0.943, p < 0.001 \)). Tested nutritional parameters were significantly increased after irbesartan treatment (Table I: albumin, \( p < 0.05 \); prealbumin, \( p < 0.001 \); and transferrin, \( p < 0.05 \)). No statistically significant differences with regard to age, sex, or diabetes status were observed.

**Discussion**

This study demonstrates that the ARB irbesartan can modify peritoneal transport, reduce peritoneal protein losses and proteinuria, and affect peritoneal clearance of small molecules without significant change in blood pressure. The effect of ARBs on proteinuria has already been described, even in patients with advanced CRF (8), but so far this effect has not been described in patients undergoing dialysis.

Patients on PD are already known to maintain residual diuresis for longer than patients on hemodialysis do. The irbesartan effect could therefore be important in preserving renal function and in preventing protein losses, such as those that happen in PD patients, where considerable quantities of proteins are lost through the peritoneum.

Irbesartan affects the peritoneal membrane, increasing convective transport and decreasing diffu-
sive transport—although in a limited way—and significantly reducing peritoneal protein losses at both 4 hours’ and 24 hours’ dwell time. The mechanism of action of these effects has not been described; however, it could be related to an effect on the permeability of the peritoneal membrane capillaries, where ARBs may act directly or indirectly by blocking the renin–angiotensin–aldosterone system. Also, as we suggested in a study on the effect of captopril on the reduction of PPL in PD patients (6), other mechanisms of action mediated by prostaglandins or kinins cannot be ruled out.

Some authors have speculated that the reduction of proteinuria might be mediated through the anti-inflammatory effects of ARBs (11), although they could not demonstrate that connection. A recent review (12) emphasized that angiotensin II and aldosterone have been implicated as mediators of injurious actions in the heart and kidney, and that the growth-promoting and other fibroproliferative effects of angiotensin II have been demonstrated in several tissues.

Prolonged exposure to bioincompatible dialysis solutions stimulates fibrogenic cytokines that could induce peritoneal fibrosis. Evidence from animal models suggests that enalapril, an ACEI, inhibits the production of cytokines such as TGFβ1, which could preserve peritoneal histology and function (13). Evidence also exists that, owing to their interference with angiotensin II activity, ACEIs and ARBs improve hypertonic PD solution-induced peritoneal alterations by blocking cytokine expression (14). Several mechanisms could be involved in the effect of an ARB such as irbesartan on the peritoneal membrane, and further studies are needed to demonstrate them. However, from the results obtained in our patients, irbesartan could be used in some situations of peritoneal damage.

The improvement in nutritional parameters—a slight but significant increase in serum albumin, prealbumin, and transferrin—appears to be related to the reduction in peritoneal protein losses and proteinuria. However, irbesartan treatment in the present study was short-term. A longer treatment period is needed to determine whether reduction in protein losses has a real impact on the nutritional status of patients.

**Conclusion**

Our findings suggest that, in PD patients, treatment with irbesartan, an angiotensin II receptor antagonist, has in addition to its anti-hypertension action an effect on peritoneal transport, modifying peritoneal clearances and reducing peritoneal protein losses and

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<th>Without irbesartan</th>
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</tr>
<tr>
<td>PPL/4 h (g/L)</td>
<td>0.560 (0.197)</td>
<td>0.537 (0.166)</td>
<td>0.910 &lt;0.001</td>
</tr>
<tr>
<td>Proteinuria (g/L)</td>
<td>0.710 (0.43)</td>
<td>0.630 (0.310)</td>
<td>0.690 &lt;0.05</td>
</tr>
<tr>
<td>Peritoneal Kt/V</td>
<td>1.46 (0.5)</td>
<td>1.36 (0.4)</td>
<td>0.586 &lt;0.05</td>
</tr>
<tr>
<td>Peritoneal CCr</td>
<td>39.5 (14.9)</td>
<td>40.6 (14.9)</td>
<td>0.943 &lt;0.001</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>3.9 (0.3)</td>
<td>4.0 (0.4)</td>
<td>0.630 &lt;0.05</td>
</tr>
<tr>
<td>Prealbumin (mg/dL)</td>
<td>31.2 (8.9)</td>
<td>32.0 (7.5)</td>
<td>0.810 &lt;0.001</td>
</tr>
<tr>
<td>Transferrin (mg/dL)</td>
<td>185 (25)</td>
<td>191 (35)</td>
<td>0.551 &lt;0.05</td>
</tr>
</tbody>
</table>

PPL = peritoneal protein losses; CCr = creatinine clearance.
proteinuria. These effects appear to improve nutritional parameters. Further studies are required to elucidate the mechanisms involved.

References

Corresponding author:
Francisco Coronell, MD PhD, Servicio de Nefrología, Hospital Clínico San Carlos, C/ Prof. Martin Lagos s/n, Madrid 28040 Spain.
E-mail: fcoronel.hcsc@salud.madrid.org