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Original Articles

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Importance of normohydration for the long-term survival of haemodialysis patients

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Abstract

Background. Fluid overload and hypertension are among the most important risk factors for haemodialysis (HD) patients. The aim of this study was to analyse the impact of fluid overload for the survival of HD patients by using a selected reference population from Tassin.

Methods. A positively selected HD population (n = 50) from Tassin (Lyon—France) was used as a reference for fluid status and all-cause mortality. This population was compared to one dialysis centre from Giessen (Germany) which was separated into a non-hyperhydrated (n = 123) and a hyperhydrated (n = 35) patient group. The hydration status (ΔHS) of all patients was objectively measured with whole-body bioimpedance spectroscopy in 2003. All-cause mortality was analysed after a 6.5-year follow-up.

Results. Most of the reference patients from Tassin were normohydrated (ΔHS = 0.25 ± 1.15 L) at the start of the HD session. The hydration status of the Tassin patients was not different to the non-hyperhydrated Giessen patients (ΔHS = 0.8 ± 1.1 L) but significantly lower than in the hyperhydrated Giessen group (ΔHS = 3.5 ± 1.2 L). Multivariate adjusted all-cause mortality was significantly increased in the hyperhydrated patient group (hazard ratio = 3.41)— no difference in mortality could be observed between the Tassin and the non-hyperhydrated group from Giessen—even considering the fact that Tassin patients presented a significantly lower blood pressure.

Conclusions. Fluid overload has a very high predictive value for all-cause mortality and seems to be one of the major killers in the HD population. Patients might strongly benefit from active management of fluid overload.

Keywords: haemodialysis; hydration; hypertension; survival; volume overload

Introduction

One of the essential targets of dialysis therapy is to maintain a normal extracellular volume status and normal blood pressure (BP) levels. In various studies, it has been shown that normal BP levels can be achieved in a large majority of patients without using anti-hypertensive medications [1] by avoiding excess extracellular water through accurate and patient-specific fluid balance assessment. The concept and practice of controlling BP by reducing extracellular fluid is an established practice [2, 3] described by the term 'dry weight' which was introduced by Thomson in 1967 [4].

The essential component of the clinical assessment and management of dry weight is to reach a constantly low extracellular fluid state in the constraints of intermittent replacement therapy where large and variable volume swings can occur. At the same time, it is essential to avoid the occurrence of intradialytic morbid events. There is a greater likelihood that patients treated with long dialysis sessions (6–8 h) achieve a normal fluid status. These long dialysis sessions have been the cornerstone of treatment strategy in Tassin France for several decades [1, 5]. The Tassin approach to 'dry weight' is to maintain normotension without the need for anti-hypertensive medication by the start of the next dialysis session. Limiting salt intake and avoiding high interdialytic weight gains are key components of the Tassin treatment philosophy. Long treatment time together with the methods of clinical assessment (probing for dry weight) used in Tassin have resulted in normotension in >95% of haemodialysis (HD) patients [5]. The survival of Tassin patients has been reported to be significantly higher than in European or US dialysis facilities, which has been attributed to this approach [5, 6]. These findings offer strong evidence that fluid status in Tassin is well controlled. Thus, HD patients from Tassin could serve as a reference for fluid status and hypertension management. Nevertheless, although probing for the lowest tolerated post-weight [7] seems to be the best clinical assessment of dry weight, it is time consuming for the physician and may be uncomfortable for the patient [8].

Quantitative measures of extracellular volume status to facilitate the process of fluid balance assessment are essential to improve care and to further individualize the treatment. Bioimpedance spectroscopy [9, 10] in combination with a physiological tissue model [11] has proven its ability

to accurately, objectively and quantitatively assess hyperhydration [12–14]. In previous studies, it was demonstrated that patients benefit strongly from active management of the fluid status [15]. Recently, Wizemann [16] published data showing that hyperhydration is linked to a >2-fold increased mortality risk. Bioimpedance spectroscopy allows the objective comparison of patients and centres, independent of any differences in clinical assessment and treatment. The aim of this study was to analyse the impact of hyperhydration on mortality and to compare the outcome after 6.5 years in a positively selected subset of the Tassin HD centre (Lyon, France) (serving as a reference population) against a non-hyperhydrated and a hyperhydrated patient group from the dialysis centre in Giessen (Germany).

