Daily Ultrafiltration Results in Improved Blood Pressure Control and More Efficient Removal of Small Molecules during Hemodialysis

James P. Jones^a Edward F. Leonard^b Gagangeet Sandhu^a Gary Winkel^c
Nathan W. Levin^d Stanley Cortell^a

^aDivision of Nephrology, Department of Medicine, St. Luke's-Roosevelt Hospital Center, Columbia University College of Physicians and Surgeons, ^bDepartments of Chemical and Biomedical Engineering, Columbia University, ^cDepartment of Oncological Sciences, Mount Sinai School of Medicine, and ^dRenal Research Institute, New York, N.Y., USA

Key Words

Daily ultrafiltration · Hemodialysis · Hypertension

Abstract

Background: Although prior studies have shown that frequent hemodialysis (HD) can lead to improved control of dry weight in end-stage renal disease patients, there are no clinical studies examining whether this can improve blood pressure (BP) control and can also shorten the dialysis time needed to achieve satisfactory removal of small molecules. Several models of wearable dialysis systems are now under various stages of development. These devices present the possibility of hemodialyzing patients to their dry weights. We have built a prototype of a wearable ultrafiltration (UF) device that can provide daily UF. Apart from better fluid control, we hypothesize that separating HD from UF will result in better BP control, and adequate weekly small molecule removal could be achieved with a decreased duration of dialysis. We tested the hypothesis in current HD patients using conventional dialysis equipment. **Methods:** Thirteen patients were selected from a large urban HD center. The experimental period consisted of 4 weeks of daily UF (4 days/week of UF alone and 2 days/week of HD with UF). The duration of the HD sessions was increased by 15–30 min to main-

tain weekly standard Kt/V >2.0. The patients were then returned to their conventional 3 days/week of HD with UF and studied for 4 weeks. Predialysis BPs, interdialytic weight gains, and Kt/V results of the experimental and return periods were compared with those of the 3-month control period. No changes were made in antihypertensive or other medication during the study. **Results:** During the experimental period, mean arterial pressure decreased from 110 to 95 mm Hg ($p < 0.001$), systolic BP from 158 to 136 mm Hg ($p < 0.001$), while interdialytic weight gains were reduced from 3.25 to 1.21 liters ($p < 0.0001$). During the experimental period, weekly standard Kt/V of 2.16 was achieved in 8.24 h/week of HD, as compared to 11.14 h/week. **Conclusions:** Volume control with daily UF results in improved BP control and, by separating the UF function from HD, adequate weekly standard Kt/V >2 can be achieved with twice weekly HD.

Copyright © 2013 S. Karger AG, Basel

Introduction

The mortality of end-stage renal disease (ESRD) patients in the United States is approximately 20% per year. It is even higher among diabetic patients, and is 5 times higher than in the general population [1]. Cardiovascular

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2013 S. Karger AG, Basel
0253-5068/12/0344-0325\$38.00/0

Accessible online at:
www.karger.com/bpu

Stanley Cortell, MD
Division of Nephrology, St. Luke's-Roosevelt Hospital Center
1111 Amsterdam Ave.
New York, NY 10025 (USA)
E-Mail scortell@chpnet.org, jajones@chpnet.org, gsandhu@chpnet.org

Table 1. Baseline clinical characteristics

Parameters	Study population	Study group (n = 12)	P
Diabetes mellitus type 1 or 2	530	9	0.052
Predialysis BP (MAP), mm Hg	104	110	0.12
Intradialytic weight gain, kg	3.26	2.63	0.02
UF volume, l	2.97	3.25	0.27
HD time, min	212.5	215	0.77
Kt/v	1.57	1.41	0.02

Figures represent numbers or means as appropriate.

There was no significant difference (Bonferroni-adjusted p value = 0.01) between the eligible study population and study group with respect to their interdialytic weight gain, UF volume, HD treatment time, Kt/v, and predialysis BP.

disease accounts for the largest number of deaths among ESRD patients with hypertension as its single most important predictor [2, 3]. Medicare recognizes the severity of this problem by mandating that each ESRD patient's treatment plan 'renders the patient euvoletic and normotensive'; specifically blood pressure (BP) should be 'reduced to $\leq 130/80$ with minimal use of medications' [4].

