Article

Evolution Over Time of Volume Status and PD-Related Practice Patterns in an Incident Peritoneal Dialysis Cohort

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Abstract

Background and objectives Volume overload is frequent in prevalent patients on kidney replacement therapies and is associated with outcome. This study was devised to follow-up volume status of an incident population on peritoneal dialysis (PD) and to relate this to patient-relevant outcomes.

Design, setting, participants, & measurements This prospective cohort study was implemented in 135 study centers from 28 countries. Incident participants on PD were enrolled just before the actual PD treatment was started. Volume status was measured using bioimpedance spectroscopy before start of PD and thereafter in 3-month intervals, together with clinical and laboratory parameters, and PD prescription. The association of volume overload with time to death was tested using a competing risk Cox model.

Results In this population of 1054 participants incident on PD, volume overload before start of PD amounted to 1.9±2.3 L, and decreased to 1.2±1.8 L during the first year. At all time points, men and participants with diabetes were at higher risk to be volume overloaded. Dropout from PD during 3 years of observation by transfer to hemodialysis or transplantation (23% and 22%) was more prevalent than death (13%). Relative volume overload >17.3% was independently associated with higher risk of death (adjusted hazard ratio, 1.59; 95% confidence interval, 1.08 to 2.33) compared with relative volume overload ≤17.3%. Different practice patterns were observed between regions with respect to proportion of patients on PD versus hemodialysis, selection of PD modality, and prescription of hypertonic solutions.

Conclusions In this large cohort of incident participants on PD, with different treatment practices across centers and regions, we found substantial volume overload already at start of dialysis. Volume overload improved over time, and was associated with survival.

CJASN 14: 882–893, 2019. doi: https://doi.org/10.2215/CJN.11590918

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Introduction

Peritoneal dialysis (PD) allows an individualized dialysis prescription by combining different techniques (automated versus manual), dialysis solutions (tonicity, biocompatibility, type of osmotic agent), and number and duration of dwells to optimize maintenance of residual kidney function, preservation of the peritoneal membrane, and control of uremic symptoms, volume, and nutritional status, with the aim of prolonging technique and patient survival (1–4).

Elevated systolic BP and volume overload are associated with higher risk of mortality in patients on kidney replacement therapy (5–7), and both factors occur equally in patients on hemodialysis (HD) and PD (8). In a large cohort of incident patients on HD, baseline and cumulative volume overload over 1 year as assessed by bioimpedance spectroscopy was associated with mortality, independent of baseline BP (5). In PD, volume overload is frequent among prevalent patients (9), and associated with mortality (7). However, data in incident patients on PD were lacking until the international, multicentric study Initiative for Patient Outcomes in Dialysis-Peritoneal Dialysis (IPOD-PD) was started, studying incident participants on PD (10). Whereas relying on clinical observation might lead to an underestimation of volume overload in patients on PD (10), objective measurement of volume status as assessed by bioimpedance spectroscopy offers the opportunity to diagnose volume overload from the beginning of kidney replacement therapy, and to implement the appropriate treatment. It is postulated that the active management of volume overload may reduce the risk of technique failure (transfer to HD) (1) and improve survival in patients on PD (11,12). However, most of the strategies used to reduce volume overload also carry a risk of undesired side effects, such as faster degradation of the peritoneal membrane by the use of hypertonic exchanges, or

faster decline of residual kidney function when volume depletion ensues. It is thus also important to take into account the strategies used to maintain euvolemia. With this in mind, the IPOD-PD study investigates volume status in an incident patient population to relate patient characteristics and practice patterns over a long-term follow-up to volume status and patient-relevant outcomes.

Materials and Methods

The study was registered in January 2011 with Clinicaltrials.gov, under identifier NCT01285726.

Study Objectives and Design

This international, prospective, observational cohort study was designed to assess volume status of incident participants on PD and its evolution over time using bioimpedance spectroscopy measurement. Consecutive incident participants on PD from involved centers were invited to be recruited between January 2011 and December 2012 (Supplemental Table 1); no specific recruitment procedure has been requested for the centers. Participant follow-up was until December 2015, and lasted a minimum of 3 and maximum of 5 years.

The objective of this analysis is to describe the population and PD-related practice patterns by geographical region, with focus on volume status and time to death.

Study Procedures

Data of the latest body composition monitor (BCM; Fresenius Medical Care, Bad Homburg, Germany) measurement, together with clinical data, laboratory parameters, planned PD prescription, clinical assessment of volume status, and medication ≤3 days before start of PD therapy, were registered as baseline values (Supplemental Table 2). The same parameters were collected 1 and 3 months after the actual start of PD, and from then onward every 3 months until the participant changed kidney replacement modality, terminated the study prematurely for other reasons, or died (10). Clinicians were free to decide whether to prescribe PD regimens according to results from BCM measurement.

Routine laboratory parameters were on the basis of data provided by the laboratories of the respective centers. GFR was calculated as the average of creatinine and urea clearance on a 24-hour urine collection when available.

Center characteristics, including the number of prevalent participants on PD and HD, were defined at the inclusion of the first participant in the respective center.

