Long 3 x 8 hr dialysis: the Tassin experience

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Presented at Progress in Nephrology
Cracow, Poland
September 7, 2006

A long hemodialysis (HD), typically 3 x 8 hours/week, has been used without significant modification in Tassin since over 35 years with satisfactory morbidity and mortality outcome. It can be performed during the day or overnight. The longer patients' survival than usually achieved by the more conventional shorter dialysis sessions is mainly due to a lower cardiovascular mortality. This in turn is mainly due to the control of blood pressure including drug-free hypertension control and low incidence of intradialytic hypotension. This blood pressure control is probably the result of the tight extracellular volume normalization (dry weight achievement), although one cannot exclude the effect of other factors such as serum phosphorus control, well achieved using long dialysis. The high dose of small and, even more, of middle molecules, is another essential virtue of long dialysis, leading to good nutrition, correction of anemia, control of serum phosphate and potassium with low doses of medications and providing a very cost-effective treatment. In 2006 one must aim at an optimal rather than just adequate dialysis. Optimal dialysis needs to correct as perfectly as possible each and every abnormality due to renal failure. It can be achieved using longer (or more frequent) sessions. Overnight dialysis is the most logical way of implementing long HD with the lowest possible hindrance on patient's life.

(NEPHROL. DIAL. POL. 2006, 10, 141-146)

Key words:
- hemodialysis
- long time
- dose
- Kt/V
- extracellular volume
- blood pressure
- mortality

Długie dializy 3 x 8 godzin: doświadczenia ośrodka w Tassin

Długie hemodializy (HD), zazwyczaj 3 x 8 godzin w tygodniu są stosowane w Tassin bez istotnych modyfikacji od ponad 35 lat prowadząc do zadowalających wyników w zakresie chorobowości i śmiertelności pacjentów. Są przeprowadzane w dzień lub w nocy. Dłuższa, w stosunku do pacjentów leczonych konwencjonalnymi krótkimi hemodializami, przeżywalność wynika z niższej śmiertelności z przyczyn sercowo-naczyniowych. Wynika to z lepszej kontroli ciśnienia krwi, a w tym kontroli nadciśnienia bez konieczności stosowania leków oraz małej częstości hipotonii śródializacyjnej. Ta kontrola ciśnienia wynika prawdopodobnie z dokładnej normalizacji objętości pozakomórkowej (osiąganie „suchej masy" ciała), nie można jednak zapominać o innych czynnikach jak dobra kontrola poziomu fosforanów, osiągana przy długiej dializie. Duża eliminacja małych i średnich molekuł podczas długich hemodializ prowadzi do dobrego odżywienia, korekty niedokrwistości, kontroli poziomu fosforanów i potasu bez konieczności stosowania dużych dawek leków, co obniża koszty leczenia. W roku 2006 należy dążyć raczej do optymalnej, a nie tylko adekwatnej dializy. Optymalna dializa powinna korygować jak najlepiej wszystkie zaburzenia wynikające z niewydolności nerek. Można to osiągnąć poprzez dłuższe lub częstsze sesje dializacyjne. Dializa nocna jest najbardziej logiczną formą praktycznego zastosowania długich hemodializ w najmniejszym stopniu wpływającą na codzienne życie pacjenta.

(NEFROL. DIAL. POL. 2006, 10, 141-146)

Słowa kluczowe:
- hemodializa
- długotrwała
- dawka
- Kt/V
- objętość pozakomórkowa
- ciśnienie krwi
- śmiertelność

Introduction

Long hemodialysis (HD) 3 x 8 to 12 hours per week- on 1 sq-meter flat plate cuprophane dialyzers was in the 70's the empirical most achieved form of dialysis, the "gold standard" [1]. Technical advances, changing scientific views on uremia pathophysiology, as well as social and economical pressure to make a better use of the scarcely available dialysis stations have led to the conception and implementation of shorter dialysis sessions [4]. In Tassin though, the 8-hour dialysis has been the exclusive treatment method for almost all patients whether in the unit or at home for three decades, and remains largely used. The session time is never inferior to 3 x 5 hrs/wk, the mean prevalent cohort treatment time is 19.8 hours of dialysis per week. The follow-up of long slow dialysis representing over 8700 patient-years of this experience is worth revisiting.

Patients and methods

Typically three 8 hr sessions per week are performed overnight during the sleep or

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in the daytime according to patient's possibility and preference. Home dialysis was used in a large portion of the population up to the 80's at which time 50% of the patients were treated at home. Since then the multiplication of dialysis units (suppressing the obligation for patients to commute thrice weekly to and from the dialysis unit), the increased transplantation rate (especially in the population fit for self-dialysis at home) and the worsening patients case mix have led to a steady decrease of the proportion of patients treated overnight and/or at home. Only 35% and 5% of Tassin patients are presently treated overnight and at home, respectively.

