

## PRESERVATION OF RESIDUAL RENAL FUNCTION IN DIALYSIS PATIENTS: EFFECTS OF DIALYSIS-TECHNIQUE-RELATED FACTORS

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◆ **Objectives:** Residual renal function (RRF) is of paramount importance to dialysis adequacy, morbidity, and mortality, particularly for long-term continuous ambulatory peritoneal dialysis (CAPD) patients. Residual renal function seems to be better preserved in patients on CAPD than in hemodialysis (HD) patients. We analyzed RRF in 45 patients with end-stage renal disease (ESRD), commencing either CAPD or HD, to prospectively define the time course of the decline in RRF, and to evaluate dialysis-technique-related factors such as cardiovascular stability and bioincompatibility.

◆ **Study Design:** Single-center prospective investigation in parallel design with matched pairs.

◆ **Materials:** Fifteen patients starting CAPD and 15 matched pairs of patients commencing HD were matched according to cause of renal failure and RRF. Hemodialysis patients were assigned to two dialyzer membranes differing markedly in their potential to activate complement and cells (bioincompatibility). Fifteen patients were treated exclusively with the cuprophane membrane (bioincompatible) and the other 15 patients received HD with the high-flux polysulfone membrane (biocompatible).

◆ **Measurements:** Residual renal function was determined at initiation of dialytic therapy and after 6, 12, and 24 months. Dry weight (by chest x ray and diameter of the vena cava) was closely recorded throughout the study, and the number of hypotensive episodes counted.

◆ **Results:** Residual renal function declined in both CAPD and HD patients, although this decline was faster in HD patients (2.8 mL/minute after 6 months and 3.7 mL/min after 12 months) than in CAPD patients (0.6 mL/min and 1.4 mL/min after 6 and 12 months respectively). It declined faster in patients with bioincompatible than with biocompatible HD membranes (3.6 mL/min vs 1.9 mL/min after 6 months). Eleven percent of the HD sessions were complicated by clinically relevant blood pressure reductions, but there were no differences between the two dialyzer membrane groups. None of the CAPD patients had documented hypotensive episodes. None of the study patients suffered severe illness or received nephrotoxic antibiotics or radiocontrast media.

◆ **Conclusions:** The better preservation of RRF in stable CAPD patients corresponded with greater cardiovascular stability compared to HD patients, independently of the membrane used. Furthermore, there was a significantly higher preservation of RRF in HD patients on polysulfone versus cuprophane membranes, indicating an additional effect of biocompatibility, such as less generation of nephrotoxic substances by the membrane. Thus, starting ESRD patients on HD prior to elective CAPD should be avoided for better preservation of RRF.

KEY WORDS: Residual renal function; hydration status; biocompatibility.

Preservation of residual renal function (RRF) is of paramount importance for chronic dialysis patients, particularly for patients on continuous ambulatory peritoneal dialysis (CAPD) (1,2). Residual renal function contributes to the overall clearance of small and middle molecular weight substances and to fluid removal. Furthermore, it reflects renal endocrine function (3). Dialysis adequacy depends on RRF, and changes in RRF may necessitate modifications to the dialysis prescription. Loss of RRF may cause significant decreases in nutritional parameters, and may account for major differences in morbidity and quality of life. The CANUSA study demonstrated that every 0.5 mL/minute increase in glomerular filtration

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rate (GFR) was associated with a 9% lower risk of death (4).

Rottembourg *et al.* (5) showed in 1983 that RRF was preserved for a longer period in insulin-dependent diabetic patients on CAPD compared to hemodialysis (HD) patients. Several other reports confirmed this original observation (6-9). However, it is important to point out that the evidence cited has a number of limitations because many analyses were retrospective, were not matched for GFR or underlying renal disease, and were not controlled for administration of nephrotoxic drugs. The decline in GFR in CAPD may be biased by the presence of informatively censored data. Removal of CAPD dropouts with a lower GFR from analyses may contribute to the impression of better preservation of mean RRF in long-term CAPD patients (10). Moreover, the majority of studies utilized bioincompatible cellulosic membranes rather than biocompatible synthetic membranes.

It has not been proven yet that RRF decays faster in HD patients than in CAPD patients when biocompatible membranes are used. The present prospective investigation addressed long-term effects on RRF of bioincompatibility and cardiovascular stability related to the dialytic mode.

## MATERIALS AND METHODS

### STUDY POPULATION

Forty-five patients with end-stage renal disease starting dialytic renal replacement therapy were selected from four renal outpatient clinics of the University of Munich.