Bioimpedance Spectroscopy with the BCM

Body composition, including volume status, was assessed using multifrequency bioimpedance spectroscopy with the BCM device, measuring total body water, extracellular water, and intracellular water (ICW). The BCM measures the impedance at 50 different frequencies (minimum 5 kHz and maximum 1 Mhz). This allows for measurements of extracellular volume with low-frequency current while high-frequency currents flow through both the extracellular and intracellular volume. With this method, volume status in the different body compartments (extracellular and intracellular) can be estimated. Volume status, lean tissue, and fat tissue are calculated from the impedance data

derived from the three compartment model described by Chamney et al. (13), which contains normohydrated lean tissue, normohydrated fat tissue, and excess fluid. Volume depletion or volume overload is the expected difference between the extracellular volume and the expected amount of volume in the euvolemic tissue as estimated by a previously published algorithm (13,14), expressed in absolute values (liters) or in relative terms (percentage of extracellular volume).

Patients are considered volume depleted or volume overloaded when their relative fluid volume is below the 10th or above the 90th percentile of a presumed healthy reference population (corresponding to −7% or +7% relative volume overload) (15,16).

According to physiologic plausibility, a BCM measurement was considered as invalid and excluded from statistical analysis if one of the following five criteria was present: volume depletion <-4 L, fat tissue mass/body weight not between 0.02 and 0.62, extracellular water/ICW not between 0.61 and 2.5, BCM quality indicator <50% and volume overload >6 L, and ICW/body weight not between 0.08 and 0.42.

Ethical Considerations

The study was carried out in accordance with the Declaration of Helsinki, and according to national laws and regulations submitted to ethics committees and/or national authorities. Before enrolling a participant, the individual was informed orally and in writing about the study, and provided written informed consent according to applicable law.

Statistical Analyses

Because of the explorative character of this observational study, no formal sample size estimation was performed; only available data were considered and no substitution procedure for missing data were applied. All analyses were done with SAS v9.4 (SAS Institute Inc., Cary, NC). Baseline data were analyzed descriptively and are given as percentages for categorical variables, mean±SD for normally distributed variables, and median (25th and 75th quantile) for non-normally distributed continuous variables.

To analyze associations between factors (measured at month 1) and relative volume status at the same time point and the effect of these factors on the course of relative volume status in the next 5 months, a linear mixed model was applied using SAS MIXED procedure. All available values of relative volume at month 1, 3, and 6 were used as outcome in the model. The variable time was calculated describing the time in months since month 1 and used as covariate. Additional factors as given in Table 1 were included in the model as main effects and by interaction with time. Participant and country were used as random effects and an autoregressive process of first order for irregular time intervals was applied as covariance.

The association between variables measured at baseline or month 1 on time to death in the following 3 years was analyzed with a competing risk model (Fine and Gray regression model for the subdistribution hazard ratios [17]) with the SAS PHREG procedure. Change to HD and transplantation were considered as competing risks, and

Table 1. Baseline characteristics of 1054 participants in the study, by volume status

Characteristic	Categorized Rel FO				Total
	Volume Depleted	Euvolemic	Moderate Volume Overload	Severe Volume Overload	
N	73	377	351	253	1054
Age, yr	56±16	56±16	59±15	61±14	58±15
Men, %	40	49	64	65	57
Height, cm	163±10	165±10	168±10	166±10	166±10
Weight, kg	73±18	73±17	72±16	70±15	72±16
Body mass index, kg/m^2	27.4±6.0	26.5±4.9	25.7±4.7	25.1±4.2	26.0±4.8
Systolic BP, mm Hg	136±20	134±20	141±20	144±24	139±21
Diastolic BP, mm Hg	81±13	79±12	81±13	80±15	80±13
Primary kidney disease, %					
Diabetes	16	16	26	51	28
Glomerulonephritis	21	23	19	11	19
Hypertension	19	17	15	16	17
Hereditary/congenital disease	8	12	11	2	9
Other	22	20	15	13	17
Unknown	14	11	13	7	11
Comorbidities, %					
Hypertension	88	88	89	89	88
Diabetes (type 1+2)	26	24	33	62	36
Cardiovascular disease (NYHA stage I, II, III, IV, unknown)	14	22	25	36	26
Medication					
Use of RAAS blockers, %	47	54	54	56	54
Use of diuretics	66	62	67	76	67
Transport status, % (first assessment)					
High (fast)	3	4	8	12	7
High average	21	25	26	28	26
Low average	19	19	17	15	17
Low (slow)	19	17	13	13	15
Missing	38	35	37	32	35
Dialysis solution, %					
Polyglucose	11	15	17	13	15
Biocompatible solution	74	75	76	66	73
Standard solution	26	25	25	34	27
Volume overload					
Absolute volume overload, L	n=73	n=377	n=351	n=253	n=1054
	−0.8±2.4	0.2±0.6	2.0±0.7	4.8±2.2	1.9±2.3
Relative volume overload, %	n=65	n=377	n=351	n=253	n=1046
	−10.4±2.9	1.4±3.7	11.6±2.9	24.4±6.8	9.7±11.1
GFR at month 1 (if available), mL/min	n=26	n=127	n=126	n=104	n=383
	8±4	9±5	7±4	6±3	7±4
24 h urine output, ml	n=73	n=375	n=350	n=253	n=1051
	1644±866	1633±754	156±741	1375±727	1550±757
Blood parameter					
Albumin, g/dl	n=69	n=341	n=318	n=233	n=961
	3.9±0.5	3.9±0.5	3.8±0.5	3.4±0.6	3. ± 0.6
CRP, mg/L	n=61	n=291	n=275	n=203	n=830
	3.0 [1.0; 6.6]	4.2 [1.0; 8.2]	4.0 [1.1; 8.0]	5.0 [1.0; 13]	4.1 [1.0; 9.0]

