Volume Stress-Induced Peritoneal Endothelin-1 Release in Continuous Ambulatory Peritoneal Dialysis

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Abstract. In long-term peritoneal dialysis, functional deterioration of the peritoneal membrane is often associated with proliferative processes of the involved tissues leading to peritoneal fibrosis. In continuous ambulatory peritoneal dialysis (CAPD), failure to achieve target values for adequacy of dialysis is commonly corrected by increasing dwell volume; in case of ultrafiltration failure, osmolarity of the dialysate gets increased. In a prospective study, the impact of increasing dwell volume from 1500 ml to 2500 ml per dwell (volume trial) or changing the osmolarity of the dialysate from 1.36 to 3.86% glucose (hyperosmolarity trial) on the peritoneal endothelin-1 (ET-1) release was analyzed. ET-1 is known to exert significant proliferative activities on a variety of cell types leading to an accumulation of extracellular matrix. A highly significant difference in the cumulative peritoneal ET-1 synthesis was found between the low- and high-volume exchange, whereas differences in the hyperosmolarity setting were only moderate. Sixty minutes after initiating dialysis, the cumulative ET-1 synthesis was 2367 ± 1023 fmol for the 1500 ml versus 6062 ± 1419 fmol for the 2500 ml dwell (P < 0.0001) and 4572 ± 969 fmol versus 6124 ± 1473 fmol for the 1.36 and 3.86% glucose dwell (P < 0.05), respectively. In conclusion, increasing dwell volume leads to a strong activation of the peritoneal paracrine endothelin system. Because ET-1, apart from being a potent vasoactive peptide, contributes to fibrotic remodeling, this study indicates that volume stress-induced ET-1 release might contribute to structural alteration of the peritoneal membrane in long-term peritoneal dialysis.

In peritoneal dialysis, long-term viability of the peritoneum is of major concern. Functional deterioration of the peritoneal membrane as determined by ultrafiltration and solute clearance failure are often associated with proliferating processes of the involved tissues. Peritoneal dialysis has been described as a process of chronic injury to the peritoneal membrane, caused by its continuous exposure to a nonphysiologic environment of dialysate. On macroscopic analysis, patients who are kept on peritoneal dialysis for a considerable number of years exhibit a thickened, wrinkled peritoneum with a leathery appearance. Biopsies show a disappearance of mesothelium and instead an acellular band of hyalinized collagen. The submesothelial tissue can exhibit disorganization of the normal collagen fibers and expansion of the matrix ground substances with interstitial fibrosis (1–3). Sclerotic changes in the stromal vessels are usually prominent (4) and may progress to mural fibrosis and sclerosing encapsulating peritonitis in some cases (5). Additional ultrastructural findings are mesothelial basement membrane thickening and reduplication (6,7). Unphysiologic dialysates are believed to be responsible for these changes.

Commonly used peritoneal dialysate fluids are considered bioincompatible due to the pH of about 5.5, the lactate buffer, and the hyperosmolarity ranging between 334 and 486 mosmol/L caused by high glucose concentration of the dialysate.

Endothelin-1 (ET-1) is a 21-amino acid peptide produced by a variety of tissues and exhibiting tissue-specific patterns of expression (8). In addition to its potent vasoactive action, ET-1 is known to be mitogenic, exerting significant proliferative activity on a variety of cell types including epithelial and endothelial cells, smooth muscle cells, and fibroblasts (9,10). Furthermore, it causes the release of proinflammatory cytokines and has considerable fibrogenic activity, influencing the composition of the extracellular matrix (ECM) by altering fibroblast metabolism. In particular, ET-1 increases the deposition of ECM by regulating production and turnover of matrix components (11). ET-1 has been reported to have a role in the pathogenesis of dermal fibrosis in systemic sclerosis (12,13), in scleroderma-associated fibrotic lung disease (14), and in hepatic fibrosis (15). In addition, it was shown that a primary renal overexpression of endothelin isopeptides as observed in ET-1 transgenic mice (16) as well as in ET-2 transgenic rats (17) resulted in a fibrotic remodeling of the kidney.