The patient's choice of treatment was CAPD in 15 cases and HD in 30 cases. None of the patients had undergone renal transplantation or had been treated previously with another mode of blood purification. All were in a stable clinical condition and started dialysis electively. None of the patients had severe comorbidity or was taking nephrotoxic drugs. Exclusion criteria for the study were rapid progressive glomerulonephritis, an RRF of less than 2 mL/minute, or a predictable time of follow-up of less than 24 months in the same dialysis facility. Renal hypertension was defined by repeated blood pressure values, recorded in supine position, of more than 140/90 mmHg and was documented in the majority of patients (26/45). Prescribed medication included antihypertensive drugs, medication for the prevention of secondary hyperparathyroidism, renal anemia, and hydrosoluble vitamins.

### STUDY DESIGN

The investigation was performed as a prospective study in parallel design with matched pairs. All patients were asked to give informed consent. The study procedure was approved by the local ethics committee.

At recruitment, CAPD and HD patients were paired (1 CAPD patient with 2 HD patients) on the basis of RRF [creatinine clearance (CCr)  $\pm$  1 mL/min] and the nature of the underlying kidney disease. It was anticipated that other variables such as age, gender, hypertension, or antihypertensive drugs would be randomly distributed among the groups.

Two groups of HD patients were randomly assigned in alternate order to dialyzer membranes with different degrees of biocompatibility. Patients assigned to the biocompatible membrane (BC) were treated with a single-use, high-flux polysulfone membrane (F 60, hollow fiber, ultrafiltration coefficient 40 mL/mmHg/hour, surface area 1.3 m<sup>2</sup>, urea clearance 185 mL/min at a blood flow rate of 200 mL/min; Fresenius, Bad Homburg, Germany). This membrane is known to cause low net levels of complement activation and cell activation. The other patients were dialyzed with a so-called bioincompatible membrane (BIC) (Disscap 160 E, ultrafiltration coefficient 6.25 mL/mmHg/hr, surface area 1.22 m<sup>2</sup>, urea clearance 189 mL/min at a blood flow rate of 200 mL/min; Hospal, Nuremberg, Germany). Hemodialysis was performed three times per week for 4 to 5 hours (MTS 4008 delivery system, volumetrically controlled ultrafiltration). Blood pump speed was set at 200 - 280 mL/minute and dialysate flow rate at 500 mL/minute. Fluid removal rate was adjusted to the clinical needs of the patients to

achieve ideal postdialytic weight. Each HD patient was treated consistently with the same dialyzer membrane, dialysis prescription, water purity, and dialysate composition. Nonfractionated heparin was used for both bolus and continuous infusion. CAPD patients performed 4 to 5 exchanges (2 L each) per day using different glucose concentrations (Fresenius, Oberursel, Germany; and Baxter, Deerfield, IL, U.S.A.)

Dry weight of CAPD and HD patients was judged clinically and by chest roentgenograms and ultrasonic determination of the diameter of the inferior vena cava prior to and at the end of an HD procedure or during the CAPD procedure. Comparative studies (data not shown) between measurements of the diameter of the inferior vena cava and the right atrial pressure have previously shown that values of the diameter of the inferior vena cava above 10.5 mm indicate overhydration. Changes after HD sessions reflect reduced intravascular volume in these patients. Nutritional recommendations for patients undergoing CAPD and HD included a caloric intake of at least 35 kcal/kg body weight/day, a protein intake of 1.2 g/kg/day, and individual restrictions of phosphate, potassium, and fluid intake.

#### STUDY PARAMETERS

Patient-specific data were collected at the time of enrolment (study stratification) and encompassed demographic data, past medical history, laboratory results, RRF (24-hr CCr), and medications.

During the study period, CCr was used to determine RRF. There is no doubt that endogenous CCr may overestimate true GFR in renal failure, but repeated determinations of CCr provide sufficient information to document any change or trends in GFR. To overcome the problem of small urine volumes and changing plasma creatinine levels in patients maintained on HD, a 3-day (67 - 68 hr) collection period was used. Blood samples were obtained from the arterial line at the end of the preceding dialysis session and at the end of the urine collection period (immediately before the next dialysis session).

In CAPD patients, 24-hour urine collections for creatinine excretion were performed and two blood samples (at the start and the end of the urine collection) were taken to calculate clearances by standard formulas. Residual renal function was assessed at the start of the study and after 6 months, 12 months, and 24 months following initiation of HD or CAPD. Three repeated calculations with an interval of 1 week each around the time point (6, 12, 24 months) were used to calculate mean RRF.

Patients were instructed to document blood pressure recordings at home. Hypotensive episodes during dialysis (defined as a drop in diastolic blood pressure of 20 mmHg or symptomatic hypotension necessitating application of 250 mL saline solution) were documented.

Measurements of diameter of the inferior vena cava were performed at the beginning of the study and after 6, 12, and 24 months.

#### STATISTICAL ANALYSES

Data are given as mean  $\pm$  SD. Comparisons between CAPD and HD patients and HD patients receiving dialyzer membranes with different biocompatibility were made using the unpaired t-test. For comparison of individual changes in RRF in these patient groups, the univariate ANOVA with the Bonferoni *post hoc* test was used. Statistical significance was defined as a *p* value of less than 0.05.