Until 1996 a very poorly "biocompatible" set-up (cuprophane® membrane, acetate buffer and plain softened water) was used. The blood flow has been set at 200 to 250 ml/min throughout the experience. Since 1996 the bicarbonate buffer has progressively been substituted to acetate. Since 1998 low-flux polysulfone membrane dialyzers have progressively replaced cellulosic ones. In 1999 the Tassin unit became a part of the Fresenius Medical Care® network. This has accelerated the change toward a more biocompatible set-up. Individual generators have replaced the central delivery systems that had been preferred up to then for their simplicity, low running cost and to reduce the noise in the dialysis wards. In January 2001 this technical change has been completed by a total modification of the water treatment system which presently features a reverse osmosis system completed by ultrafiltration.

Since 1992 a "short" HD program has been proposed to the patients as a complement of the usual long HD. It uses a 3 x 5 (or 6) h/wk schedule with large area size dialyzers (1.7 to 2.5 sq-meter), and a 300 ml/min blood flow. The dialysate flow remains unchanged at 500 ml/min. This "shortened" schedule is presently used by 45% of Tassin patients.

The HD dose provided is large. The average delivered urea spKt/V using 2nd generation Daugirdas method is over 2.0 per session [6]. It allows for a satisfactory nutrition. The mean normalized PCR is over 1.2. The mean protein and calories intake are 1.2 g/kg and 32 Kgcal/KgBW/day, respectively. The patients are requested to maintain a reasonably low salt diet. No salt is added to the food and processed food is avoided. The effective average sodium chloride intake is 5 g per day [9]. The mean interdialytic weight gain is 1.8 kg (i.e. 2.6% of mean dry weight). The dialysate sodium is set at 138 mmol/l. The patients are not requested to restrain from drinking.

All antihypertensive medications are stopped in each and every patient within the two first months of HD [7] – in 90% of cases, in the first two weeks. It is a crucial point that during the initial few weeks of dialysis each patient undergoes a systematic antihypertensive treatment withdrawal in conjunction with the lowering of his extracellular volume (ECV) to achieve "dry weight" and normotension [5]. If after several months of efforts it turns out that blood pressure cannot be brought back to normal by the ECV control alone (mostly due to patient's compliance problem with the salt restriction) an antihypertensive treatment is started again. This is the case for less than 5% of long (3 x 7-8 h/wk), and for 13% of "short" (3 x 5-6 h/wk) dialysis Tassin patients respectively.

The overall Tassin experience at May 1, 2006, concerned 1509 patients, and an overall risk exposure of 8746 patient-years. The mean dialysis duration was 5.8 years of treatment per patient. As shown on table I, 294 patients were dialyzed for more than 10 years. Among them 8 were dialyzed for more than 30 years (one of them reaching 40 years).

One third of the patients (497/1509, i.e. 32.9%) were females. The overall mean age of the population at initiation of treatment was 57.2 ± 17.1 years, but it increased very

Table I
The Tassin overall experience (1509 patients, 8749 patient years risk exposure)

Follow-up time	Number
< to 5 yrs	930
5-10 yrs	285
10- 20 yrs	216
20-30 yrs	70
30-40 yrs	8
Total	1509

Table II
Causes of renal failure in 1509 patients

Etilogy of renal failure	number	percent
Polycystic kidney disease	137	9.08
chronic glomerulonephritis	316	20.94
intersticial nephritis	192	12.72
nephroscerosis	264	17.50
systemic diseases/cancer	88	5.83
diabetes mellitus	301	19.95
others	68	4.51
unknown	143	9.48
TOTAL	1509	100.00

Table III
Demographic and comorbid factors vs. survival at 5,10,15 and 20yrs of dialysis.

	% patients surviving					
Initial age:	patient	5 yr	10 yrs	15 yrs	20 yrs	p
< 35 y.o.	186	91	85	79	71	
35-44 y.o.	176	85	76	60	34	
45-54 y.o.	269	81	67	45	19	
55-64 y.o.	257	70	40	16	5	
65-74 y.o.	263	47	24	5	3	
≥ 75 y.o.	197	24	2	–	–	<0.001
Etiology:						
Chronic GN	290	80	69	51	37	
Interstitial N	183	83	65	49	27	
Polycystic KD	129	87	70	36	31	
Nephrosclerosis	236	51	28	13	8	
Diabetes	233	36	10	2	-	
Systemic Dis/cancer	85	48	30	15	9	
Others	64	67	59	49	32	
Unknown	128	78	56	33	12	<0.001
Atheroma:						
2 CV antecedents	222	32	14	3		
1 CV antecedent	281	55	27	10	3	<0.001
no antecedent	650	84	69	52	35	
Gender:						
Females	453	73	56	38	27	
Males	895	63	46	29	19	0.005
TOTAL	1348	69	46	34	20	

regularly from one 36.1 years in 1968 to 66.9 in 2005. The causes of renal failure are displayed on table II. Again, an important change occurred with calendar years, diabetes mellitus and nephrosclerosis prevalence in the incident population crept up from 0 and 6% in 1968 to 44 and 19%, respectively in 2005. Besides, the proportion of patients with a significant cardiovascular story (coronary, cerebrovascular, and peripheral vascular disease) increased from 6 to 65% of incident patients along the same 37 years of follow-up.