Chronic fluid overload and the inability to maintain dry weight play a major role in the generation and prevalence of hypertension among ESRD patients [5]. Up to 93% of the ESRD patients in the United States rely on in-center hemodialysis (HD). While improved control of hypertension has been reported with treatment models such as six times per week in-center HD or nocturnal dialysis, there is no frequent HD system that is economically feasible or not so burdensome for the patient and clinical staff as to be practical to the broad demographic of ESRD patients [6–8]. Less than 1% of ESRD patients in the United States receive home HD, probably because of the bulk, complexity, and infrastructure requirements needed for home therapy, as well as reimbursement considerations. Overall, only a minority (1/5th) of the patients are interested in more frequent in-center HD schedules [9, 10]. A simple, economically feasible system which would reduce fluid overload could thus have a major impact on the morbidity and mortality of ESRD patients.

Since the 1980s, there has been steadily increasing interest in developing wearable dialysis systems [11–13]. We have built a prototype of an ambulatory ultrafiltration (UF) device that can remove fluid continuously. The device is currently being tested on animals, and is based on

plasmapheresis at high blood shear rates through a flat silicon nitride microfilter consisting of millions of uniform pores and having a surface area of $<10\text{ cm}^2$. The resultant plasma, only, then flows through a conventional hollow-fiber ultrafilter with a surface area of just 250 cm^2 . The greatly reduced blood contact area and short contact time allow the system to deliver a continuous UF rate of 60 ml/h without the need for anticoagulation [14].

Our hypothesis is that by maintaining HD patients as close to their dry weight as possible, BP will be better controlled, while separating HD from UF will result in adequate removal of small molecules with decreased weekly dialysis time. The concept that separating UF from HD results in more efficient removal of small molecules during HD has been documented, but its effectiveness has not previously been shown in a therapeutic setting [15].

Patients and Methods

Thirteen ESRD patients on chronic HD were recruited at the Upper Manhattan Dialysis Center in New York City; all were ≥ 18 years of age, and had been treated for at least 3 months. These patients were representative of the general population at that center (see table 1). All patients were hypertensive with a mean predialysis sitting BP of $\geq 135/85\text{ mm Hg}$. All patients had residual renal clearance $<1.5\text{ ml/min per }35\text{ l}$ of (urea) volume and predialysis serum sodium levels of $>136\text{ mEq/l}$.

Adequate sample size was determined from the work of Kooistra et al. [16]. Power analysis was based on a paired t test comparing subjects' hemodynamic control outcomes at baseline with their 8-week outcomes, following O'Brien and Muller's approach [17]. Sample size was determined setting α at 0.05 and power at 0.80. Outcomes included systolic and diastolic BP, mean arterial pressure (MAP), and UF volume. Suggested sample sizes ranged between 9 and 13 patients.

The study consisted of three phases: the 'control phase' (the 3 months prior to the daily UF phase), the 'daily UF phase' and the 'return phase'. There were no changes made in subjects' anticoagulation regimes, blood flow rates, dialysate flow rates, vascular accesses, or the methodologies used to measure BP (electronic cuff on the machine). Outcome data were measured on each treatment day during both the daily UF and return phases.

In the control phase (phase I), baseline 3-month retrospective data were collected for all 13 patients prior to initiation of the daily UF phase.

In the daily UF phase (phase II), each patient received UF only, using conventional dialysis equipment at the HD center, on Monday, Wednesday, Thursday, and Saturday, and HD and UF on Tuesday and Friday for 4 weeks. The study center was closed on Sundays, so this study simulated daily UF with 6 treatments per week. On UF-only days, the blood flow rate was set at 200 ml/min , the minimum UF rate was set at 250 ml/h , and the maximum UF time could not exceed 4 h. Also during this phase, no changes were made to a patient's HD prescription (e.g. dialyzer, dialysis fluid, blood flow, dialysis flow, and UF prescription), except that