### RESULTS

#### CHARACTERISTICS OF THE STUDY GROUPS

There were no significant differences in mean age, mean body weight, cause of end-stage renal disease, systolic and diastolic blood pressure, or number of patients on

TABLE 1  
Patient Characteristics at Recruitment (Mean±SD)

	CAPD	All HD	BIC HD (low-flux)	BC HD (high-flux)
<i>N</i>	15	30	15	15
Age (years)	39±3	44±10	43±10	45±9
Gender (M/F)	7/8	19/11	9/6	10/5
Weight (kg)	68±13	70±14	70±16	70±14
Chronic renal disease				
Glomerulonephritis	7	14	7	7
Interstitial nephritis	4	8	4	4
Polycystic kidney disease	2	4	2	2
Diabetes mellitus	2	4	2	2
Blood pressure (mmHg)				
Systolic	128±12	131±13	130±13	131±13
Diastolic	74±11	82±9	81±8	82±10
Drugs				
ACE inhibitors	9	17	8	9
Erythropoietin	10	22	12	10
Vitamin D analogs	14	29	15	14
RRF (mL/min/1.73 m <sup>2</sup> )	7.4±1.2	7.5±1.7	7.4±1.8	7.6±1.6

CAPD = continuous ambulatory peritoneal dialysis; HD = hemodialysis; BIC = bioincompatible membrane (strong activation of complement and cells); BC = biocompatible membrane (little activation of complement and cells); ACE = angiotensin-converting enzyme; RRF = residual renal function.

TABLE 2  
Decline in Residual Renal Function (mL/min/1.73 m<sup>2</sup>; Mean±SD) in Patients Receiving Different Renal Replacement Modalities

Months	0	6	12	24
CAPD	7.4±1.2	6.8±1.2 <sup>a</sup>	6.0±1.2 <sup>a</sup>	3.1±0.5 <sup>a</sup>
Hemodialysis				
Cellulosic, low-flux	7.4±1.8	3.8±1.0 <sup>a,b</sup>	3.0±0.7 <sup>a,b</sup>	1.2±0.3 <sup>a,b</sup>
Polysulfone, high-flux	7.6±1.6	5.7±1.2 <sup>a,c</sup>	4.5±1.0 <sup>a,c</sup>	2.3±0.5 <sup>a,c</sup>

<sup>a</sup>  $p < 0.05$  compared to corresponding value at recruitment.

<sup>b</sup>  $p < 0.05$  compared to corresponding value for CAPD or biocompatible polysulfone hemodialysis.

<sup>c</sup>  $p < 0.05$  compared to corresponding value for CAPD.

angiotensin-converting enzyme (ACE) inhibitors, recombinant human erythropoietin, or vitamin D analogs between the patient groups treated with CAPD or HD with or without biocompatible membranes (Table 1).

All patients completed the study period of 24 months. Four HD patients (2 had vascular access problems, 1 had diverticulitis, 1 had pneumonia) and 4 CAPD patients (2 had bleeding from a gastric/duodenal ulcer, 2 had pneumonia) were hospitalized during the study period. Neither the intercurrent medical problem nor its therapy affected residual renal clearance acutely.

#### DECLINE IN RRF

Residual renal function declined in both CAPD and HD patients; the decline was faster in the HD populations than in CAPD patients. The mean loss of RRF was 0.6 mL/minute after 6 months, and 1.4 mL/min after 12 months for CAPD patients. For HD patients, it was 2.8 mL/min and 3.7 mL/min after 6 and 12 months respectively. At the end of the study period, the rate of decline for HD patients was more than twice as high as for CAPD patients.

TABLE 3  
 Characteristics of Hydration Status in Patients with End-Stage Renal Disease  
 Receiving Different Renal Replacement Modalities

Months	0	6	12	24
Blood pressure (mmHg)				
CAPD				
Systolic	128±12	136±14	132±13	140±15 <sup>a</sup>
Diastolic	74±11	78±12	78±10	82±9
Post BIC HD				
Systolic	130±13	135±14	140±12	132±10
Diastolic	81±8	84±10	80±9	84±10
Post BC HD				
Systolic	131±13	136±11	138±12	130±11
Diastolic	82±10	80±11	78±9	80±9
Dry weight (kg)				
CAPD				
Post BIC HD	68±13	72±12 <sup>a</sup>	71±12 <sup>a</sup>	73±12 <sup>a</sup>
Post BC HD	70±16	71±12	72±11	72±11 <sup>a</sup>
Diameter inferior vena cava (mm)				
CAPD				
Pre BIC HD	9.1±0.8	9.4±0.9 <sup>a,b</sup>	9.6±0.6 <sup>a,b</sup>	9.7±0.7 <sup>a,b</sup>
Post BIC HD	10.8±1.4	10.4±0.8	11.0±1.2	10.5±0.8
Pre BC HD	8.8±1.2 <sup>a</sup>	8.4±0.8 <sup>a</sup>	8.4±0.6 <sup>a</sup>	8.5±0.6 <sup>a</sup>
Post BC HD	11.7±0.7	10.4±0.8	10.8±1.2	9.9±0.8
Post BC HD	8.7±0.7 <sup>a</sup>	8.2±0.6 <sup>a</sup>	8.3±0.5 <sup>a</sup>	8.4±0.5 <sup>a</sup>