Results

1. Mortality

Due to the increase in risk factors (age, high risk causes of ESRD and cardiovascular antecedents), the crude mortality has steadily increased along calendar years. The mean half-life of the cohort of patients starting dialysis between 1968 and 1975 was 18.0 years, it dropped for the most recent cohort (starting HD after 1992) to only 5.5 years [11]. But in the first calendar cohort patients were young (mean age at HD start 39 years) and almost free of co morbid conditions (9%) or of high risk causes of renal failure (cancer, diabetes, systemic and vascular diseases, altogether < 8%). At opposite, in the most recent one they were more aged (mean 64 years), co-morbid conditions were present in 58%, and high risk causes of renal failure were present in more than 60% of them. The intermediate cohorts had intermediate survival. So the crude mortality increased progressively with calendar years in spite of the unchanged treatment.

The weight of demographic and co morbid conditions appears clearly on Kaplan Meier survival curves as already reported (table III) elsewhere in detail [9], and is confirmed by the Cox proportional hazard model analysis (table IV). Females survive longer than males, non diabetic patients risk of death is 68.6% of diabetics, and for patients started on dialysis without significant cardiovascular story the mortality risk ratio is 42.1% of what it is for those who start HD with one or several cardiovascular antecedents. For each 10-year increment of the age at dialysis start the risk of death increases by 53%.

To get a more realistic view of the dialysis patients' mortality taking into account the population change, the Standardized Mortality Ratio (SMR) adjusts for age, race, and cause of renal failure. Using the SMR and the United States Renal Data System standard mortality table [35] the average observed mortality in Tassin is about 50% of the expected value according to US standards for similar patients. This ratio calculated each year since 1989 has remained quite stable around this value over the last 15 calendar years, in spite of the worsening condition of the dialysis population (table V). Due to the increasing proportion of patients dialyzing 3 times 5 or 6 hours weekly in Tassin, we have been able to calculate the independent SMR for "short" and "long" Tassin dialysis patients along the last 10 years (unpublished data). As shown on Table 6, there is a clear-cut trend for the long dialysis patients to survive longer. The average SMR over the last decade were 0.69 and 0.40 for "short" and "long" strategies, respectively. As SMR adjusts for age, race and cause of renal failure, the observed survival difference between the 2 groups is due either to other powerful risk factors (e.g. cardiovascular story) or unnoticed selection bias, or to the longer session per se. Among selection bias powerful enough to explain a large survival difference, the physician selection of the shorter dialysis schedule for the more fragile patients is very unlikely. As a matter of fact the fragile and high risk patients in Tassin are actually firmly pushed to the long slow schedule. The patient's compliance (the patients poorly compliant to dialysis duration being more prone to escape the diet and the medications) might be another hypothesis but again the Tassin physicians' practice is to prolong or increase the number of the sessions for this type of patients. Two recent reports about larger sets of patients on long dialysis (6593 and 22 000 patients respectively) tend to favor the alternative hypothesis, i.e. that longer dialysis improves survival [27,30].

The comparison of Tassin patients' mortality to the only available long-term French series of 4-5hr hemodialysis reported by Degoulet et al. several years ago [15] showed that long HD mortality was lower (52.4 vs. 99 deaths per 1000 pt-yrs, p<0.001). There was no difference in specific (infection, cancer, or others) causes of mortality between the two series but for cardiovascular mortality that was much lower on long HD (19.8 vs. 44.6 cardiovascular deaths per 1000 pt-yrs, p<0.001) [12].

To analyze the effect of BP control on mortality in HD patients we splitted Tassin long dialysis population in 2 equal number cohorts according to their pre-dialysis mean arterial pressure (MAP) calculated over the whole dialysis treatment (integrated) time, and then analyzed their Kaplan-Meier survival [22]. The subgroup of patients with the

Table IV
Cox proportional hazard model in 1509 Tassin patients (2006).

	DDL	Coef	Err. Std	Coef/ES	Chi-2	p	Exp (Coef)
diab: 0	1	-0,377	0,099	-3,818	14,577	0,0001	0,686
sex: f	1	-0,193	0,083	-2,315	5,360	0,0206	0,824
Atcd: 0	1	-0,866	0,088	-9,870	97,420	<0,0001	0,421
agedeb	1	0,052	0,003	17,043	290,480	<0,0001	1,053

Table V
Standardized mortality ratio, Tassin vs. USRDS.