ET-1 synthesis can be triggered by a variety of environmental factors, including hyperosmolality stress and mechanical shear forces (18–22). Both stimuli are present in peritoneal dialysis. The aim of our study was to analyze whether volume and/or hyperosmolality stress led to a local peritoneal ET-1 release. Ten patients were subjected to a hypertonic and iso-
Materials and Methods

Patients

Ten stable peritoneal dialysis patients (four women and six men) were asked to participate in this study. The study protocol was approved by the local ethics committee. All patients were in good clinical condition and free of peritonitis at the time of and during the last 3 mo before the study. Peritoneal transport characteristics were routinely assessed according to Twardowski’s standardized peritoneal equilibration test (23) and did not change during the last 24 mo of peritoneal dialysis in all patients. There was no significant difference between the patients in terms of age, dialysis duration, comorbidity, body mass index, or serum albumin levels. Mean duration on peritoneal dialysis was 16 ± 7 mo. The underlying renal diseases were autosomal dominant polycystic kidney disease in one case, focal segmental glomerulosclerosis in one case, glomerulonephritis of unknown origin in three cases, diabetic nephropathy in two cases, tubulointerstitial nephropathy in two cases, and bilateral tumor nephrectomy in one case.

Clinical Setting

To investigate the influence of hyperosmolarity and volume stress on peritoneal ET-1 release, standardized 3-h dwells were performed. Commercially available dialysate (Dianeal®; Baxter Healthcare, Castlebar, Ireland) was used throughout the study. All patients were asked to use a 2-L 2.27% glucose bag as the first dwell after the overnight period. The study protocol started after the first dwell period in the morning. Patients were lying in the supine position for the test. A dwell time of 3 h was chosen to increase patient compliance. The hyperosmolarity trial was always started with the 1.36% glucose followed by the hypertonic 3.86% glucose dwell; the volume trial was started with the low followed by the high volume dwell. Tests for hyperosmolarity and volume stress were done on two separate days. The interval in-between ranged from 5 to 12 d.

For testing hyperosmolarity, a 2-L dwell of 1.36% glucose (344 mosmol/L; 75 mmol/L glucose, 40 mmol/L lactate, pH 5.5) was compared to a hyperosmolar 2-L dwell of 3.86% glucose (483 mosmol/L; 75 mmol/L glucose, 40 mmol/L lactate, pH 5.5). Volume stress was tested by comparing a 1.5- to a 2.5-L dwell using 2.27% glucose dialysate (395 mosmol/L; 119 mmol/L glucose, 40 mmol/L lactate, pH 5.5).

A volume of 20 ml dialysate was sampled at 30, 60, 120, and 180 min. To avoid the effect of dead space, all samples were collected after a temporal drainage of approximately 200 ml. All patients were instructed to roll from side to side immediately before each sampling to assure that the entire cavity was well mixed. At the end of each dwell, patients were asked to stand up and move around to minimize residual volume during dwell draining. Probes before the 30 min were not taken for practical reasons because the filling time in peritoneal dialysis takes about 10 to 20 min. Creatinine, urea, glucose, osmolarity, and ET-1 were measured in the effluent. Blood samples were taken immediately before and at the end of the dwell. The drain volume was documented in each case. Dialysate samples were stored at −80°C until assay, and blood samples were immediately analyzed.

To characterize mass transfer across the peritoneal membrane, dialysate × volume/plasma ratio (DV/P) of creatinine and urea was calculated. The mass transfer area coefficient (MTAC) was calculated as a parameter to describe changes in the effective peritoneal surface area (24,25). MTAC was calculated as follows: \( MTAC \text{ (ml/min)} = \left( \frac{V_d}{t} \right) \ln \left( \frac{[V_d]}{[V_d] - [D_{in}] + [D_{in}]} \right), \) where \( D_{in} \) is the dialysate concentration of the solute after a 3-h dwell period, \( P \) is the mean plasma concentration, \( V_d \) is the initial intraperitoneal volume (which is assumed to be equal to the instilled volume), and \( V_d \) is the volume in the drain bag.

For calculation of the cumulative endothelin release, the net ultrafiltration volume at the end of the 3-h dwell was used for all time points. This might lead to slight underestimation of the initial values in patients with high ultrafiltration.