Materials and methods

Measurements

Extracellular and intracellular resistance and reactance were assessed with the Hydra 4200 (Xitron San Diego) (whole-body bioimpedance spectroscopy) at 50 frequencies from 5 to 1000 kHz. Based on this raw data, body composition and hydration state (ΔHS) were calculated to reflect the outputs of the BCM—Body Composition Monitor—Fresenius Medical Care D GmbH, which was not yet available at the start of the study. Measurements were performed before the start of the HD treatment with the patient in a recumbent position. All patients were measured after a short dialysis interval, by a trained nurse. No BCM measurements had been made previously in the patients and the results were blinded to the clinicians. The fluid volumes: extracellular (ECW), intracellular (ICW) and total body water (TBW) were determined using the approach described by Moissl [17] which has been validated against bromide and deuterium in HD patients and healthy subjects—an overview about the validation of this device is given in [14]. The hydration status (ΔHS) was calculated based on a physiological tissue model described in Chamney [18]. This method calculates the normal hydration status, i.e. the expected normal values for ECW and ICW that would result with healthy kidney function. As normal ECW or ICW can be determined for a given weight and body composition, ΔHS can be calculated from the difference between the normal ECW expected and the measured ECW. To allow for patients with different ECW owing to body size, ΔHS was normalized to the measured ECW (which includes fluid overload) and expressed as relative hydration state ($\Delta HS_{rel} = \Delta HS/ECW$). Although patients' plasma fluid contains minerals and other solutes, the difference in volume between pure water and fluid is negligible for all practical purposes [18]—therefore, the term 'fluid status' and 'hydration status' may be used interchangeably in this context.

The BP was taken before (before connection) and after the treatment in recumbent position before rinsing saline infusion. BP measurements of six treatments were averaged.

Patients and therapy

Tassin. Potential patients were screened in Tassin according to the following inclusion criteria:

- patients on dialysis between 1 and 10 years (to avoid possible anabolic or catabolic periods);
- patients not hospitalized in the 3 months prior to the study initiation;
- patients without any clinical condition liable to interfere with dryweight stability;
- patients without anti-hypertensive medication (not for cardioprotective reasons) and
- patients without amputation of a major limb or implanted pacemaker.

Fifty (out of a total number of 160) patients from the Tassin population were recruited to serve as a positively selected reference population with respect to fluid status. All patients were defined as being in the optimal fluid status by the clinical criteria from Tassin (probing for dry weight). Patient's demography did not differ from the overall Tassin dialysis population and patients were treated with 3 × 5–8 h/week with polysulphone low-flux membrane dialysis and 220–250 mL/min of blood flow range. All patients were treated with the Fresenius 4008 dialysis machine. A low-salt diet was actively encouraged to limit interdialytic weight gain with an effective average sodium chloride intake of 5 g/day.

Giessen. All patients in the dialysis centre in Giessen who met the BCM inclusion criteria (no pace maker or amputation of a major limb) and who agreed to participate in the study were measured ($n = 158$ of a total available HD population in Giessen of 172 patients). No other selection criteria were applied, thus providing a representative cross-section of the centre. HD therapy was performed three times per week for 4–5 h with a mean blood flow of 420 mL/min. The majority of patients were treated using 4008 series Fresenius Medical Care dialysis systems. Dialysis membranes were primarily high flux. No active salt restriction policy was ongoing in Giessen—the salt intake is assumed to be ~12 g/day.

Informed consent was obtained from all patients and the study adhered to the Declaration of Helsinki.

Lab tests, anti-hypertensive medication, erythropoetin and iron medication

The most recent monthly lab values of serum albumin, serum sodium and haematocrit prior to the BCM measurement were recorded. Similarly, the last month's dose of erythropoetin (EPO) and iron and the actual dose of anti-hypertensive medication were recorded to represent baseline conditions. Not included were any anti-hypertensive medication given for cardioprotective reasons.

Symptoms

The symptoms were assessed with an advanced clinical score [19]. The last six treatments prior to treatment involving the BCM measurement were analysed for the occurrence of symptoms.