CalendarYear	O/E deaths*	SMR	p value
1989	23 / 43,7	0,53	<0,005
1990	14 / 42,4	0,33	<0,001
1991	18 / 44,7	0,40	<0,001
1992	15 / 46,1	0,33	<0,001
1993	23 / 47,7	0,48	<0,001
1994	20 / 50,3	0,40	<0,001
1995	23/57	0,40	<0,001
1996	27/56,4	0,51	<0,001
1997	25/48,5	0,52	<0,001
1998	26/47,6	0,55	<0,005
1999	27/67,5	0,41	<0,001
2000	38/71,1	0,53	<0,001
2001	30/73,5	0,41	<0,001
2002	32/75,33	0,42	<0,001
2003	35/70,6	0,64	<0,01
2004	31/59,3	0,52	<0,001
2005	30/65,46	0,46	<0,001
* O/E: Observed vs. Expected number of deaths			

Table VI
SMR according to session duration ion Tassin (5-6 vs. 7-8 hours per session, 1996 to 2005).

Calendar year	SMR <7h x 3	SMR ≥ 7h x 3
1996	0,82	0,41
1997	0,59	0,51
1998	0,66	0,51
1999	0,63	0,35
2000	0,76	0,33
2001	0,66	0,36
2002	0,65	0,42
2003	0,73	0,56
2004	0,7	0,3
2005	0,7	0,22
mean SMR for 10 yrs	0,69	0,397

Table VII
Causes of 739 deaths in HD, Tassin 1968-2006.

Cause of death	number	%	n/1000pt-yrs
Cardiovascular	277	37,48	31,68
Infection	130	17,59	14,87
Cancer	74	10,01	8,46
Surgical	50	6,77	5,72
cachexia	44	5,95	5,03
Dementia/stop	30	4,06	3,43
GI tract	25	3,38	2,86
Accident/suicides	27	3,65	3,09
miscellaneous	41	5,55	4,69
unknown	41	5,55	4,69
TOTAL	739	100,00	84,51

lowest MAP (n=382 pts; mean pre-dialysis MAP=89 mm Hg) had a significantly lower mortality (p=0.003) than the subgroup with a slightly more elevated MAP (n=383 pts; mean pre-dialysis MAP=105 mm Hg). The difference in survival was mainly explained by a lower cardiovascular mortality in the lower MAP subgroup: 12.7 vs. 28.1 cardiovascular deaths per 1000 pt-yrs (p<0.005).

The main causes of death are reported on table VII. The expression of causes of death in percentage of the causes of death is not very informative. Cardiovascular mortality is largely predominant in dialysis as in non uremic patients. It has a moderate intra-country but a wide inter-country variability as shown in table VIII for France and United States (median column). On the other hand the prevalence of specific mortality varies widely (right column). The cardiovascular mortality in Tassin is 8 fold higher than the French background mortality, the US dialysis patients cardiovascular mortality is 17-fold higher than US background mortality.

2. The dialysis dose issue

The National Cooperative Dialysis Study (NCDS) was the first prospective randomized study on dialysis. Using a 2 X 2 factorial design it tested the respective effects of time-averaged concentration of urea (50 vs. 100 mg/dl) and the session time duration (3 vs. 4-4.5 hours). It concluded that the time-average concentration (TAC) of urea was a very important factor of clinical outcome whereas the session time had only a marginal (p=0.059) effect [26]. A few years later, Gotch and Sargent based on the NCDS results the integrated urea clearance (Kt/V) concept [20]. In their mechanistic analysis of dialysis they described a discontinuous, stepwise relationship between Kt/V and clinical outcome. According to this study, the clinical outcome is poor if the patient receives a Kt/V inferior to 0.9 per session, but good if he receives a dose of 1.0 or more. In the same time the authors pointed at the fact that no clinical benefit was to be expected from increasing the delivered dose much over 1.0.

The mechanistic analysis has had a deep impact on hemodialysis delivery all over the world. It brought up an objective way of analyzing the dialysis dose but in the same time it was unfortunately the alibi for a progressive reduction of dialysis dose and time, especially in the United States. The continuous decrease in the delivered dose of dialysis has been deleterious, followed by a worsening clinical outcome [2]. In 1990 the Morbidity and Mortality conference in Dallas drew the attention to the very high and increasing mortality of dialysis patients in the United States [21]. Since then the delivered dialysis dose has been increased and the session time stopped to be decreased. The National Kidney Foundation 2000 DOQI dose guideline reevaluation has suggested a minimal 1.3 Kt/V prescribed dose [28] and most published guidelines have also advocated higher doses of dialysis than the 0.9-1.0 initially advocated by Gotch [17].

More recently the long-term prospective randomized HEMO study went to its end [16]. It reported no significant impact of the Kt/V dose on survival after 5 years of follow-up. This result came as a surprise considering the accumulated observational experience leading to the opposite conclusion. But three main comments are needed at that point about the HEMO study. First, one may question if the 1.25 and 1.65 single pool Kt/V levels used for the study managed a sufficient range to allow for a significant difference in clinical outcome. As a matter of fact Gotch's update of kinetic modeling [18] shows that the weekly standard Kt/V change induced by increasing the equilibrated session Kt/V from 1.25 to 1.65 has negligible effects on the weekly standard Kt/V. Second, the Kt/V concept itself may be flawed because V, a proven independent significant outcome factor is included in the Kt/V formula. Subsequently Kt has a better correlation with clinical outcome than Kt/V [25]. The third point to be kept in mind is that small molecule removal is only one among several factors known to condition outcome. As stated by Gotch himself [19] "It is perhaps unreasonable to expect that the clinical difference will be manifest when only a portion of the patient-dialyzer system is quantified and controlled".