Table 2. The average predialysis systolic, diastolic, and mean arterial BP for the 12 subjects for the 3 months prior to initiation of the study, the daily UF phase, and the return phase

Patient	Before trial			Daily UF phase			Return phase		
	systolic	diastolic	MAP	systolic	diastolic	MAP	systolic	diastolic	MAP
1	121	66	84	118	68	84	130	74	92
2	158	99	119	149	92	111	148	90	110
3	155	96	116	132	81	98	140	89	106
4	154	88	110	144	79	101	152	82	105
5	150	74	100	139	71	94	162	79	107
6	151	78	102	135	72	93	167	82	110
7	191	103	133	135	73	94	157	84	108
8	173	91	119	144	70	95	n.a.	n.a.	n.a.
9	168	78	108	140	64	89	170	79	109
10	149	92	111	120	77	91	137	83	101
11	157	79	105	140	69	93	149	76	101
12	164	88	113	134	77	96	171	95	121
Average	158	86	110	136	74	95	153	83	106

n.a. = Not available.

with the concurrence of the IRB, the dialysis time was increased by 15–30 min per session to ensure that the patient's target standard Kt/V was ≥ 2.0 .

During the return phase (phase III), all patients resumed their prior schedule of three weekly HD and UF sessions for 4 weeks.

Systolic and diastolic BPs were measured before and after treatments. MAP was determined from the formula $MAP = [systolic\ BP + (2 \times diastolic\ BP)]/3$.

Target weight for UF was determined as the amount of excess fluid to be removed at every treatment session in accordance with the historical practice of comparing predialysis weights with the patient's estimated dry weight at the study center. The pretreatment weight at each visit was subtracted from the estimated normal hydration state using conventional clinical assessment methods. In other words, the total volume difference between current and estimated normal hydration was removed in one treatment. Additionally, whole-body and calf bioimpedance was measured at the same time using a multifrequency bioimpedance spectroscopy (BIS) analysis with the Hydra 4200 Monitor (Xitron Technologies, San Diego, Calif., USA), performed once per week, before and after dialysis, and expressed as a percentage of total body water (TBW). Extracellular (ECV) and intracellular fluid volumes in the body were calculated according to resistance and reactance from frequencies of 5–1,000 kHz by whole-body BIS [18]. A previously published study established hydration state using calf normalized resistivity (nRho) at 5 kHz [19]. Bioimpedance measurement was performed once per week before and after dialysis (15 min) with the patient in the supine position. The degree of hydration in patients was expressed by normalized resistivity nRho. The normal range of nRho was defined when $nRho > 18.3 (\Omega \cdot m^3/kg) \cdot 10^{-2}$ in males and $> 20 (\Omega \cdot m^3/kg) \cdot 10^{-2}$ in females [18].

The KDQOL-Short Form questionnaire was self-administered to all patients before and after the daily UF phase [20]. Blood urea nitrogen, serum phosphorus, potassium, and creatinine were

measured each week during both phases of the study, on Friday during the daily UF phase and, on Thursday or Friday, during the return phase.

A general linear model repeated-measures analysis of variance was conducted for all outcomes in which the three study phases were compared to one another [21]. If the overall model was statistically significant, the mean for each phase was compared with the means of the other phases with a Tukey adjustment for multiple comparisons [22].

Since multiple outcomes were being assessed, the critical value for statistical significance was Bonferroni adjusted [23].

Results

Patient Population

Baseline clinical characteristics are shown in table 1. There was no significant difference (Bonferroni adjusted p value = 0.01) between the eligible study population and the study group with respect to their interdialytic weight gain, UF volume, HD treatment time, Kt/V, and predialysis BP.

For both the BP and dialysis adequacy outcomes below, the critical p value was Bonferroni adjusted. Significant findings are based on a p value < 0.01 .