Statistics/analysis

Variables were compared by analysis of variance tests or with chi-square test. The level of significance was set to $P < 0.05$. Survival functions according to baseline hydration status were described using the Kaplan–Meier technique. Cox proportional hazard models were used to compare survival according to baseline hydration status adjusting for demographic data (age and gender), co-morbid conditions (diabetes) and other predictors (dialysis vintage, BP, serum albumin and haematocrit). Both Kaplan–Meier curves and Cox model used the same end point (time to death) and patients were censored when they were transferred to another dialysis unit, received a kidney graft or were still on extracorporeal treatment on the final observation date (31 May 2009). When Cox proportional hazard regression was applied, stepwise methods were used to obtain the best multivariate model. Estimated relative risks (hazard ratios) and their 90% confidence intervals were calculated with the use of the estimated regression coefficients and their standard errors. The contribution of covariates to explain the dependent variable was assessed by means of a two-tailed Wald test, with $P < 0.05$ considered significant. All statistical analyses were performed using SPSS software, version 15 (SPSS Inc., Chicago, IL).

Results

The Giessen patient cohort was separated retrospectively into a non-hyperhydrated ($Gi_{non\text{-}hy}$) and a hyperhydrated (Gi_{hyper}) group on the basis of the BCM measurement, (Figure 1). The earlier specified criteria of $\Delta HS_{rel} = 15\%$ relative expansion of the extracellular compartment was used as cut-off [15, 16, 20]. There was no significant difference in the dialysis vintage between the three groups.

The hydration status of the $Tassin_{ref}$ cohort (considered to be a reference for HD patients) was comparable to the range found in healthy subjects [21]. The majority (75%) of $Tassin_{ref}$ patients were within the normohydration range ($-7\% < \Delta HS_{rel} < 7\%$) before the dialysis session. There was no significant difference between the non-hyperhydrated

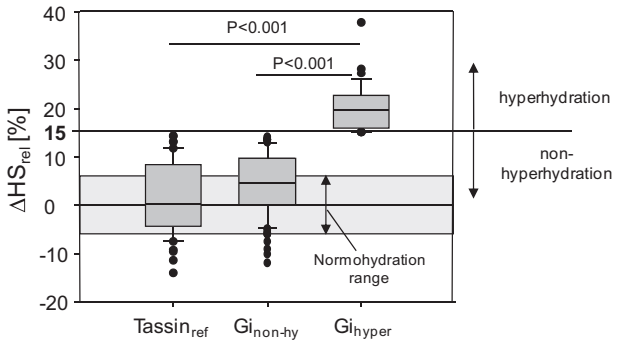

Fig. 1. Comparison of the relative hydration status before the dialysis (ΔHS_{rel}) between Tassin ($Tassin_{ref}$), Giessen non-hyperhydrated ($Gi_{non\text{-}hy}$) and hyperhydrated patients (Gi_{hyper}). Depicted in grey is the normohydration range of healthy subjects with normal kidney function ($-7\% \leq \Delta HS_{rel} \leq 7\%$). Additionally, the range of hyperhydration and non-hyperhydration is shown.

Giessen patients ($Gi_{non\text{-}hy}$) and the $Tassin_{ref}$ patients regarding the fluid status (Table 1).

The dialysate sodium concentration was not different between the three groups. The serum sodium concentration was significantly lower in the $Tassin_{ref}$ group; no difference was observed between the two groups from Giessen.

Both the systolic and the diastolic BP before and after the treatment were significantly lower in the $Tassin_{ref}$ group. No difference in BP was observed between the $Gi_{non\text{-}hy}$ and Gi_{hyper} patient group, (Figure 2).

The unadjusted Kaplan–Meier analysis revealed that the all-cause mortality of $Tassin_{ref}$ and $Gi_{non\text{-}hy}$ patients was not significantly different. The Gi_{hyper} patients presented a significantly increased mortality in the 6.5-year follow-up period, (Figure 3).

Table 2 shows the results of the multivariate Cox adjusted model.

The $Tassin_{ref}$ patient group was used as a reference in the multivariate Cox analysis. In the Cox model, the only remaining parameters of significance were age, presence of diabetes, haematocrit, albumin and hyperhydration (Gi_{hyper}). The hazard ratio due to the presence of fluid overload (Gi_{hyper}) was more predictive of all cause mortality than diabetes (Figure 4).

The fully adjusted hazard ratio for the $Gi_{non\text{-}hy}$ group did not indicate significantly higher hazard ratio than $Tassin_{ref}$. The unadjusted hazard ratios were 1.05 [0.6–1.81 (lower and upper confidence interval)] for the $Gi_{non\text{-}hy}$ patients and 2.87 (1.26–5.28) for the Gi_{hyper} patient group. After the full adjustment, the hazard ratio for all-cause mortality was found to be 1.26 (0.66–2.41) for the $Gi_{non\text{-}hy}$ and 3.41 (1.62–7.17) for the Gi_{hyper} group, with $Tassin_{ref}$ assumed as the reference. Significantly higher haematocrit was observed in the $Tassin_{ref}$ group, despite lower doses of EPO and iron than compared with the Giessen groups (not significant). The occurrence of intradialytic symptoms was low in all three groups—there was no statistically significant difference.