Replacing kidney function needs much more than controlling small molecule removal. It needs at least controlling the other more powerful clinical outcome factors i.e. middle molecule removal, nutrition, extracellular volume control, blood pressure control. To achieve the optimal dialysis we are aiming at today, each of these factors must be fulfilled. Any of them if lacking will suffice

Table VIII
Specific mortality in percentage and in incidence, USRDS and Tassin

Population	% of overall mortality	CV deaths/1000 patient-years
Tassin hemodialysis patients	35.2	31.7
French non uremic population[1]	33.5	3.8
USRDS hemodialysis patients[2]	55.0	95.2
US non uremic population[3]	50.1	5.6

1: Mortalité et causes de déces en France 1994
2: US Renal data system 1998 report
3: Statistical facts, Am Heart Assoc 1996

Table IX
Dietary energy and protein intake, comparison of Tassin long dialysis to literature references (see text) on 3 x 4 h/wk dialysis.

1st author'yr	Number pts.	Enquiry method	DEI1	DPI2
Schoenfeld'83	183	5 days	24.5	0.92
Wolfson'84	30	3 days	26.4	1.0
Lorenzo'96	29	3 days	26.8	1.2
Sharma'99	106	4 days	29	0.93
Tassin'99	47	5 days	29.3	1.21

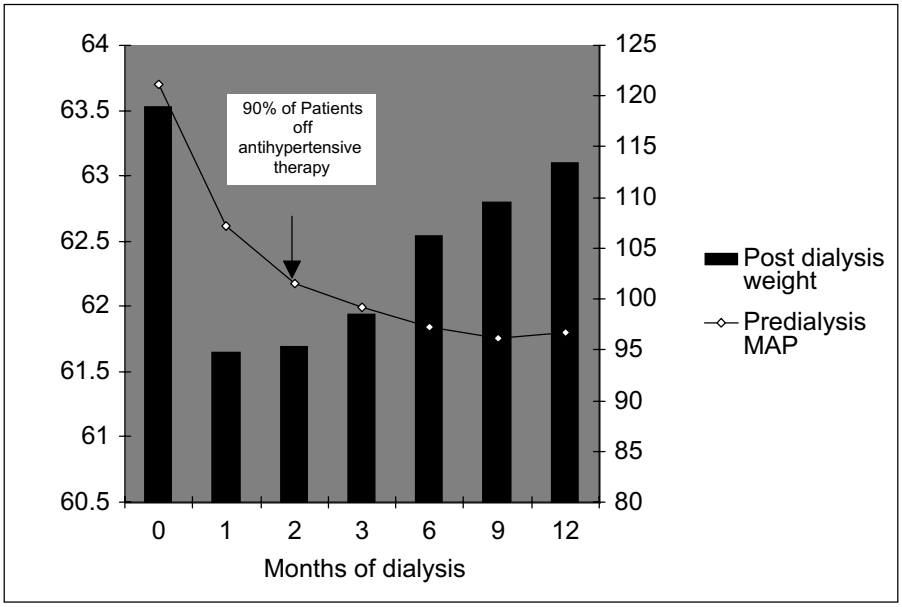

Figure 1
Evolution of post-dialysis weight and pre-dialysis mean arterial pressure of 712 Tassin hemodialysis patients during their 1st treatment year.

to ruin the entire clinical outcome. Each of these factors depends directly of the session time (or frequency). The longer and the more frequent the dialysis sessions, the better the issue.

3. Extra cellular volume (ECV) and blood pressure control

An essential goal of dialysis treatment is to maintain normal the ECV and the BP. An essential feature of long HD is that it regularly achieves a good control of BP. The mean observed casual pre-dialysis BP (128/79 mm Hg) is within the normal range advised by the VIIth Joint National Committee on BP [14]. Besides, the ambulatory BP monitoring values are also within the normal range at least for daytime (121/72 mm Hg) and circadian values (119/71 mm Hg) [13]. However the nighttime values (118/67 mm Hg) are slightly more elevated than normal (106/64 mm Hg) due to the lack of nocturnal dip in 50% of the patients [13].

The relationship between ECV and BP is illustrated by the first year of long HD treatment displayed on figure 1. The initial sharp ECV drop (an average 2 kg or 2 liters of ECV) contrasts with the more progressive pre-dialysis MAP decrease over months. The lag time between a change in ECV and the BP response [7] is a very important point. It is usually thought to be due to the vascular remodeling and eventually to the slow removal of some middle-molecular vasoactive mediators such as asymmetric dimethyl arginine and Na-K-ATPase [23]. Staff and patients must know this delay. It explains why a sustained decrease of the post-dialysis weight is often not followed immediately by the BP normalization. After 2 months of dialysis (figure 1) BP continues to decrease. Antihypertensive medications have been withdrawn in over 95% of the patients, but weight then typically increases. This gain in weight does not reflect an increase in ECV but a gain in lean and fat body mass due to the improved appetite and anabolism following the initiation of maintenance dialysis.