Data are given as mean±standard deviation, percentage or median and interquartile range (CRP).
Volume depleted: rel FO < −7%, euvolemic: −7% ≤ rel FO ≤7%, moderate volume overload: 7% < rel FO ≤17.3%, severe volume overload: rel FO >17.3%. Rel FO, relative fluid overload; NYHA, New York Heart Association; RAAS, renin-angiotensin-aldosteron-system; CRP, C-reactive protein.

dropouts for other reasons were censored. Backward variable selection according to the Akaike Information Criteria (18) were used to reduce the number of fixed effects and to find a good trade-off between the goodness of fit and the complexity of the model. Candidate variables for both models were region, age, sex, presence of liver disease and cardiovascular disease at baseline, and the following variables measured at month 1: diabetes status, PD modality, transport status, ultrafiltration, and volume overload (yes/no). Volume overload was defined as >17.3%

(corresponding to the 75% quantile of relative volume status at month 1). In case of an omitted visit at month 1, baseline values were used instead in all three models described above.

Results
Participants
A total of 1092 participants were recruited in 135 centers from 28 countries grouped into Western Europe, Eastern

Europe and Middle East, Asia Pacific, and Latin America (Table 2). Of note, all except two participants from Asia Pacific were recruited in South Korea. After exclusion because of violation of inclusion criteria ($n=2$), missing follow-up visits ($n=6$), and missing valid measurements of volume status at baseline ($n=30$), the final analysis population consisted of 1054 participants (Supplemental Figure 1), being slightly more than in the interim analysis (10). Whereas 36% of participants were euvolemic at start of PD, the majority showed either moderate or severe volume overload (33% and 24%, respectively), with some differences between regions (Table 2).

The characteristics of the overall population at baseline by category of volume status are given in Table 1. In more than one third of participants, no peritoneal membrane status test was documented within the first 6 months of dialysis. More than 30% were identified at the first test as high/high average transporter.

PD Prescription

At study start, 77% of the participants were treated with continuous ambulatory peritoneal dialysis (CAPD). The proportion of automated peritoneal dialysis (APD) increased in all regions to 38% during the first 3 years on dialysis (Figure 1A). Biocompatible solutions (defined as PD fluids prepared in two-chamber bags) were prescribed to the majority of participants (73% at baseline), with some differences between the different regions.

At baseline, 31% of the entire cohort were prescribed hypertonic PD solutions, defined as at least one exchange with a dextrose concentration $>1.5\%$. This percentage increased steadily to 51% at month 36. Hypertonic solutions were prescribed at baseline to 34% and 28%, and at month 36 to 50% and 53%, of volume-overloaded and nonvolume-overloaded participants, respectively. Use of hypertonic exchanges was substantially different between regions (Figure 1B). The percentage of participants using polyglucose as an osmotic agent increased from 15% at baseline to 25% at month 36, but prescription was very heterogeneous across regions, likely because of differences in local availability.

Dropout from PD

The cumulative dropout during 3 years was 74%, with the main cause being transfer to HD (23%), followed by transplantation (22%). Overall, dropout for any reason was lowest in the Asia Pacific region (60% of the participants were still on PD after 3 years versus 26%, 23%, and 16% in Western Europe, Eastern Europe and Middle East, and Latin America).

Volume Status

Mean volume overload as measured before start of the PD treatment was 1.9 ± 2.3 L, with a reduction to 1.2 ± 1.8 L during the first year, and it remained rather stable at year 2 and 3, at 1.4 ± 1.8 L and 1.4 ± 1.7 L, respectively. This corresponds to a relative volume overload of $9.7\%\pm11.1\%$ at baseline, $6.6\%\pm9.5\%$ after 1 year, $7.4\%\pm9.6\%$ after 2 years, and $7.7\%\pm8.9\%$ after 3 years. The course of BP, GFR, and urine output over 3 years is given in Supplemental Figures 2–4.

Volume overload was at all time points higher in men than in women, and higher in participants with versus without diabetes. The course of relative volume overload showed a slight and similar decrease over time in all groups (Figure 2, A and B). After 3 years of follow-up, the mean relative volume overload in the remaining cohort was lower than at baseline in participants from all regions, except those from Latin America, where it increased (Figure 2C).

Before the start of PD, 57% of the participants showed a relative volume overload of $>7\%$. This proportion decreased to 48%, 49%, and 53% after 1, 2, and 3 years of follow-up, respectively. Relative fluid depletion ($<-7\%$) was found in approximately 3%–8% of the participants at all time points. On average, mean relative volume increased in the first year in participants with volume depletion at baseline, whereas in participants with volume overload at baseline, a decreasing trend in mean relative volume in the first year was observed (Figure 3). The follow-up observations showed that both groups (with volume depletion and volume overload) tended toward euvolemia.