All patients were stratified by systolic BP and hydration status as defined in [20], see Figure 5. For the four resulting patient groups, the unadjusted Kaplan–Meier analysis was performed using the BP cut-off of BPsys = 140 mmHg and the hydration status cut-off of $\Delta HS_{rel} = 15\%$. Both groups with $\Delta HS_{rel} > 15\%$ showed significantly increased mortality (Figure 6). An additional multivariate Cox analysis revealed that hyperhydrated patients show an increased mortality risk independent of the BP (Figure 7). An elevated BP of BPsys >140 mmHg does not lead to a significant further increase in the mortality risk.

Discussion

The survival data in Tassin have been reported previously and may be regarded as a gold standard for survival of HD patients [23, 24]. For several decades, maintaining optimal fluid balance has been an important factor of the Tassin treatment approach. Dry weight assessment is performed through the method of dry weight probing [7]. One of the main successes has been the control of hypertension by adequate fluid removal [5, 8, 25] achieved with long treatments and restriction of dietary salt intake [26]. The 50 selected Tassin patients were normohydrated according to the clinical assessment of dry weight probing and daily monitoring of symptoms and signs. This tight control of fluid balance was reflected in the BCM measurements, which indicated a large number of patients in the healthy range [20]. Across Europe, ~30% of patients present an increased hydration status with $\Delta HS_{rel} > 15\%$ [20, 27].

In Giessen and Tassin, the fluid status of the patients was assessed with the same objective and quantitative method (BCM), which has allowed for the first time assessment of the impact of fluid overload on the survival of different patient groups. The patients from the Giessen centre were grouped retrospectively by the measured hydration status using the criteria of $\Delta HS_{rel} > 15\%$ [20]. The only significant difference between the non-hyperhydrated and the hyperhydrated population from Giessen was the fluid status—no other clinical parameter achieved significance. However, despite the difference in hydration between the two Giessen groups, the interdialytic weight gain was nearly identical. This suggests that interdialytic weight gain is of limited value in characterizing overall fluid status. Although increased interdialytic weight gain and high ultrafiltration rates are also associated with increased mortality [28–30], recent analysis has shown that the impact of ‘chronic’ or ‘permanent’ fluid overload on mortality is likely to be stronger [16, 31]. Hyperhydration is associated with a significant increased mortality risk [16]. Therefore, it was not surprising to observe that the Giessen hyperhydrated patients were associated with lower survival.

The long-term low-salt diet of the Tassin reference patients is well reflected in the results of the pre-dialysis serum sodium content. Even if all patient groups are treated with the same dialysate sodium concentration (as only limited individualization to the patient can be observed), the Tassin reference patients have a significantly lower pre-dialysis serum sodium content, which can be expected from the different salt intake in Tassin and Giessen patients. This might also be one of the reasons for the significantly lower BP and interdialytic weight gain in the $Tassin_{ref}$ group.

The clinical parameters show clear advantages for the selected Tassin patients in a number of risk factors

Table 1. Tassin and Giessen patient characteristics[a]