Switching the same group of patients from short to long HD and conversely highlights the effect of dialysis session time. Some years ago 124 patients were transiently dialyzed in Tassin while waiting for a kidney transplantation in Lyon. They were unselected. All had been treated for 6 months or more on a 3 x 5 hr (or less) HD schedule. Half of them received a regular antihypertensive treatment. Three months after they were switched to the 8-hour dialysis treatment their average post-dialysis weight was reduced by 0.5 kg, their pre-dialysis MAP was back to an almost normal value (mean=101 mm Hg) and antihypertensive medications had been stopped in all but one patient. Thereafter, pre-dialysis MAP continued to decrease slowly but, due to anabolism, patients' weight increased progressively to plateau after one year around its initial value [12] while BP had reached a stable normal level (average MAP: 96 mm Hg). In the same one-year time the mean pre-dialysis hematocrit level had increased from 24 to 29% without erythropoietin and stopping all blood transfusions in the 27 patients who needed them while on short dialysis (historical group). In spite of the increased delivered dialysis dose, the pre-dialysis urea increased by 10% and the pre-dialysis creatinine by 25%, strongly suggesting that patients had been building up lean body mass.

Conversely, 49 Tassin 8-hour dialysis patients were switched to a 5-hour schedule. All had been dialyzed 3 x 8 hr since at least 6 months. All were normotensive without antihypertensive medication. The dialyzer area and blood flow were increased to maintain a stable urea Kt/V when the patients were switched to the shorter schedule. After one year the delivered Kt/V per session had almost not changed (1.86 to 1.77) but the pre-dialysis MAP had rose significantly by 10 mm Hg in spite of a mean 2.5 kg post-dialysis weight reduction and of the introduction of antihypertensive medications in 4 patients [12]. Besides, in this second group of patients the pre-dialysis urea and creatinine decreased by 8 and 19% respectively suggesting that the patients had been losing lean body mass. The mean hematocrit decreased from 31.5 to 27.5, despite the fact that 3 patients had had to be started on EPO. Shortening the session time without decreasing significantly the dialysis dose was therefore associated with an impaired BP control and with an impaired nutritional state.

The other aspect of blood pressure control in dialysis patients is the prevention of intradialytic hypotensive episodes. They are less prevalent on long than on short dialysis: 57 events per 1000 sessions on 8 hr dialysis vs. 121 events on 5hr dialysis ($p<0.005$) in our own unit [10]. This is in sharp contrast with the last decade reported prevalence of 15 to 30% [32].

That shorter dialysis sessions lead to more interdialytic hypertension on one hand and to more intradialytic hypotension on the other hand may seem paradoxical. In fact this can be explained by the "vicious circle" of excessive dialysis time reduction [8]. Shortening dialysis time leads to use higher ultrafiltration (UF) rates, with subsequently more intradialytic events (especially hypotensive episodes). The patient has a poor perception and acceptance of HD and asks for shorter sessions, which will only increase the hypotensive episodes prevalence. On the other hand, the nurse has to face the hypotensive episodes by cutting down the UF rate or giving saline so that the prescribed dry weight is not achieved and the patient becomes saline overloaded. The physician impressed by the intradialytic events often re-evaluates (wrongly) the prescribed dry weight leading to more saline overload. Besides, to reduce cramps and hypotension he often prescribes a higher dialysate Na^+ concentration that reduces the diffusive drag of Na^+ out of the body and leads to increased osmolality, thirst, and interdialytic weight gain. The patient gets progressively more volume overloaded and more hypertensive, therefore he needs more UF. The vicious circle is closed. Things get even worse as hypertension causes and/or aggravates left ventricular hypertrophy. The left ventricular function is impaired and the heart cannot adjust its output to compensate for hypotension during UF. When they are used, antihypertensive drugs potentiate further the hypotensive episodes. Interdialytic hypertension and intradialytic hypotension keep on amplifying each other in a vicious circle. A very short session behaves as an amplifier of BP variations, a longer session time (or more frequent HD) allows to reduce the ultrafiltration rate without jeopardizing the ECV control, the cornerstone of BP normalization.

4. Other benefits of long dialysis sessions

- Nutrition and Phosphate control

A recent 5yr follow-up study of 47 Tassin long HD patients nutrition shows stable protein (mean dietary protein intake 1.21 g/kgBW/day) and energy (mean calories intake 1.29 kgCal/kgBW/day) intakes. Compared to published data in different series using the same nutritional enquiry method [24,31,33,36] this turns out to be quite satisfactory, the protein and calories intake rank among the highest.