Table 2.   Proportion of participants at baseline by region of enrollment and categories of volume overload within the 1054 participants in the study

Region[a]	Countries	Clinics	Participants	Volume Depleted		Euvolemic		Moderately Volume Overloaded		Severely Volume Overloaded	
	N	N	N	N	%	N	%	N	%	N	%
Western Europe	16	101	715	54	8	279	39	244	34	138	19
Eastern Europe and Middle East	7	15	80	5	6	26	33	32	40	17	21
Latin America	3	13	130	10	8	38	29	31	24	51	39
Asia Pacific	2	6	129	4	3	34	26	44	34	47	36
Total	28	135	1054	73	7	377	36	351	33	253	24

Volume depleted: relative fluid overload $<-7\%$, euvolemic: $-7\% \leq$ relative fluid overload $\leq7\%$, moderately volume overloaded: $7\% <$ relative fluid overload $\leq17.3\%$, severely volume overloaded: relative fluid overload $>17.3\%$.
[a]Western Europe: Belgium, Czech Republic, Finland, France, Germany, Greece, Italy, Netherlands, Portugal, Spain, Sweden, Switzerland, UK, Norway, Denmark, and Austria. Eastern Europe and Middle East: Bosnia, Croatia, Israel, Estonia, Latvia, Lithuania, and Turkey. Latin America: Brazil, Cuba, and Venezuela. Asia Pacific: Korea and India.
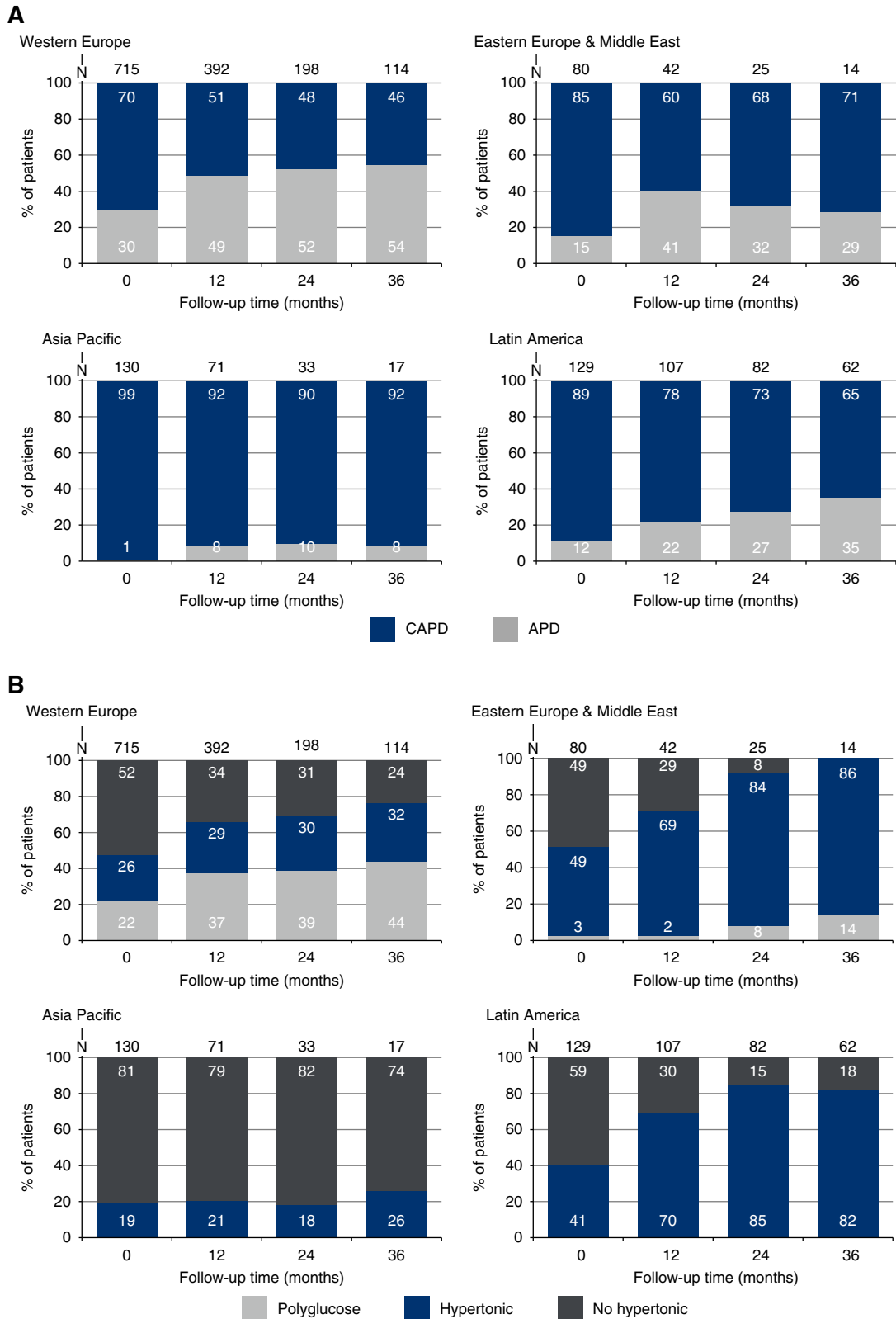
A

B

Figure 1. | **Patterns of prescription practice by region, with (A) use of APD versus CAPD and (B) use of polyglucose and hypertonic solution.**