	$Tassin_{ref}$	$Gi_{non\text{-}hy}$	Gi_{hyper}
N	50	123	35
Centre change	2	6	2
Transplanted	11	15	2
Percentage of male patients	44	47.9	54.3
Age (years)	72.5 ± 12.1*****	64.7 ± 13.8***	65.4 ± 14.4***
Dialysis vintage (years) (median, 25 and 75% percentile)	3.4; 1.82; 5.0	3.02; 1.2; 6.1	4.6; 2.3; 16.6
Dialysis time (hours 3× per week)	6.8 ± 1.3	4.5 ± 0.3	4.5 ± 0.3
Dialysate sodium (mmol/L)	138.0 ± 0.1	138.9 ± 1.7	138.6 ± 1.9
Pre-weight (kg)	72.1 ± 19.1	74.0 ± 13.0	67.3 ± 15.8
Serum sodium (mmol/L)	135.3 ± 3.5*****	138 ± 2.7***	137.7 ± 3.2***
IDWG (%)	2.2 ± 1.3*****	3.1 ± 1.0***	3.3 ± 1.3***
Observation period (years)	6.0 ± 0.0	6.6 ± 0.5	6.4 ± 0.5
Height (cm)	162.3 ± 10.1	166.1 ± 9.5	166.5 ± 9.6
BMI (kg/m^2)	27.2 ± 6.2	26.9 ± 5.1	24.1 ± 3.1
Prevalence of diabetes (%)	14 (30% in total Tassin population)	37	23
Haematocrit (HCT) (%)	37.5 ± 4.0*****	33.9 ± 4.1***	33.0 ± 4.2***
% Patients with HCT <30%	4****	14**	23**
% Patients with HCT >36%	72*****	25***	23***
Erythropoetin (EPO) (IU/week)	3590 ± 3970	5015 ± 5250	5320 ± 4990
% Patients on EPO	76	70	71
Iron (mg/week)	21.6 ± 19.3	37.0 ± 42	32.9 ± 32.7
% Patient on iron	76****	54**	60**
Albumin (g/L)	38.3 ± 3.2	41 ± 2.9	39.3 ± 3.7
ECW (L)	15.1 ± 3.5	16.2 ± 3.0	17.1 ± 3.7
ICW (L)	16.6 ± 3.7	17.9 ± 4.1	16.0 ± 3.8
TBW (L)	31.7 ± 6.9	34.2 ± 6.8	33.1 ± 7.3
BPpre sys (mmHg)	127 ± 17*****	139 ± 21***	140 ± 20***
BPpre dia (mmHg)	68 ± 11*****	76 ± 11***	74 ± 13***
BPpost sys (mmHg)	110 ± 22*****	132 ± 19***	140 ± 19***
BPpost dia (mmHg)	63 ± 11*****	75 ± 11***	76 ± 12***
Number of AHT p.patient	0.04 ± 0.2	1 ± 1.1	0.8 ± 0.8
% Patients on AHT	4	54	57
$Hydration\ status_{pre}$ (L)	0.25 ± 1.15*	0.8 ± 1.1*	3.5 ± 1.2*****
$Hydration\ status_{post}$ (L)	−1.25 ± 1.23*	−1.5 ± 1.4*	1.3 ± 1.4*****
Relative $hydration\ status_{pre}$ (%)	1.4 ± 7.5*	4.6 ± 6.3*	20.2 ± 4.8*****
Relative $hydration\ status_{post}$ (%)	−10.3 ± 10.9*	−11.8 ± 11.2*	8.1 ± 7.8*****
TAFO (L)	−0.5 ± 1.1*	−0.35 ± 1.2*	2.4 ± 1.6*****
Crude mortality per year (%)	6*	6.4*	11.2*****

[a]Tassin patients were regarded as the reference group ($Tassin_{ref}$). Giessen patients were subdivided into the non-hyperhydrated and hyperhydrated groups ($Gi_{non\text{-}hy}$ and Gi_{hyper}, respectively). For each parameter (except for the dialysis vintage), the mean and the SD are displayed. IDWG, interdialytic weight gain; AHT, anti-hypertensive drugs; TAFO, weekly time averaged fluid overload [(HS_{pre} + HS_{post})/2]; BMI, body mass index.
*****Significantly different to both other groups ($P < 0.001$).
****Significantly different to both other groups ($P < 0,05$).
***Significantly different to $Tassin_{ref}$ ($P < 0.001$).
**Significantly different to $Tassin_{ref}$.
*Significantly different to Gi_{hyper} ($P < 0.001$).

(BP, interdialytic weight gain and haematocrit) but nevertheless, the survival of the Tassin and the non-hyperhydrated Giessen patients was not significantly different. This is especially interesting in the light of the significantly lower systolic BPs in the Tassin population. Therefore, an additional analysis was performed to separate the effect of hydration and hypertension status. The stratification of patients by hydration and hypertension status was recently proposed by Wabel [20] and Sinha [22], see Figure 5. In this stratification, the patients are separated into four groups depending on their hydration and hypertension status (Groups I–IV). The unadjusted Kaplan–Meier analysis for the four resulting patient groups revealed that hyperhydration (Groups I and IV) is a significantly stronger risk factor than hypertension (Groups II and III). Analysing the four patient groups with the multivariate Cox model clarified that there was no survival difference between hyper- and normotensive patients if the fluid status was below $\Delta HS_{rel} = 15\%$. Patients without hyperhydration (Groups II and III) have a lower mortality risk independent of BP. Additionally, all hyperhydrated patients (Groups I and IV) suffered from a significantly increased mortality risk, highest in the patient group that presented low/normal BPs together with hyperhydration (Group IV).