Some years ago Block & coll. [3] showed that high serum phosphate correlates with an increased cardiovascular mortality. Our own data on long dialysis confirm the same trend. Compared to commonly reported data [24,29] long dialysis achieves a better control of serum phosphate with a minimal use of PO4 binders (only 35% of the long HD patients need to use phosphate binders). The average mid-week serum phosphate level pre-dialysis is 1.30 mmol/l (4 mg/dl).

- Anemia control

The control of anemia achieved by the 3 x 8 hr dialysis is satisfactory with an average pre-dialysis hematocrit of 34.2%, using EPO in 56% of patients with an average dose of 5700 units per week, i.e. about 1/3rd of the USRDS reported average dose in United States.

The reduced need for medications improves patient's nutrition, and life comfort. On top of that it reduces the cost and participates (together with the reduced nurse/patient ratio) in making long dialysis a very cost-effective treatment.

Discussion

Long dialysis allows for good clinical results because prolonging dialysis session time has several positive effects. It increases the dose of dialysis delivered (leading to good nutrition, control of anemia and serum phosphate). It makes easy to control the ECV and the BP. Besides, long dialysis is gentle, it generates few intradialytic events. It is less "unphysiologic" than the shorter HD. It is also cost-effective as it needs less nursing personal because intradialytic morbidity is limited. The patients have less morbidity and hospitalizations, and they use less medications.

In 2006 after 46 years of maintenance dialysis the target cannot be anymore a slim just adequate but an optimal therapy. Its aim should not be limited to avoidance of the several complications accumulating with time, but in preventing them and in offering the patient a life as normal as possible, without dietary restriction (with the exception of sodium), and as few medications as possible.

To achieve this, additive conditions must be gathered, large small and middle molecular weight solute dialysis doses (including PO4 which behaves as a middle

molecule), large protein and calories nutrition, continuous control of ECV, control of BP without need for antihypertensive medications are the major issues. Out of the small molecule dialysis dose that can be provided within a limited time, the other conditions need to increase the dialysis session time (and/or frequency). The long session thrice weekly might be the solution for most patients, particularly when it can be performed overnight during the sleep.

One should point at the fact that these basic additive conditions of an optimal dialysis are all necessary. Each of them is mandatory. Any of them, if lacking suffices to ruin the patient's clinical outcome. As a matter of fact it is not what we perform best which governs the patient's evolution, it is what we do worst that pull the overall result to the bottom. Therefore in the follow-up each factor must be regularly checked and improved as much as possible.

One of the main virtues of long dialysis is that it covers very widely the patient's needs, not leaving much place to hazard. Long slow dialysis can be performed efficiently without pushing each operational condition of the dialysis to its maximum. This explains that, if it is very difficult to provide an excellent very short dialysis, it is rather easy to provide a very efficient long dialysis.