Assays

Both in plasma and dialysate, urea and creatinine were measured by standard enzymatic methods. Glucose, creatinine, and urea were determined using a Hitachi 747 (Boehringer Mannheim). The principles and methods used are: for glucose hexokinase, glucose 6-P-dehydrogenase (Glucose UV-Fluidtest), for urea, the ultraviolet determination with glutamate dehydrogenase (Harnstoff-UV-Fluidtest), both taken from Rolf Greiner (Biochemica, Flacht, Germany), and for creatinine, determination enzymatic assay with creatininasamin, sarcosine oxidase, peroxidase, and aminophenazon (Enzymatischer Farbstoff, Boehringer Mannheim). Osmolarity was determined using the cryoscopic osmometer Gonotec (Gesellschaft für Mess- und Regeltechnik, Berlin, Germany).

To determine ET-1 concentration in blood and dialysate, a commercially available enzyme immunoassay (Biomedic, Vienna, Austria) was used, as recently described (22). Cross reactivity for the ET-1 enzyme-linked immunosorbent assay is: ET-1: 100%; ET-2: 100%; ET-3: <5%; Big ET-1: <1%; Big ET-2: <1%.

To exclude an interaction of the high glucose concentration of the dialysate on the ET-1 detection capacity of the enzyme-linked immunosorbent assay, defined amounts of exogenous ET-1 were given into fresh 1.36 and 3.86% dialysate samples and its recovery rate was analyzed. The calculated recovery rate was 104 ± 7.8%. Intra-assay variance was 3.3 ± 0.5% (n = 11), and interassay variance was 5.8 ± 0.9% (n = 12).

Statistical Analyses

Results are expressed as mean ± SD. For comparison, paired and unpaired \( t \) tests were used for parametric data, and Mann–Whitney and Wilcoxon signed rank tests were used for nonparametric variables. Paired analyses between baseline values (1.36 and 1500 ml) and test values (3.86% and 2500 ml) were used. A \( P \) value <0.05 was considered significant.

Results

Ten stable CAPD patients participated in this study. There were no significant differences with regard to age, dialysis duration, comorbidity, body mass index, or serum albumin levels. The 2000-ml 3.86% and 1.36% glucose as well as the 1500- and 2500-ml bags were well tolerated, and no side effects have been observed.

Mean ultrafiltration rate was 89 ± 183 ml in the 1.36% glucose dwell and 627 ± 203 ml in the 3.86% glucose dwell, 128 ± 67 ml in the 1500-ml dwell and 534 ± 147 ml in the 2500-ml dwell, respectively (Table 1).

Mean ET-1 plasma levels before (PL0) and at the end (PLE) of the dwell did not differ significantly between the hyperosmolarity and the volume trial. In the volume trial, plasma endothelin values before the 1.5-L dwell were 0.78 ± 0.47 fmol/ml and 0.77 ± 0.30 fmol/ml at the end of the dwell (NS).
Values for the 2.5-L dwell were $PL_0 = 0.77 \pm 0.30$ fmol/ml versus $PL_E = 0.78 \pm 0.24$ fmol/ml (NS). In the hyperosmolarity trial, $PL_0$ and $PL_E$ were $0.75 \pm 0.68$ fmol/ml and $0.76 \pm 0.40$ fmol/ml (NS) for the 1.36% glucose dwell and $0.70 \pm 0.44$ fmol/ml and $1.0 \pm 0.64$ fmol/ml for the 3.86% glucose dwell (NS).

**Volume Trial**

Cumulative peritoneal ET-1 release 30 min after starting peritoneal dialysis was $2824 \pm 1647$ fmol in the 1.5-L dwell compared to $6730 \pm 2500$ fmol for the 2.5-L dwell ($P < 0.005$). Values at 60 min were $2367 \pm 1023$ fmol versus $6062 \pm 1419$ fmol ($P < 0.0001$), $2416 \pm 1708$ fmol versus $6400 \pm 2597$ fmol at 120 min ($P < 0.0001$), and $2309 \pm 1916$ versus $5977 \pm 1268$ fmol at 180 min ($P < 0.001$) (Figure 1). Table 2 gives an overview of the ET-1 concentration in fmol/ml at various time points during the volume and hyperosmolarity trial.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Glucose, 1.36%</th>
<th>Glucose, 3.86%</th>
<th>Volume, 1500 ml</th>
<th>Volume, 2500 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>2.24 ± 0.32</td>
<td>2.29 ± 0.35</td>
<td>2.10 ± 0.46</td>
<td>2.23 ± 0.75</td>
</tr>
<tr>
<td>60</td>
<td>2.21 ± 0.38</td>
<td>2.30 ± 0.43</td>
<td>1.76 ± 0.37</td>
<td>2.01 ± 0.41</td>
</tr>
<tr>
<td>120</td>
<td>1.89 ± 0.29</td>
<td>1.96 ± 0.28</td>
<td>1.75 ± 0.81</td>
<td>2.11 ± 0.65</td>
</tr>
<tr>
<td>180</td>
<td>1.95 ± 0.26</td>
<td>1.98 ± 0.26</td>
<td>1.70 ± 0.46</td>
<td>1.98 ± 0.42</td>
</tr>
</tbody>
</table>