Elevated BP can be reduced with anti-hypertensive medication or treated with adequate ultrafiltration. Our data indicate that ultrafiltration may be the better choice whenever possible [32]. The efficient correction of the extracellular fluid overload with the goal of improving the high burden of cardiovascular mortality among dialysis patients remains one of the key challenges for nephrologists in the coming years [33]. Hyperhydration is a modifiable risk

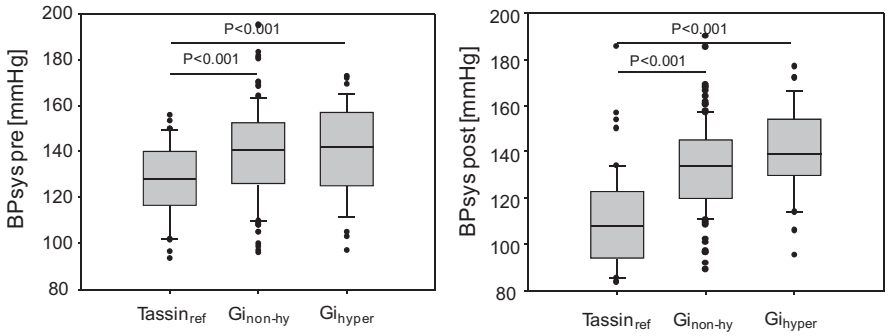

Fig. 2. Comparison of the systolic BP before and after HD treatment (BPsys pre, BPsys post).

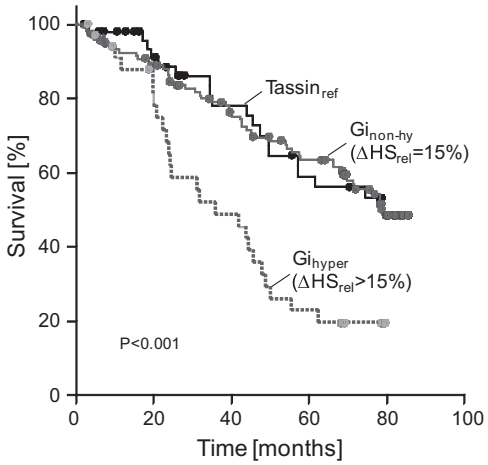

Fig. 3. Unadjusted Kaplan–Meier analysis for the three patient groups (Tassin$_{ref}$, Gi$_{non-hy}$, Gi$_{hyper}$) and the follow-up period of 6.5 years. All-cause mortality was considered as event.

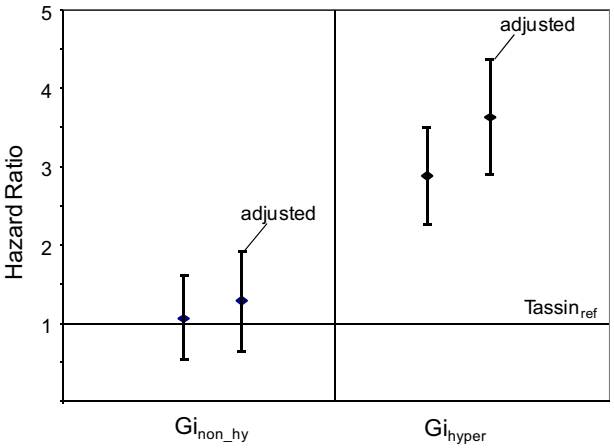

Fig. 4. Unadjusted and adjusted hazard ratio for the non-hyperhydrated (Gi$_{non-hyper}$) and the hyperhydrated (Gi$_{hyper}$) patient group using Tassin$_{ref}$ as the reference. The hazard ratio along with the upper and lower confidence interval is depicted.