Blood Pressure

Predialysis systolic and diastolic BPs were lower as compared to baseline in 11 of 12 patients in the study group during the daily UF phase. Table 2 demonstrates the average predialysis systolic, diastolic, and mean arte-

Table 3. Dialysis adequacy: weekly HD treatment time, average eKt/V, average standard Kt/V, and intradialytic weight gain during the study

Patient	Prestudy phase				Daily UF phase				Return phase			
	HD time h/week	average eKt/V	average weekly standard Kt/V	intra-dialytic weight gain, l	HD time h/week	average eKt/V	average weekly standard Kt/V	intra-dialytic weight gain, l	HD time h/week	average eKt/V	average weekly standard Kt/V	intra-dialytic weight gain, l
1	10.08	1.39	2.54	1.84	9.00	1.98	2.33	0.98	10.15	1.57	2.65	2.21
2	10.03	1.37	2.19	2.81	9.25	2.07	2.16	1.02	10.18	1.49	2.34	2.53
3	9.00	1.43	2.41	2.31	8.00	2.45	2.26	1.34	9.00	2.07	2.64	3.08
4	12.10	1.61	2.46	5.15	8.15	2.07	2.08	1.25	11.00	1.71	2.57	2.90
5	9.46	1.27	2.26	3.03	8.05	1.61	1.92	1.28	10.28	1.41	2.13	2.43
6	12.00	1.60	2.76	3.63	9.00	2.16	2.15	1.77	12.00	1.80	2.69	4.04
7	11.24	1.52	2.42	2.51	7.59	1.78	2.12	0.73	11.09	1.49	2.78	3.05
8	12.23	1.44	3.04	3.71	9.26	1.84	2.12	0.83	n.a.	n.a.	n.a.	n.a.
9	12.04	1.36	2.60	4.21	7.31	1.52	2.13	1.52	9.31	1.49	2.40	3.79
10	10.03	1.25	2.48	2.51	7.10	1.74	2.16	1.15	10.25	1.55	2.59	2.15
11	12.00	1.24	2.79	4.13	10.32	1.82	2.34	1.73	12.00	1.74	3.01	3.37
12	12.13	1.28	2.60	3.11	8.00	1.46	2.09	0.96	12.07	1.25	2.64	2.31
Average	11.14	1.40	2.55	3.25	8.24	1.88	2.16	1.21	10.52	1.60	2.56	2.90

n.a. = Not available.

rial BP for the 12 subjects during the 3 months prior to initiation of the study, the daily UF phase, and the return phase. There were statistically significant differences among the study phases in each of the three outcomes (systolic = 17.65, $p < 0.0001$; diastolic = 14.93, $p < 0.0001$; MAP = 16.68, $p < 0.0001$).

Post hoc comparisons of the means showed there was a significant ($t_{21} = 5.56$; $p < 0.0001$) reduction in the mean systolic BP from 158 to 136 mm Hg, a significant ($t_{21} = 5.28$; $p < 0.0001$) reduction in mean diastolic BP from 86 to 74 mm Hg, and a significant ($t_{21} = 5.51$; $p < 0.0001$) reduction in MAP from 110 to 95 mm Hg during the daily UF phase as compared to baseline. The return phase showed significant (all p values < 0.002) elevation in BP within 4 weeks of discontinuation of daily UF.

Dialysis Adequacy

In the control phase, the study group had an average standard Kt/V of 2.55 with an average interdialytic weight gain of 3.25 l. Table 3 lists the weekly HD treatment time, average eKt/V, average standard Kt/V, and interdialytic weight gain during the study. The formula used for calculating standard Kt/V is available online (<http://www.hdcn.com/calcf/ley.htm>), and requires the urea reduction ratio value for computation [24]. As per protocol, the dialysate flow at the study HD center is 1.5 times the blood

flow rate. The maximum blood flow rate is between 450 and 500 ml/min depending on the patient's type of vascular access. No changes were made in the type of access or the blood flow rate over the duration of the study.

Mean URR increased from 72.7 to 76.7 ($p = 0.0011$) between the control phase and the daily UF phase. There was a 23.3% decrease in dialysis time during the daily UF phase, which was statistically significant ($t_{21} = 9.02$; $p < 0.0001$), while standard weekly Kt/V was > 2.0 . The average interdialytic weight gain decreased by 62% from 3.25 to 1.21 liters during the daily UF phase, which was statistically significant ($t_{21} = 9.38$; $p < 0.0001$).