In a linear mixed model increasing age, male sex, the regions Asia Pacific and Eastern Europe and Middle East, intake of diuretics, presence of diabetes were associated with elevated relative volume overload at month 1. For participants with a slow peritoneal membrane transport, relative volume was estimated at 6% higher for participants
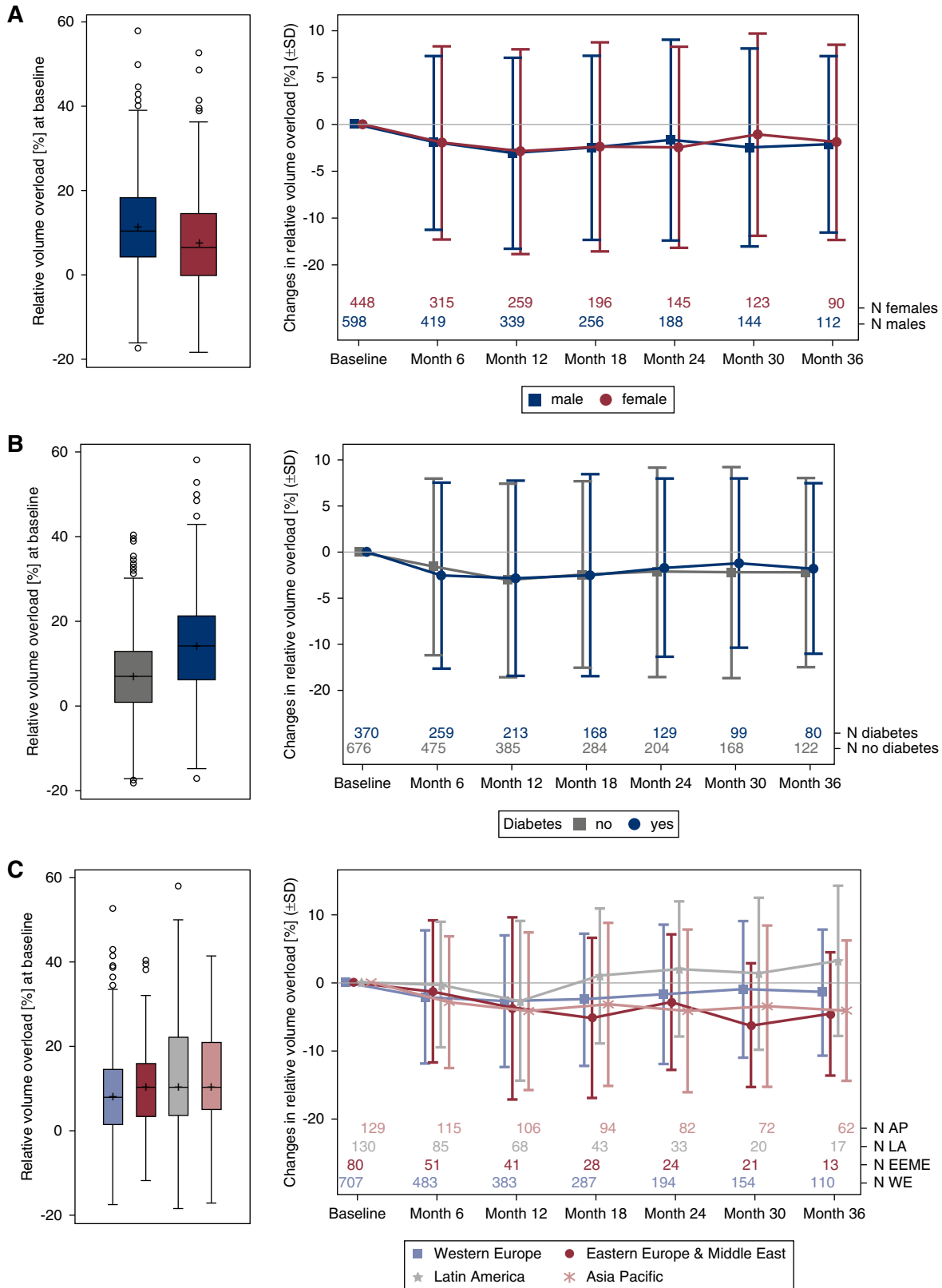
Figure 2. | Relative volume overload at baseline (left panel) and mean change during the study (right panel) by (A) sex, (B) diabetes status, and (C) region. The Δ of relative volume overload/depletion in percent points was calculated for each patient and visit (baseline, month 1, month 3, month 6, and so on, until month 36) as the absolute difference between relative volume overload or depletion at the respective visit and at baseline. The plots show the interquartile range (IQR; box), mean (cross), median (line), minimum and maximum value within the IQR±1.5 IQR (whiskers), and outliers (circles). AP, Asia Pacific; LA. Latin America; EEME, Eastern Europe & Middle East; WE, Western Europe.
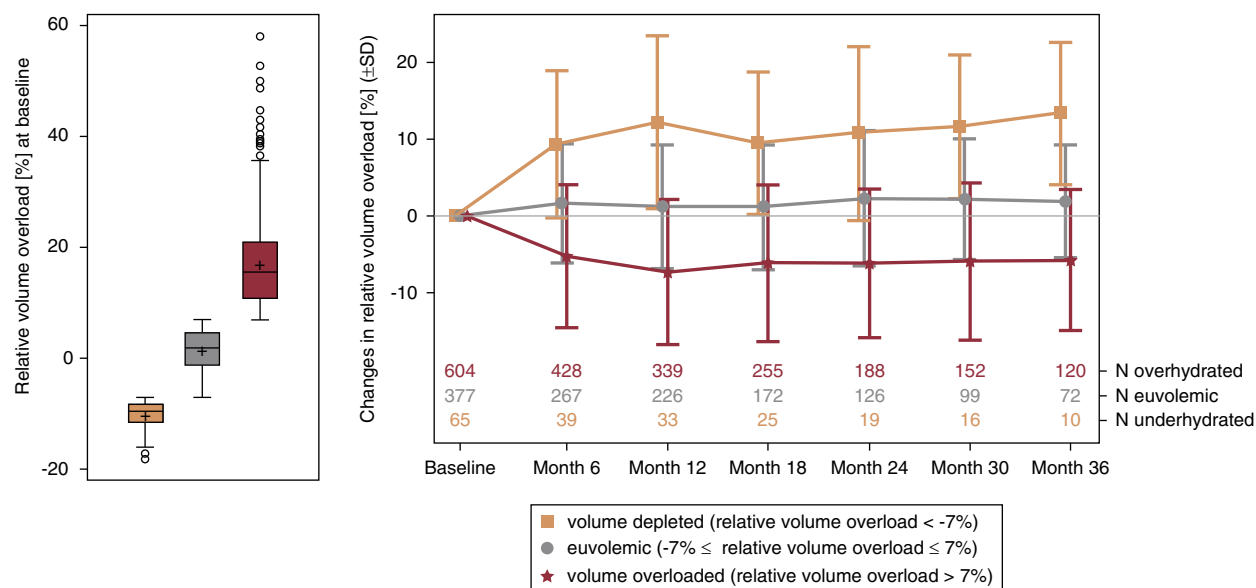
Figure 3. | **Relative volume overload at baseline (left panel) and mean change of relative volume overload (right panel) of participants in the following categories: volume depleted (<−7%), euvolemic (−7% ≤ relative volume status ≤7%), and volume overloaded (>7%).** The plots show the interquartile range (IQR; box), mean (cross), median (line), minimum and maximum value within IQR±1.5 IQR (whiskers), and outliers (circles).