Table 2. Results of the multivariate Cox adjusted model[a]

	Hazard ratio	Confidence low	Confidence high	Significance
Gender (male/female)	1.34	0.86	2.08	0.20
Age (1/a)	1.05	1.02	1.07	<0.0001
Diabetes (yes/no)	1.85	1.15	2.99	0.01
Haematocrit (1/%)	0.92	0.87	0.97	<0.0001
BPsys pre (1/mmHg)	1.00	0.99	1.01	0.65
Dialysis vintage (log)	0.89	0.76	1.04	0.15
BMI (1/kg/m^2)	0.96	0.91	1.01	0.09
Albumin (1/g/L)	0.92	0.85	0.99	0.02
Gi$_{non-hy}$	1.26	0.66	2.41	0.48
Gi$_{hyper}$	3.41	1.62	7.17	<0.0001

[a]The Tassin$_{ref}$ patient group was chosen as reference (hazard ratio = 1). BMI, body mass index.

factor [34], it can be assessed objectively [14] and corrected without the occurrence of additional intradialytic adverse events [15]. Objective and quantitative assessment of the hydration status and combining this information with important clinical information (e.g. BP, symptoms, medication and lab tests) should be the first step to achieve further improvements in the survival of chronic kidney disease patients. The risk that anti-hypertensive medications might be falsely comforting and entertain chronic fluid overload by reducing hypertension, its most pertinent marker has never been evaluated and will have to be addressed in the future. A technology like the BCM will help to know if the supposed benefit of anti-hypertensive medications as recently reported [35, 36] is independent or not of fluid excess.

The Tassin experience shows clearly that it is possible to achieve excellent survival without the presence of hyperhydration with long dialysis sessions. The experience from Machek [15] (using bioimpedance to optimize fluid status) or Ozkahya [37] (strict sodium control) demonstrates that it is possible to avoid hyperhydration in ~75–80% of HD patients with 4.5 h HD/haemodiafiltration treatment. After applying volume control, ~20–25% of patients remain hyperhydrated and might strongly benefit from prolonged treatment time or additional ultrafiltration sessions to lower their long-term fluid load. Individualization of HD therapy might be one of the key issues to solve the hyperhydration problem and the associated increased mortality risk. In the Tassin experience, all patients benefited from the long treatment hours that might only be necessary in a certain subset of patients. Some of the Tassin patients might have been hyperhydrated if dialysed in Giessen with the shorter treatment times.

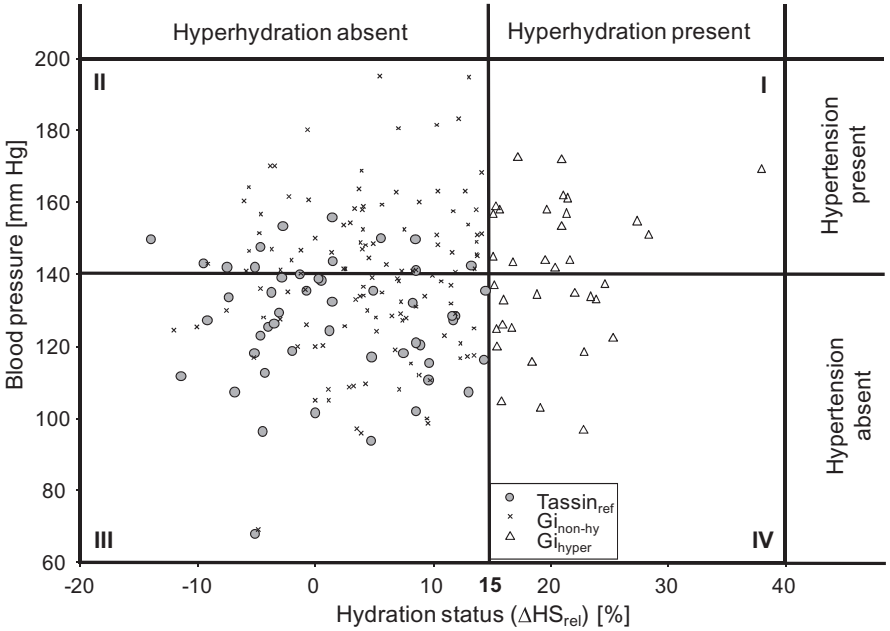

Fig. 5. Stratification of the three patient groups (Tassin$_{ref}$, Giessen non-hyperhydrated = Gi$_{non\text{-}hy}$, Giessen hyperhydrated = Gi$_{hyper}$) by systolic BP and hydration status (ΔHS_{rel}) before the HD treatment according to [20, 22]. A significant number of patients presented normal fluid status and an increased BP, while 50% of the hyperhydrated patients had a normal or low BP despite significant fluid overload.