In the control phase, the study group had average phosphorus of 5.69 mEq/dl, potassium of 4.84 mEq/dl and hemoglobin of 11.6 g/dl. There was no significant change in values during the daily UF phase: phosphorus 5.93 ($p = 0.54$), potassium 4.99 mEq/dl ($p = 0.17$), and hemoglobin 12.04 g/dl ($p = 0.19$).

Quality of Life

Twelve patients answered the KDQOI-Short Form questionnaire at the start and conclusion of the daily UF phase. Although the results showed a trend toward an improvement, no statistically significant changes in energy/fatigue, effects of kidney disease, cognitive function, quality of social interaction, and symptoms before, dur-

Table 4. Comparison of quality of life measures between daily UF and twice-weekly HD as compared to conventional HD (3×/week) (using a Bonferroni-adjusted p value of 0.002)

KDQOL	Conventional treatment	Daily UF with dialysis 2×/week	p
<i>Health survey</i>			
Symptom/problem list (12)	65.37	77.31	0.02
Effects of kidney disease (8)	53.61	61.25	0.15
Burden of kidney disease (4)	35.1	38.75	0.46
Work status (2)	23.08	35	0.20
Cognitive function (3)	77.44	80.67	0.77
Quality of social interaction (3)	77.44	76	0.75
Sexual function (2)	72.5	95.83	A
Sleep (4)	44.81	57.25	0.06
Social support (2)	73.08	76.67	0.22
Dialysis staff encouragement (2)	52.88	43.75	0.99
Overall health (1)	48.46	57	0.14
Patient satisfaction (1)	41.03	41.67	0.50
<i>ESRD-specific survey</i>			
Physical functioning (10)	50.38	65.5	0.10
Role limitations, physical (4)	21.15	42.5	0.26
Pain (2)	48.65	61.75	0.16
General health (5)	38.85	47.5	0.43
Emotional well-being (5)	74.46	78.4	0.23
Role limitations, emotional (3)	61.54	73.33	0.47
Social function (2)	67.31	78.75	0.17
Energy/fatigue (4)	47.69	57.5	0.37
SF-12 Physical Health Composite	31.39	38.3	0.09
SF-12 Mental Health Composite	50.75	53.32	0.39

A = Excessive amount of missing data precluded a statistical test.

ing, and after dialysis were seen. Table 4 lists the comparison of QOL measures between daily UF and twice-weekly HD as compared to conventional HD (3×/week) using a Bonferroni adjusted p value of 0.002.

Body Bioimpedance

The body fluid volume (ECV and TBW) were significantly decreased, and calf nRho was increased during HD due to ECV removed by UF. Comparison of the daily UF and return phases shows that body weight, ECV and nRho differ significantly at predialysis. However, no difference was observed at the postdialysis measurement (table 5).

Postdialysis bioimpedance measurements were done 15 min after the end of HD session. These data imply that the patients were not at their dry weight when receiving conventional 3×/week HD treatment.

Table 5. Body bioimpedance

	HD phase	UF phase	p value
<i>Before dialysis</i>			
Weight, kg	85.2 ± 10	83 ± 10	<0.01
nRho, ($\Omega \cdot m^3/kg$) · 10 ⁻²	14 ± 4.3	15.1 ± 4.2	<0.05
ECV, l	18.9 ± 3.1	17.7 ± 2.9	<0.05
ICV, l	20.4 ± 3.3	19.9 ± 3.2	n.s.
TBW, l	39.3 ± 6	37.6 ± 5.7	<0.01
<i>After dialysis</i>			
Weight, kg	82.1 ± 9.3	81.5 ± 9	n.s.
nRho, ($\Omega \cdot m^3/kg$) · 10 ⁻²	16.1 ± 4.9	17 ± 5	n.s.
ECV, l	16.5 ± 2.9	16 ± 2.6	n.s.
ICV, l	21.4 ± 4.3	19.9 ± 3.4	n.s.
TBW, l	38 ± 6.3	35.9 ± 5.5	n.s.