References

1. **Barber S., Appleton D. R., Kerr D.N.**: Adequate dialysis. Nephron 1975, 14, 209.
2. **Barth R. H.**: Short hemodialysis: big trouble in a small package. Death in hemodialysis: preventable or inevitable? [In:] E. A. Friedman. Dordrecht, Boston, London, Kluwer Academic Publishers 1994, 143-157.
3. **Block G. A., Hulbert-Shearon T. E., Levin N.W., Port F.K.**: Association of serum Phosphorus and CalciumxPhosphate product with mortality risk in chronic hemodialysis patients: a national study. Am. J. Kidney Dis. 1998, 31, 607.
4. **Cambi V., Savazzi G, Arisi L. et al.**: Short dialysis schedule (SDS): finally ready to become routine? Proc. Eur. Dial. Transplant. Assoc. 1975, 11, 112.
5. **Charra B.**: How important is volume excess in the etiology of hypertension in dialysis patients? Semin. Dial. 1999, 12, 297.
6. **Charra B.**: Is there a magic in long nocturnal dialysis? Cardiovascular disorders in hemodialysis. [In:] C. Ronco, A. Brendolan and N.W. Levin. Basel, Karger. 2005, 149, 100.
7. **Charra B., Bergström J., Scribner B.H.**: Blood pressure control in dialysis patients. The importance of the lag phenomenon. Am. J. Kidney Dis. 1998, 32, 720.
8. **Charra B., Calemard E., Laurent G.**: Importance of treatment time and blood pressure control in achieving long-term survival on dialysis. Am. J. Nephrol. 1996, 16, 35.
9. **Charra B., Chazot C.**: Long thrice weekly hemodialysis: the Tassin experience. Int. J. Art. Intern. Organs 2004, 27, 265.
10. **Charra B., Chazot C., Jean G. et al.**: Long 3 x 8 hr dialysis: a three-decade summary. J. Nephrol. 2003, 16, (Suppl. 7), S64.
11. **Charra B., Chazot C., Jean G., Laurent G. et al.**: Long, slow dialysis. Miner. Electrol. Metab. 1999, 25, 391.
12. **Charra B., Laurent G.**: Long hemodialysis: the key to survival? Complications of long-term dialysis. [In:] E. A. Brown and P. S. Parfrey. Oxford, New York, Tokyo, Oxford University Press, 228.
13. **Chazot C., Charra B., Laurent G. et al.**: Interdialysis blood pressure control by long hemodialysis sessions. Nephrol. Dial. Transplant. 1995, 10, 837.
14. **Chobanian A. V., Bakris G. L., Black H.R. et al.**: The seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. The JNC 7 Report. JAMA 2003, 289, 2560.
15. **Degoulet P., Legrain M., Reach I. et al.**: Mortality risk factors in patients treated by chronic hemodialysis. Nephron 1982, 31, 103.
16. **Eknoyan G., Beck G. J., Cheung A.K. et al.**: Effect of Dialysis Dose and Membrane Flux in Maintenance Hemodialysis. N. Engl. J. Med. 2002, 347, 2010.
17. **Gotch F. A.**: Dialysis of the future. Kidney Int. 1988, 33, (Suppl. 24), S100.
18. **Gotch F. A.**: Kinetic Modeling in Hemodialysis: Urea Kinetic Modeling to Guide Hemodialysis Therapy in Adult. Dialysis Therapy. [In:] A.R. Nissenson and R.N. Fine. Philadelphia, Hanley & Belfus, Inc.: 117.
19. **Gotch F. A., Sargent J.A.**: A theoretical definition of minimal acceptable dialysis therapy. Kidney Int. 1978, 13, (Suppl. 8), S108.
20. **Gotch F. A. Sargent J.A.**: A Mechanistic analysis of the National Cooperative Study (NCDS). Kidney Int. 1985, 28, 526.
21. **Hull A. R., Parker T. F.**: Proceedings from the morbidity, mortality and prescription of dialysis symposium, Dallas, Texas, September 1989: introduction and summary. Am. J. Kidney Dis. 1990, 15, 375.
22. **Kaplan E.L., Meier P.**: Non parametric estimation from incomplete observations. J. Am. Statist. Assoc. 1958, 53, 457.
23. **Khosla U.M., Johnson R.J.**: Hypertension in the hemodialysis patient and the "lag phenomenon": insight into physiopathology and clinical management. Am. J. Kidney Dis. 2004, 43, 739.
24. **Lorenzo V., de Bonis E., Rufino M. et al.**: Caloric rather than Protein deficiency predominates in stable Chronic Hemodialysis Patients. Nephrol. Dial. Transplant. 1995, 10, 1885.
25. **Lowrie E. G., Chertow G. M., Lew N.L. et al.**: The urea (clearance x dialysis time) product (Kt) as an outcome-based measure of hemodialysis dose. Kidney Int. 1999, 56, 729.
26. **Lowrie E. G., Laird N. M., Parker T.F., Sargent J.A.**: Effect of the hemodialysis prescription on patient morbidity. Report from the National Cooperative Study. N. Engl. J. Med. 1981, 305, 1176.
27. **Marshall M. R., Byrne B. G., Kerr P.G., McDonald S.P.**: Associations of hemodialysis dose and session length with mortality risk in Australian and New Zealand patients. Kidney Int. 2006, 69, 1229.
28. National Kidney Foundation: K/DOQI Clinical Practice Guidelines for Hemodialysis Adequacy, 2000. Am. J. Kidney Dis. 2001, 37, (Suppl. 1), S7.
29. **Ritz E., Schomig M., Bommer J.**: Osteodystrophy in the millennium. Kidney Int. 1999, 56, (Suppl. 73), S94.
30. **Saran R., Bragg-Gresham J. L., Levin N.W. et al.**: Longer treatment time and slower ultrafiltration in hemodialysis: Associations with reduced mortality in the DOPPS. Kidney Int. 2006, 69, 1222.
31. **Schoenfeld P. Y., Henry R. R., Laird R.N., Roxe D.M.**: Modeling success or failure of dialysis therapy: Assessment of nutritional status of the NCDS population. Kidney Int. 1983, 23, (Suppl. 13), s95.
32. **Schreiber M.J.J.**: Clinical Dilemmas in Dialysis: Managing the hypotensive patient. Setting the stage. Am. J. Kidney Dis. 2001, 38, (Suppl. 4), S1.
33. **Sharma M., Rao M., Jacob S., Jacob C.K.**: A dietary survey in Indian hemodialysis patients. J. Ren. Nutr. 1999, 9, 2.
34. **Shinzato T., Nakai S., Akiba T. et al.**: Current status of renal replacement therapy in Japan: results of the annual suvey of the Japanese Society for Dialysis Therapy. Nephrol. Dial. Transplant. 1997, 12, 889.
35. **Wolfe R. A., Gaylin D. S., Port F.K. et al.**: Using USRDS generated mortality tables to compare local ESRD mortality rates to national rates. Kidney Int. 1992, 42, 991.
36. **Wolfson M., Strong C. J., Mintum D. et al.**: Nutritional status and lymphocyte function in maintenance hemodialysis patients. Am. J. Clin. Nutr. 1984, 39, 547.