using APD than CAPD (P=0.05). No significant effect of any factor on the course of relative volume until month 6 could be found (Table 3).

Time to Death

In a competing risk model on time to death, controlling for change to HD and transplantation, the variables volume overload (defined as >17.3%; the 75th percentile of relative volume overload at month 1 in our cohort), age, cardiovascular disease, liver disease, and diabetes were used (Table 4). The subdistributional hazard ratio for volume-overloaded participants is 1.59 compared with nonvolume-overloaded participants (95% confidence interval, 1.08 to 2.33; P=0.02). The cumulative incidence curve is visualized in Figure 4.

Discussion

The IPOD-PD study represents the largest cohort of incident patients on PD providing data on volume status as measured by bioimpedance spectroscopy, dialysis practices, and outcome. Overall, we found a substantial volume overload, which tended to improve over time of observation, but was at all times higher in men versus women and in participants with versus without diabetes. The results also indicate a variation in PD-related practices across regions, with an effect on volume status and dropout from PD. In a competing risk analysis, a relative volume overload >17.3% at month 1 was associated with time to death over the 3-year observation period.

Although volume overload is frequent in patients on kidney replacement therapy, the IPOD-PD study demonstrates that this volume overload is already present before the start of kidney replacement therapy. Volume overload tended to improve from baseline over the next 6 months, and stabilized afterward. It is difficult to determine whether this is a true improvement, rather a regression to the mean

or selection bias by informative dropout of those who are volume overloaded. Participants who were euvolemic at start mostly remained euvolemic, whereas the extent of volume depletion or volume overload tended to decrease.

As in prevalent patients, age, diabetes, and male sex are risk factors for being more volume overloaded in incident patients. Participants with diabetes are at risk for volume overload as they have more upregulation of vasopressin because of the hyperosmolar state induced by the hyperglycemia. The use of hypertonic exchanges can induce hyperglycemia, even in patients without diabetes (19). Adequate control of glycaemia is thus essential to maintain volume status in patients on PD. Fernandes *et al.* (20) also found a higher level of volume overload in patients with versus without diabetes, and associated this with a lower transperitoneal ultrafiltration capacity in patients with diabetes.

Several studies document higher odds of volume overload in men versus women on kidney replacement therapy. A recent small cohort study found a negative association between low testosterone and volume overload (21), and other cohort studies report a more substantial loss of lean tissue in men versus women on dialysis (8), suggesting that hormonal disturbances might play an important role in the observed volume overload in men. Poor adherence with therapy is a less likely explanation because our data indicate that the sex disparity in volume status is already present before start of kidney replacement therapy.