BIC = bioincompatible membrane (strong activation of complement and cells); HD = hemodialysis; BC = biocompatible membrane (little activation of complement and cells).

<sup>a</sup>  $p < 0.05$  compared to value at recruitment.

<sup>b</sup>  $p < 0.05$  compared to value of hemodialysis patients.

During the first 6 months, there were significant differences between the courses of declining residual renal CCr among patients treated with membranes differing in biocompatibility (1.9 mL/min for BC HD and 3.6 mL/min for BIC HD). During the following months (months 6 - 24 of the study), the decline in RRF was on a similar scale. Twenty-four months after initiation of maintenance HD, patients on cellulosic membranes had only 50% of the RRF preserved in patients on the biocompatible polysulfone membranes (Table 2).

#### CARDIOVASCULAR STABILITY

Blood pressure was controlled in both CAPD and HD patients. Although there was a tendency for higher values for CAPD patients with prolonged treatment time (Table 3), measurements of the diameter of the inferior vena cava demonstrated normal or slightly increased values for CAPD patients. In HD patients, ultrafiltration resulted in a significant reduction in the diameter of the inferior vena cava toward normal values. While none of the CAPD patients had documented hypotensive episodes, 11% of the HD sessions were complicated by a clinically relevant reduction in diastolic blood pressure. The choice of HD membrane did not affect cardiovascular instability [10% (cellulosic) vs 11% (polysulfone) hypotensive episodes].

#### DISCUSSION

The gradual deterioration of RRF in patients with end-stage renal disease starting dialytic therapy depends not on a single mechanism but rather on a number of factors operating simultaneously (9). Confirming previous publications, the results of our

prospective investigation clearly demonstrate that extracorporeal dialysis accelerates loss of residual CCr. While CAPD and HD patient groups did not differ in determinants of renal function, such as etiology of renal failure, RRF at recruitment, age, blood pressure levels, or antihypertensive medications, there were modality-specific differences in cardiovascular stability and systemic biocompatibility during the course of the study.

Patients on CAPD do not need rapid ultrafiltration. Unless CAPD patients are clearly dehydrated, acute hypotensive episodes during CAPD are infrequent compared to HD. In a study by Charytan *et al.* (11) including 92 patients on HD and 72 on CAPD treatment for up to 26 months, there were 15.6 hypotensive episodes per patient per year on HD versus 0.46 episodes per patient per year on CAPD. This frequency is in accordance with our data. Aggressive ultrafiltration in HD patients may induce rapid changes in extracellular/intracellular fluid volumes as shown by measurements of the diameter of the inferior vena cava. This may result in an acute fall in systemic blood pressure and probably causes a reduction of renal blood flow and further deterioration of renal function.

Most (12-16) but not all (9,17) studies suggest that HD with cellulosic membranes may be nephrotoxic, and hence could cause loss of RRF at a rate faster than the natural progression due to the primary renal disease. Blood-dialyzer membrane and blood-dialysis fluid interactions in patients treated with cuprophane membranes cause intensive activation of the complement system and circulating leukocytes. Complement compounds, leukotrienes, and cytokines may directly or indirectly cause vascular and/or inflammatory injury to the diseased kidneys. The membrane attack complex and reactive oxygen species may enhance toxic glomerular basement membrane degranulation (18). Absence of such nephrotoxic substances or a low potential to activate bioincompatibility pathways may permit a natural rate of progression of renal disease and, in many cases, better preservation of RRF for a longer period.

The contribution of RRF to total clearance may be significant and can be used to enhance dialysis adequacy, particularly in the early stages of dialysis dependence. CAPD, with its natural semipermeable membrane and its capacity for continuous ultrafiltration, minimizes the generation of blood-borne nephrotoxicity and severe fluctuations of volume status, and may be of significant benefit in preservation of RRF. Serial monitoring of individual patients for changes in RRF are warranted since biochemical and clinical parameters may fail to signal early changes in renal function. Loss of RRF may necessitate adjustment in CAPD prescription. In targeting an optimal Kt/V for HD patients, preservation of RRF might well be considered a functional reserve of which we should take advantage.

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