Figures did not differ between both groups. Values for creatinine were $10.35 \pm 4.54$ for the low-volume dwell and $9.96 \pm 5.31$ for the high-volume dwell (NS). MTAC values were $18.98 \pm 3.83$ and $18.04 \pm 1.82$, respectively (NS).

The mean dialysate to plasma ratio of ET-1 ($D_{ET-1}/P_{ET-1}$) at the end of the dwell was $2.73 \pm 0.56$ for the low-volume dwell and $2.89 \pm 0.65$ for the high volume dwell (NS).

**Hyperosmolarity Trial**

Cumulative ET-1 release 30 min after the start of peritoneal dialysis was $4714 \pm 908$ fmol for the 1.36% glucose dwell compared to $5809 \pm 778$ fmol for the 3.86% glucose dwell ($P < 0.05$). Values were $4572 \pm 969$ fmol versus $6124 \pm 1473$ fmol at 60 min ($P < 0.05$), $3970 \pm 793$ fmol versus $5239 \pm 968$ fmol at 120 min ($P < 0.01$), and $4082 \pm 765$ fmol versus $5137 \pm 906$ fmol at 180 min ($P < 0.01$) (Figure 2).

The ET-1 concentration in fmol/ml is given in Table 2. Values did not differ between the two groups.

The initial (30 min) intraperitoneal glucose concentration was $156 \pm 17.0$ mmol/L in the 3.86% dwell compared to $65.7 \pm 6.6$ mmol/L in the 1.36% dwell. Values declined to

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**Table 1.** Net ultrafiltration (ml) and mass transfer parameters for creatinine and urea are compared in the volume and hyperosmolarity trial.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Glucose, 1.36%</th>
<th>Glucose, 3.86%</th>
<th>Volume, 1500 ml</th>
<th>Volume, 2500 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net ultrafiltration</td>
<td>$89 \pm 183^b$</td>
<td>$627 \pm 203$</td>
<td>$128 \pm 67^d$</td>
<td>$534 \pm 147$</td>
</tr>
<tr>
<td>$DV/P_{creat}$</td>
<td>$1449 \pm 813$</td>
<td>$1943 \pm 1011$</td>
<td>$957 \pm 259^e$</td>
<td>$1647 \pm 350$</td>
</tr>
<tr>
<td>$DV/P_{urea}$</td>
<td>$1672 \pm 551^c$</td>
<td>$2306 \pm 474$</td>
<td>$1338 \pm 577^d$</td>
<td>$2251 \pm 289$</td>
</tr>
</tbody>
</table>

*a* $DV/P_{creat}$ dialysate volume to plasma ratio of creatinine; *DV/P_{urea}* dialysate volume to plasma ratio of urea.

*b* $P < 0.001$ compared with 3.86% glucose.

*c* $P < 0.05$ compared with 3.86% glucose.

*d* $P < 0.001$ compared with 2500 ml.

*e* $P < 0.005$ compared with 2500 ml.

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**Figure 1.** Cumulative endothelin-1 (ET-1) release and plasma osmolarity at 0.5, 1, 2, and 3 h after initiating a 1500-ml dwell and a 2500-ml dwell (mean ± SD).
84 ± 19.8 mmol/L and 39.9 ± 9.0 mmol/L at 180 min, respectively.

Osmolarity values at 30 min were 426 ± 21.1 mosmol/L in the 3.86% dwell and 327 ± 7.8 mosmol/L in the 1.36% dwell. Values at 180 min were 343 ± 15.4 versus 312 ± 13.7 mosmol/L (Figure 2). Mass transfer (DV/P) parameters are given in Table 1. Values for creatinine did not differ between the two groups, and values for urea were higher in the hyperosmolarity setting (P < 0.05).