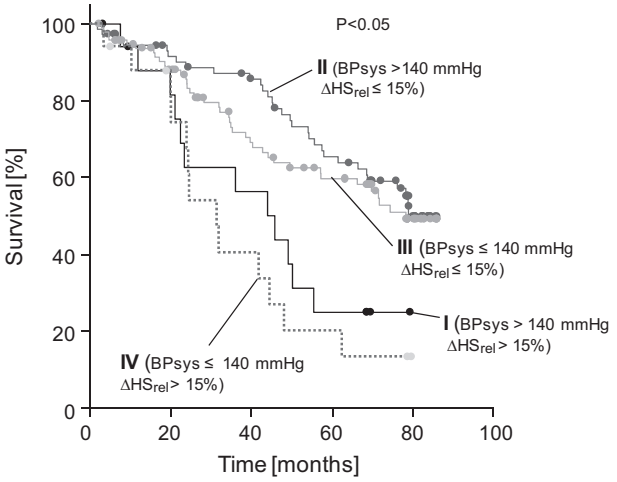

Fig. 6. Unadjusted Kaplan–Meier curves for the patient stratification groups (Groups I–IV) as defined in [20] for the follow-up period of 6.5 years, including all patients.

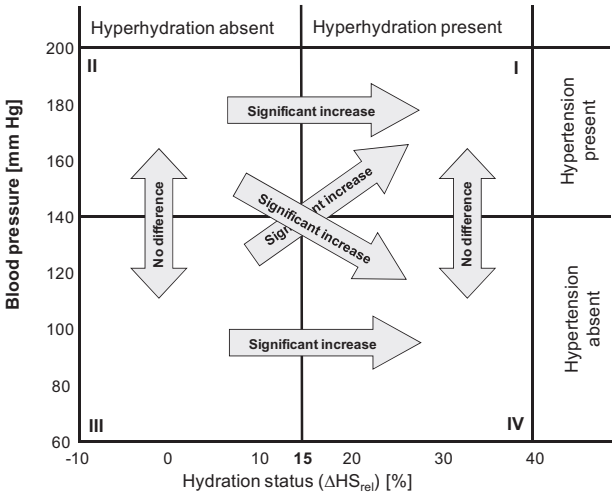

Fig. 7. Differences in the mortality risk between the four different patient groups (Groups I–IV) from the multivariate Cox analysis. Hyperhydrated patients (Groups I and IV) showed a significantly increased mortality risk independent of BP. In hyperhydrated or non-hyperhydrated patients, the BP level was not associated with a significantly increased mortality risk. The arrows indicate the mortality differences between the four patient groups (Groups I–IV).

Weaknesses of the study

The selected patients from Tassin were chosen to represent reference patients concerning clinical assessment of fluid overload. This resulted in the exclusion of most of the diabetic patients (prevalence 30%).

In the study, only the all-cause mortality was considered. The German death register is not reliable enough to separate safely between cardiovascular and non-cardiovascular death.

Moreover, this study is a pure retrospective analysis, therefore some caution should be exercised in the interpretation of the findings. A major drawback is that there was no longitudinal information on hydration status available, which contributes to some uncertainty. As dry weight can vary within the individual patient over time, clearly the fluid status of some patients may have improved or worsened. Future mortality analysis should also include time-variant changes.

In the study, no information about cardiac parameters was included. This limits strongly the interpretation of the results especially in the direction of a possible link between hyperhydration and cardiac dysfunction. It is also not clear if the observed hyperhydration is the cause or the

consequence of some observed co-morbidities (e.g. malnutrition).

Conclusions

Fluid overload leads to an increased mortality risk although the clinical signs may not be evident in all patients. Fluid overload has a higher predictive value for an increased mortality risk than BP. Indirect markers of fluid overload such as BP appear not to be predictive in HD patients in this study. Fluid overload seems to be one of the major killers for the dialysis patients. Patients will benefit strongly if the issue of long-term hyperhydration is solved. Regular measurement with an objective method may allow more consistent assessment of fluid balance in different centres. It remains to be demonstrated in prospective studies whether objective identification of hyperhydration can, through more rational treatment strategies, lead to improved survival.

Conflict of interest statement. P. W., P. C. U. M. and S. W. are employees of Fresenius Medical Care.

(See related article by Canaud and Lertdumrongluk. Probing 'dry weight' in haemodialysis patients: 'back to the future'. *Nephrol Dial Transplant* 2012; 27: 2140–2143.)

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