There were substantial differences in volume status between regions and clinical practices, which in turn may have an effect on volume status. In Asia Pacific, the usage of hypertonic bags and polyglucose was low; however, despite this, the initial volume overload could be successfully reduced. In contrast, in Latin America, volume overload even increased over time despite a high percentage using hypertonic solutions after 2 and 3 years. An

Table 3. Associations of clinical characteristics with volume overload and its change over time

Fixed Effects		Baseline Relative Volume Overload (%), Mean (95% CI) at 1 mo	Adjusted Difference (95% CI) in Baseline Relative Volume Overload (%) at 1 mo	Change in Relative Volume Overload (% per mo), Mean (95% CI)	Adjusted Difference (95% CI) in Change in Relative Volume Overload (% per mo)
Age	1 yr increase in age		0.1 (0.0–0.1)[a]		0.0 (0.0–0.0)
Sex	Women	10.6 (8.4 to 12.9)	0 (ref)	−0.4 (−1.1 to 0.4)	0 (ref)
	Men	14.0 (11.8 to 16.2)	3.4 (2.1 to 4.7)[a]	−0.3 (−0.1 to 0.4)	0.1 (−0.2 to 0.4)
Region	Western Europe	9.6 (7.6 to 11.6)	0 (ref)	−0.3 (−1.0 to 0.4)	0 (ref)
	Eastern Europe, Middle East	14.2 (11.0 to 17.5)	4.6 (1.7 to 7.5)[a]	−0.8 (−1.6 to 01)	−0.5 (−1.1 to 0.1)
	Latin America	12.2 (9.1 to 15.2)	2.6 (−0.1 to 5.3)	0.0 (−0.7 to 0.8)	0.3 (−0.1 to 0.8)
	Asia Pacific	13.3 (9.8 to 16.8)	3.7 (0.4 to 7.0)[a]	−0.3 (−1.0 to 0.5)	0.0 (−0.5 to 0.5)
Diuretics	No	11.4 (9.0 to 13.8)	0 (ref)	−0.3 (−1.0 to 0.5)	0 (ref)
	Yes	13.3 (11.1 to 15.4)	1.8 (0.4 to 3.3)[a]	−0.4 (−1.1 to 0.3)	−0.1 (−0.5 to 0.2)
Diabetes	No	9.9 (7.7 to 12.2)	0 (ref)	−0.3 (−1.0 to 0.4)	0 (ref)
	Yes	14.7 (12.5 to 17.0)	4.8 (3.3 to 6.2)[a]	−0.3 (−1.1 to 0.4)	0.0 (−0.3 to 0.3)
Polyglucose	No	12.5 (10.4 to 14.5)	0 (ref)	−0.4 (−1.1 to 0.3)	0 (ref)
	Yes	12.2 (9.6 to 14.8)	−0.3 (−2.1 to 1.6)	−0.3 (−1.0 to 0.5)	0.1 (−0.3 to 0.5)
Transport status dialysis modality[a]	CAPD/slow	8.4 (5.6 to 11.2)	0 (ref)	0.1 (−0.7 to 0.9)	0 (ref)
	CAPD/average	11.8 (9.9 to 13.8)	3.4 (0.6 to 6.3)[a]	−0.4 (−1.0 to 0.3)	−0.5 (−1.1 to 0.1)
	CAPD/fast	14.9 (11.5 to 18.4)	6.5 (2.4 to 10.6)[a]	−0.4 (−1.3 to 0.6)	−0.5 (−1.4 to 0.4)
	CAPD/missing	13.1 (11.5 to 14.7)	4.7 (1.9 to 7.4)[a]	−0.4 (−1.0 to 0.3)	−0.5 (−1.1 to 0.1)
	APD/slow	14.5 (8.7 to 20.3)	6.1 (0.0 to 12.2)	−0.7 (−2.2 to 0.7)	−0.9 (−2.3 to 0.6)
	APD/average	12.6 (9.1 to 16.1)	4.2 (0.2 to 8.2)[a]	−0.4 (−1.3 to 0.5)	−0.5 (−1.4 to 0.4)
	APD/fast	10.9 (0.0 to 1.8)	2.5 (−8.7 to 13.7)	−0.2 (−2.5 to 2.1)	−0.4 (−2.7 to 1.9)
	APD/missing	12.4 (10.1 to 14.6)	4.0 (0.9 to 7.1)[a]	0.3 (−0.9 to 0.4)	−0.4 (−1.1 to 0.3)

Linear mixed-model analyzing the association between variables measured at month 1 and relative volume overload (VO) at the same time point as well as the potential influence of these variables on changes in relative volume overload until month 6. Least square means for month 0 and for changes in 1 month were calculated for each categorical variable *via* least square means and estimate statement in PROC MIXED procedure in SAS. The adjusted differences in mean and in change of relative VO are always comparing the named categories with the reference category. The reference categories are marked as (ref). 95% CI, 95% confidence interval; ref, reference; CAPD, continuous ambulatory peritoneal dialysis; APD, automated peritoneal dialysis.
[a]Significant difference between category and reference category.

Table 4. Competing risk analysis for death, with censoring for dropout because of transfer to hemodialysis or transplantation.

Parameter		Subdistribution Hazard Ratio	Lower 95% CI	Upper 95% CI	P Value
Relative volume overload	Relative volume overload >17.3%	1.59	1.08	2.33	0.02
Age	per 1 year	1.06	1.04	1.07	<0.001
Cardiovascular disease	Yes	1.86	1.29	2.68	<0.001
Liver disease	Yes	2.11	1.14	3.90	0.02
Diabetes	Yes	1.49	1.04	2.15	0.03

Participants with dropout before month 1 (*n*=44) were excluded from this analysis. Volume overload is defined as relative volume overload >17.3% (75th percentile of the cohort). 95% CI, 95% confidence interval.

influence on volume overload by the use of hypertonic exchanges might be only limited and possibly superimposed by differences in adherence to salt and fluid restriction. However, our results indicate that it is possible to maintain good volume status even without the use of hypertonic exchanges, polyglucose, or APD.