MTAC values for creatinine were 9.47 ± 5.0 for the 1.36% dwell and 9.77 ± 6.72 for the 3.86% dwell (NS). Values for urea were 22.42 ± 13.7 and 24.62 ± 3.51 (NS). The dialysate to plasma ratio of ET-1 (D_{ET-1}/P_{ET-1}) at the end of the test period was 3.01 ± 0.67 for the 1.36% dwell and 3.15 ± 0.72 for the 3.86% dwell (NS).

**Discussion**

The aim of our study was to analyze whether volume stress and/or hyperosmolarity led to a local peritoneal ET-1 release. Ten stable CAPD patients were subjected to a hypertonic and isotonic as well as to a low- and high-volume dwell exchange. ET-1 was measured in the dialysate and plasma. Highly significant differences in the cumulative ET-1 release were found throughout the dwell period when comparing high- (2500 ml) versus low-volume (1500 ml) dwell exchange. Initial values (30 min) were approximately 2.5-fold higher in the high-compared to the low-volume dwell. Follow-up values were even more pronounced. We found a moderate but also significant difference in the cumulative amount of ET-1 release in the hyperosmolarity trial, with higher values for the hypertonic dwell. Because the peritoneal cell count remains equal in both settings, the only explanation for an increase in the cumulative ET-1 amount is an increase in the peritoneal ET-1 synthesis. Considering the findings in the volume trial, differences in the cumulative ET-1 release in the hyperosmolarity trial may be explained in part by the differences in the intra-abdominal dialysate volume. Because of higher ultrafiltration in the hypertonic dwell, intraperitoneal volume at the end of the dwell period differed significantly between the 3.86% (2627 ± 203 ml) and the 1.36% dwell (2089 ± 183 ml, P < 0.001).

Surprisingly, we found no linear increase in the peritoneal ET-1 concentrations throughout the 3-h test period in the osmolarity or in the volume setting. ET-1 concentrations at 30 min did not differ significantly from those taken at 60, 120, or 180 min. Two major factors may contribute to this phenomenon. First, peritoneal volume stress over time is maximal in the initial phase of dialysis, when dialysate enters the peritoneal cavity. Mechanical stress has been found to be a major stimulant for ET-1 release in a variety of tissues (19–21). Second, pH equilibration of the intraperitoneal dialysate from the initial value of 5.5 to normal or even alkalotic values takes place in the first 30 min after starting dialysis (26). A low pH is a potent trigger for ET-1 release in a variety of tissues (27). Lactate may also play a role in this regard, as lactate load is high in the initial phase and increases with increased instillation volume.

ET-1 is a mainly paracrine-acting hormone. Plasma and/or dialysate ET-1 concentration only weakly reflects the more important tissue concentration (28,29). Zoja et al. found that proximal tubular cells show a polarized secretion of ET-1 with up to a fourfold higher secretion into the basolateral compared to the apical compartment when challenged with albumin (29).

In our trial, plasma concentrations of ET-1 were always lower than peritoneal ET-1 concentrations. In addition, plasma ET-1 was not altered during peritoneal dialysis. These findings strongly suggest that ET-1 is locally generated within the peritoneal cavity. A recent study has shown that peritoneal mesothelial cells are not involved in ET-1 production (30). Other cells, notably macrophages, polymorphonuclear cells, smooth muscle cells, and fibroblasts, are known to synthesize ET-1 and thus might be the source of peritoneal ET-1 release (18,31). Physical shear stress is a well-known stimulus for ET-1 release as shown in other systems. Waters et al. demonstrated a twofold increase in the ET-1 release of rat visceral pleural cells by cyclic strain stress of 20% and up to a fivefold increase due to fluid shear stress (19).

The conventional CAPD regimen uses four 2-L exchanges per day. This regimen has proven to be insufficient in a large number of patients in terms of achieving adequacy targets, namely fractional urea clearance rate (Kt/V) and weekly creatinine clearance (32–34).