Comparison of the UF and HD phases shows that body weight, ECV and nRho differed significantly before dialysis. However, no difference was observed at the postdialysis measurement. These data imply that the patients were not at their dry weight when receiving three times weekly treatment.

ICV = Intracellular fluid volume; n.s. = no statistical difference.

Adverse Events

Thirteen patients were recruited for the study. One patient had a graft infection during the first week of the daily UF phase and was withdrawn from the study. Another patient (No. 8) developed lower back pain during the return phase and was hospitalized. Twelve patients completed the study without any serious adverse events.

Discussion

Adequate control of BP in HD patients is a major clinical problem in ESRD patients. Only 30% of hypertensive HD patients achieve effective BP control [25]. In fact, ESRD patients typically begin their dialysis session with MAPs above 100 mm Hg [26]. An important impediment to BP control is the great variation in volume that occurs routinely between dialysis sessions. While HD successfully removes metabolic solutes and uremic toxins, the HD session is frequently associated with inadequate fluid removal. In order to reach their estimated dry weight, patients require aggressive UF rates, typically 1.0–1.5 l/h, just to remove excess fluid, often resulting in nausea, cramping, and episodes of hypotension and cardiovascular instability [27–29]. Diabetics, the largest single group

of patients with ESRD, gain 30–50% more weight in interdialytic periods compared to non-diabetics [30]. The correlation between excess volume and increased mortality was shown in the HEMO study: those with the lowest interdialytic fluid retention (<1.0 kg) had a survival advantage and the lowest cardiovascular death risk irrespective of confounders [31].

In many patients, the interval between dialysis treatment sessions is too long to avoid excessive accumulation of volume, while the large weight gains make removal of the volume difficult without precipitating cardiovascular instability [27]. Consequently, the inability to attain dry weight within the therapeutic confines of three times per week HD and UF contributes to the high prevalence of hypertension among ESRD patients.

With daily UF (simulated in our study here at 6 days/week) and conventional HD and UF 2 days/week, a statistically significant reduction in BP in the cohort of 12 hypertensive ESRD patients with no change in their medications is shown. By improving the efficiency of dialysis and minimizing the need for UF during the HD sessions, the study group achieved adequate weekly standard Kt/V >2.0 with only 2 HD sessions/week, and no decrease in hematocrit. Although there was a slight trend towards a worsening of the serum phosphorus, it was not significant ($p = 0.54$). However, it is possible that increased food intake resulted in the trend toward an increase in serum phosphorus, especially since the dose of phosphate binders was not increased during the study.

The modality of frequent dialysis sessions (FD) is an effective alternative method to treat hypertension among ESRD patients, and it provides a dramatic contrast to the depressing statistics regarding cardiovascular disease and mortality associated with less frequent dialysis. Studies have shown that over 90% of the cohort of FD patients achieved normalized BP with either short daily dialysis or long, frequent nocturnal dialysis at least five times per week; most likely because these modalities render patients euvolemic throughout the week [32, 33]. Once interdialytic ECV is effectively controlled, a virtuous cycle soon emerges: the patients feel better, they require less use of phosphate binders, lower doses of erythropoietin, and reduced usage or even complete elimination of antihypertensive medications [34, 35]. Most recently, the Frequent Hemodialysis Network trials have demonstrated that both daily and nightly dialysis reduced BP, number of antihypertensive medications, and serum phosphorous concentrations [35–37].

The daily UF trial reported here was undertaken to investigate the preliminary validity of a new treatment

modality that, in part separates solute from excess fluid removal. The study demonstrates with statistically significant results, in an appropriately powered study, that hypertension (an effect of excess fluid) can be significantly reduced without impairing (and, in fact, may improve) solute removal.

The authors recognize that a broader study, preferably using the ambulatory UF device currently in development instead of conventional equipment, would be useful in determining the effect of this approach on medications, hospitalization, morbidity, and mortality of chronic HD patients. To evaluate the long-term clinical course of such patients, predialysis values of serum urea nitrogen, creatinine, β_2 -microglobulin, phosphorous, total protein, albumin, and erythropoiesis-stimulating agent dosing would also likely need to be investigated. Ambulatory BP readings would be prognostic, and would also be included in such a subsequent study.