Patients with a faster transport status are at highest risk of volume overload, and this exists before the start of PD (10). Thus, the volume overload observed in fast transporters is not only due to PD-related factors, suggesting that common factors explain both the fast transport status and volume overload, such as inflammation (22) and/or salt intake (23).

In Asia Pacific, PD dropout was substantially lower than in other regions, despite a limited usage of APD, hypertonic exchanges, and/or polyglucose. It could be speculated that this might be due to physiognomy, *e.g.*, a lower body weight and body mass index in participants from Asia Pacific versus the other regions. Furthermore, the

centers from Asia Pacific are characterized by the highest percentage of patients on PD versus HD and the highest number of incident patients on PD. Center size and number of incident patients on PD per year seem to have an effect on technique success (24).

The choice of modality (CAPD versus APD) and type of solution was certainly also governed by local availability. This is reflected in the absence of polyglucose prescription, the low use of APD, and the difference in use of biocompatible solutions in Asia Pacific and Latin America, with practically 100% use in Asia Pacific and nonusage in Latin America. The proportion of APD versus CAPD increased over time, but was always highest in Western Europe and lowest in Asia Pacific, in line with recent epidemiologic analysis on PD use worldwide (25).

In a recent meta-analysis (26), volume overload as assessed by bioimpedance was independently associated with mortality or hospitalization in prevalent kidney replacement therapy. This relationship remained after
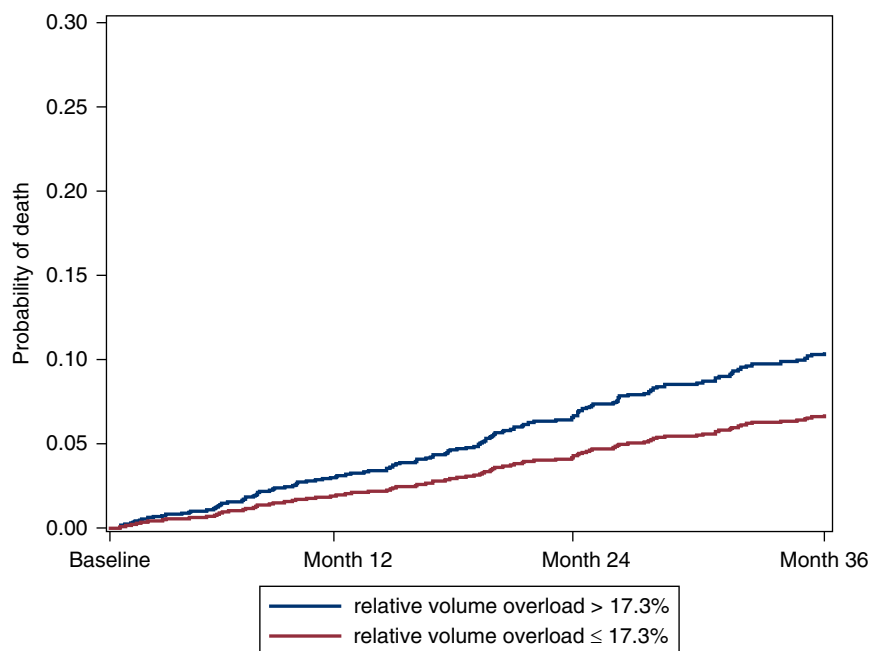
Figure 4. | Cumulative incidence of death by volume status 1 month after initiating PD, adjusted for competing risks of transfer to HD and transplantation in participants with relative volume overload >17.3% versus ≤17.3% for a participant with median age, no diabetes, and no cardiovascular disease.

adjustment for nutritional status and inflammation, contradicting the hypothesis that the association between bioimpedance-defined volume overload and survival only reflects cachexia, and supporting a direct toxic effect of hypervolemia. Our data confirm that this association is also present in incident kidney replacement therapy.

The strength of this study is the size of the cohort, with data on volume status from the start of kidney replacement therapy for a period equivalent to or even longer than the median survival time on PD. Furthermore, it comprises participants from a broad geographical origin and thus treatment practices.

The limitations of this study are the observational nature of the study, limiting the derivation of cause-effect associations. Our ability to derive associations between prescription patterns and volume status might be limited by the range of such patterns over the regions and countries, and by our sample size. The generalizability of our observations is hampered by the fact that the percentage of patients on PD versus HD is much higher than average in that region, indicating that there might be a selection bias in favor of more experienced PD centers.

In conclusion, our study found that substantial volume overload was present in this incident cohort of participants on PD, with men and patients with diabetes being more affected. Volume overload was associated with mortality. The study revealed different treatment practices across centers and regions. Despite not using hypertonic exchanges, APD, or polyglucose, the best technique survival was noted in Asia Pacific.

Disclosures

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.11590918/-/DCSupplemental.

Supplemental Table 1. Inclusion and exclusion criteria.
Supplemental Table 2. Documented parameters by visit.

Supplemental Figure 1. Flow diagram of the analysis population.
Supplemental Figure 2. Course of (A) systolic and (B) diastolic BP.
Supplemental Figure 3. Course of GFR during the study.
Supplemental Figure 4. Course of 24-hour urine output during the study.

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