In patients with deteriorating renal function, adequacy of dialysis can only be achieved by increasing dialysis volume, and it is occasional practice to provide patients with the maximum tolerated exchange volume in the face of declining residual renal function to compensate for and to achieve higher values for solute clearances. Gradual increase of dwell volume from a standard of 2 L to 2.5 L or even 3 L/dwell is a common procedure. In our trial, we found a highly significant increase in the mass transfer values by increasing dialysate volume.

The theoretical gains on small solute clearance by increasing dwell volume are best described by the Pyle–Popovich model, claiming an increase of approximately 20% after an increase in exchange volume of 22% (35,36). In a 1-yr follow-up study,
Harty et al. failed to demonstrate an adequate increase in peritoneal dialysis Kt/V and creatinine clearance despite an increase in dwell volume from 2000 to 2500 ml/dwell (34). Values after 1 yr were only 12% for Kt/V and 9% for creatinine clearance. There was a major decrease in the 24-h D/P of urea and creatinine ratios between baseline and 3-mo assessment, whereas values remained stable in the control group (unchanged PD regimen). These findings were in agreement with findings made by George et al. (37), who observed a percentage increase of only 14% for urea clearance and 9.5% for creatinine clearance despite an increase of 25% in the dwell volume.

For low molecular weight solutes such as urea (60 Daltons) and creatinine (113 Daltons), transport across the peritoneal membrane is determined mainly by unrestricted diffusion (38–40). Changes in the MTAC values of these solutes can be considered to be caused by changes in the effective peritoneal surface area. The vascular wall of the peritoneal capillaries is probably the most important restriction barrier in this regard, because it has been found that the osmotic barrier resides neither in the mesothelial layer nor in the interstitium (39–41). Any factor that influences the capillary status, in the short but also in the long term, may thus have an impact on dialysis capacity. Douma et al. found significant increased MTAC values and clearances for low and high molecular solutes by adding the nitric oxide (NO) donor nitroprusside to a standard 4-h peritoneal dialysis dwell (42). Adding 4.5 mg/L sodium nitroprusside to a 2-L 1.36% glucose dwell led to a significant increase in the MTAC of creatinine, urea, and urate (P < 0.05 for all). NO is a potent vasodilating agent and the main antagonist of ET-1. One might conclude that if NO increases small solute clearances, then increased ET-1 synthesis may lead to vasoconstriction with a consequent decline in solute clearances. In our trial, MTAC values calculated with the Garred model did not differ significantly between the groups in each setting, indicating a less significant impact of ET-1 on the immediate peritoneal vasoregulation. Nevertheless, our study suggests that volume stress increases peritoneal ET-1 synthesis. The ET-1 release observed was in a range in which biologic effects can surely be expected (9,10). The biologic effects of ET-1 depend on tissue- and cell-specific expression of ET receptors (43,44). They can further be distinguished in immediate and long-term effects. In the vascular system, the foremost immediate effect of ET-1 is a short-lasting vasodilation followed by a long-lasting vasoconstriction (43). In the long term, the mitogenic effect on fibroblasts and the involvement of this effect in the induction of collagen synthesis predominate, which might lead to an accumulation of ECM components. ET-1 directly stimulates collagen type I synthesis in smooth muscle cells derived from coronary arteries and the aorta (45). ET-1 has also been proven to induce increased fibronectin expression in human bronchial epithelial cells, which is a potent chemotactic factor for fibroblasts (46,47). In addition, ET-1 is a strong chemoattractant for circulating monocytes and activated macrophages (47,48). Long-term changes in the peritoneal morphology may explain the observations made by Harty et al. and George et al. of a lower response in Kt/V after increasing dialysis volume.

In conclusion, our study demonstrated for the first time that volume stress is a very potent stimulus of the paracrine peritoneal endothelin system. Because ET-1 is a well known factor that promotes fibrosis, we suggest that the volume stress-induced ET-1 release might play a role in the process of fibrotic remodeling of the peritoneum. Our study further suggests that locally applied endothelin antagonists might be a therapeutic approach to reduce peritoneal fibrosis in the CAPD patient. However, this needs to be proven in future studies using endothelin receptor antagonists.

Acknowledgments

This study was supported in part by Grant Ho 16652/1 from the Deutsche Forschungsgemeinschaft (to Dr. Hocher). We thank Pia Hambach and Christine Lehmann for technical assistance.

References