Conclusion

We have shown for the first time that those patients in whom fluid overload was reduced towards achieving normal hydration by daily UF not only benefit from enhanced BP control but require less dialysis time/week to achieve adequate clearance of small molecules. These results (utilizing conventional dialysis equipment) suggest that application of an ambulatory UF device combined with conventional HD could be used to provide a new treatment regimen for ESRD with measurable advantages.

Acknowledgements

The authors are grateful for the support of the National Institutes of Health (Grant No. 1R21HL088162), and Vizio Medical Devices LLC.

Disclosure Statement

The authors have no conflicts of interest to disclose.

References

- 1 US Renal Data System, USRDS 2008 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2008.
- 2 Foley RN, Parfrey PS, Sarnak MJ: Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998; 32:S112–S119.
- 3 Locatelli F, Marcelli D, Conte F, et al: Survival and development of cardiovascular disease by modality of treatment in patients with end-stage renal disease. *J Am Soc Nephrol* 2001;12:2411–2417.
- 4 Centers for Medicare and Medicaid Services (CMS), HHS: Medicare and Medicaid Programs; Conditions for Coverage for End-Stage Renal Disease Facilities. Final rule. *Fed Regist* 2008;73:20369–20484.
- 5 Charra B: Fluid balance, dry weight, and blood pressure in dialysis. *Hemodial Int* 2007;11:21–31.
- 6 FHN Trial Group, Chertow GM, Levin NW, et al: In-center hemodialysis six times per week versus three times per week. *N Engl J Med* 2010;363:2287–2300.
- 7 Suri RS, Nesrallah GE, Mainra R, et al: Daily hemodialysis: a systematic review. *Clin J Am Soc Nephrol* 2006;1:33–42.
- 8 Walsh M, Culleton B, Tonelli M, Manns B: A systematic review of the effect of nocturnal hemodialysis on blood pressure, left ventricular hypertrophy, anemia, mineral metabolism, and health-related quality of life. *Kidney Int* 2005;67:1500–1508.
- 9 Ok E, Duman S, Gulay A, et al: Comparison of four and eight hours dialysis sessions in thrice weekly in-center hemodialysis. *Nephrol Dial Transplant* 2011;26:1287–1296.
- 10 Suri RS, Nesrallah GE, Mainra R, et al: Daily hemodialysis: a systematic review. *Clin J Am Soc Nephrol* 2006;1:33–42.
- 11 Ronco C, Davenport A, Gura V: A wearable artificial kidney: dream or reality? *Nat Clin Pract Nephrol* 2008;4:604–605.
- 12 Shaldon S, Beau MC, Deschodt G, Lysaght MJ, Ramperez P, Mion C: Continuous ambulatory haemofiltration. *Trans Am Soc Artif Organs* 1980;26:210–211.
- 13 Davenport A, Gura V, Ronco C, Beizai M, Ezon C, Rambod E: A wearable haemodialysis device for patients with end-stage renal failure: a pilot study. *Lancet* 2007;370:2005–2010.
- 14 Ye A, Amar L, Jones J, Cortell S, Howard J, van Rijn CJM, Baggerman J, Hill MI, Leonard EF: Design and in vitro performance of a wearable ultrafiltrator; in XXXVIII Congr Eur Soc Artif Organs, Porto, October 2011.
- 15 Schneditz D, Zaluska WT, Morris AT, Levin NW: Effect of ultrafiltration on peripheral urea sequestration in haemodialysis patients. *Nephrol Dial Transplant* 2001;16: 994–998.
- 16 Kooistra M, Vos J, Koomans H, et al: Daily home haemodialysis in The Netherlands: effects on metabolic control, haemodynamics, and quality of life. *Nephrol Dial Transplant* 1998;13:2853–2860.
- 17 O'Brien RG, Muller KE: *Applied Analysis of Variance in Behavioral Science*. New York, Marcel Dekker, 1993, pp 297–344.
- 18 De Lorenzo A, Andreoli A, Matthie J, Withers P: Predicting body cell mass with bioimpedance by using theoretical methods: a technological review. *J Appl Physiol* 1997;82: 1542–1558.
- 19 Zhu F, Kuhlmann MK, Kotanko P, et al: A method for the estimation of hydration state during hemodialysis using a calf bioimpedance technique. *Physiol Meas* 2008;29:S503–S516.
- 20 Rand Corporation's Medical Outcomes Study Short Form-36 (SF-36).
- 21 Kirk RE: *Experimental Design: Procedures for the Behavioral Sciences*, ed 3. Pacific Grove, Brooks-Cole, 1993.
- 22 Tukey JW: The problem of multiple comparisons. Unpublished manuscript; in *The Collected Works of John W. Tukey VIII. Multiple Comparisons: 1948–1983*. New York, Chapman and Hall, 1953.
- 23 Toothaker LE: *Multiple Comparisons for Researchers*. Newbury Park, Sage Publications, 1991.
- 24 Gotch FA: The current place of urea kinetic modelling with respect to different dialysis modalities. *Nephrol Dial Transplant* 1998; 13(suppl 6):10–14.
- 25 Health Care Financing Administration: 1995 Annual Report. ESRD Core Indicators Project. Opportunities to improve care for adult incenter hemodialysis patients. Baltimore, Health Care Financing Administration, Department of Health and Human Services, 1996.
- 26 Agarwal R, Nissenson AR, Batlle D, Coyne DW, Trout JR, Warnock DG: Prevalence, treatment, and control of hypertension in chronic hemodialysis patients in the United States. *Am J Med* 2003;115:291–297.
- 27 Zucchelli P, Santoro A, Zuccala A: Genesis and control of hypertension in hemodialysis patients. *Semin Nephrol* 1988;8:163–167.
- 28 Herrera-Acosta J: Hypertension in chronic renal disease. *Kidney Int* 1982;22:702–712.
- 29 Degouiet P, Reach I, Berger C, et al: Dialysis-computer program. IV. Summary report. Epidemiology of complications. *J Urol Nephrol (Paris)* 1977;83:925–983.
- 30 Miles AMV, Friedman EA: Diabetic dialysis patients; in Henrich WL (ed): *Principles and Practice of Dialysis*, ed 2. Baltimore, Williams & Wilkins, 1999, pp 477–489.
- 31 Kalantar-Zadeh K, Regidor DL, Kovesdy CP, et al: Fluid retention is associated with cardiovascular mortality in patients undergoing long-term hemodialysis. *Circulation* 2009;119:671–679.
- 32 Katzarski K, Charra B, Luik AJ, Nisell J, Divino Filho JC, Leyboldt JK, Leunissen KM, Laurent G, Bergström J: Fluid state and blood pressure control in patients treated with long and short haemodialysis. *Nephrol Dial Transplant* 1999;14:369–375.
- 33 Chazot C, Charra B, Laurent G, et al: Interdialysis blood pressure control by long haemodialysis sessions. *Nephrol Dial Transplant* 1995;10:831–837.
- 34 Nesrallah G, Suri R, Moist L, Kortas C, Lindsay RM: Volume control & blood pressure management in patients undergoing quotidian hemodialysis. *Am J Kidney Dis* 2003; 42(suppl 1):13–17.
- 35 Ting GO, Kjellstrand C, Freitas T, Carrie BJ, Zarghamee S: Long-term study of high-comorbidity ESRD patients converted from conventional to short daily hemodialysis. *Am J Kidney Dis* 2003;42:1020–1035.
- 36 Rocco MV, Lockridge RS Jr, Beck GJ, Eggers PW, Gassman JJ, Greene T, et al: The effects of frequent nocturnal home hemodialysis: the Frequent Hemodialysis Network Nocturnal Trial. *Kidney Int* 2011;80:1080–1091.
- 37 Stokes JB: Nocturnal hemodialysis: analysis following the Frequent Hemodialysis Network trial. *Semin Dial* 2011;24:614–620.