

Survival as an index of adequacy of dialysis

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Editorial: Adequate control of blood pressure in patients on chronic hemodialysis. Shortly after our first patient, Mr. Clyde Shields, began long term hemodialysis in March of 1960, he developed malignant hypertension, and death seemed imminent [1]. Since we were unable to control his blood pressure with the few antihypertensive drugs then available, we decided that our only hope of saving him was to try aggressive removal of extracellular fluid by ultrafiltration during his once weekly 24-hour hemodialysis [1]. During the subsequent weeks cramping was severe as we tried to maximize fluid removal during each dialysis. Gradually, however, his blood pressure came under control. Eventually he became normotensive off medication, and remained so until his death from a myocardial infarction in 1971. This dramatic episode made a lasting impression on our approach to the control of blood pressure in our hemodialysis patients. Even after effective antihypertensive medications became available, we continued to make control of the extracellular volume (ECV) the cornerstone of treatment of hypertension in our dialysis population.

The first published validation of this approach came in 1983 from Charra and his colleague in Tassin, France [2]. This same group now publishes in this article impressive evidence that this approach to control of blood pressure not only works in 98% of the 445 hemodialysis patients in their series, but is the major factor accounting for the excellent patient survival they report.

The rationale for using control of ECV to maintain normal blood pressure in the dialysis population can be summarized as follows: (1) Hypertension in these patients is volume dependent. (2) Even small increments in ECV can cause significant increases in the resistance to antihypertensive medications. (3) This effect leads to the use of larger doses of antihypertensive medications. (4) The presence of large amounts of these medications makes fluid removal during hemodialysis more difficult because of hemodynamic instability. (5) This problem can result in further increases in the ECV and even greater resistance to blood pressure control.

In our experience, severe hypertension poorly controlled by drugs most often is seen in patients who are just starting hemodialysis. In such instances, it usually takes several weeks or months of aggressive ultrafiltration combined with gradual withdrawal of antihypertensive drugs to obtain control of blood pressure off medications. During this transition period, it requires patience and persistence on the part of the dialysis staff, and willingness to tolerate occasional episodes of cramping and hypotension on the part of the patient. Furthermore, if the patient cannot comply with a no added salt diet, control of blood pressure using ultrafiltration without drugs becomes more difficult as the sodium intake increases.

The excellent survival results presented in this issue by Charra et al provide strong additional support for the concept that normalization of blood pressure in the dialysis patient delays or prevents death from the complications of atherosclerosis. Adequate control of blood pressure now must become a part of the definition of adequacy of dialysis along with an adequate dose of dialysis and adequate intake of protein.

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Survival as an index of adequacy of dialysis. To examine how patient survival substantiates dialysis adequacy, 20-year actuarial survival experience was calculated for 445 unselected hemodialysis (HD) patients (97 patients accepted on a temporary basis—and usually kept on their regular dialysis scheme—were left out). The dose of dialysis has been the same and unchanged for all patients since beginning: 24 square meter hours of Kiil dialysis (cuprophane) per week with acetate buffered dialysate. KT/V mean (SD) was 1.67 (0.41). Six months after starting dialysis, 98% of patients were normotensive and off all blood pressure (BP) medication. The mean population hematocrit, excluding the only 6 patients receiving erythropoietin supplementation, was 28%. Survival rate was 87% at 5 years, 75% at 10 years, 55% at 15 years, and 43% at 20 years of HD. The satisfactory control of BP without using

potentially toxic BP drugs and the higher than usual dose of dialysis are two possible explanations for survival data better than usually reported. We suggest that patient survival should be considered as the best overall index of adequacy of dialysis.

In most chronic illness, patient survival is a key index of the overall adequacy of treatment. However, in the case of chronic hemodialysis, patients survival data are rather scarce and usually cover periods of 5 to 10 years at the most, even though this treatment has been in existence for over 30 years [1].

We present herein survival data on 445 unselected patients (97 patients accepted on a temporary basis, and usually kept on their usual dialysis scheme, were excluded) that not only covers periods of up to 20 years, but are superior to survival data of any other series published to date. We publish these survival data in the hope that they will both serve as a standard for

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Table 1. Demographic data concerning the 445 patients

Parameter	Value	Number	%
Sex	Female	142	32.5
	Male	303	67.5
Etiology	CGN	148	33.2
	IN	89	20.0
	PKD	59	13.3
	NS	43	9.7
	DM/SD	42	9.4
	Unknown	64	14.4
Age start years	<30	66	14.9
	30–39	84	18.9
	40–49	111	24.9
	50–60	99	22.2
	>60	85	19.1

Abbreviations are: CGN, glomerulonephritis; IN, interstitial nephritis; PKD, polycystic kidney disease; NS, nephrosclerosis; DM/SD, diabetes mellitus and systemic diseases.

Table 2. Demographic features of the patients (1978–1990): Mean age at start and % of causes of chronic renal failure

Calendar years	<1970	71–75	76–80	81–85	86–90
Mean age at start years	36.2	43.5	46	47.5	52.9
Cause of CRF %					
Diabetes mellitus	0	1.9	3.2	3.2	7.9
Vascul & system d. ^a	4.1	8.6	13.3	12.6	19.9
Other etiologies	95.9	89.5	83.5	84.2	72.2

^a Vascular & systemic diseases including nephrosclerosis, systemic and malignant diseases

comparison as well as encouraging other centers to evaluate their overall adequacy of dialysis therapy by compiling their survival results. Accurate and comparable patient survival data are badly needed at this juncture, because the recent introduction of new dialysis technology such as shortened time high efficiency dialysis, while showing very promising early results [2], may in some centers be having a serious adverse effect on patient survival, as has been reported recently [3].

Methods

The charts of 445 unselected patients were reviewed. The demographic data are shown in Table 1. The ratio between female (F) and male (M) was about 1:2. The causes of chronic renal failure (CRF) included 20% of "high-risk" etiologies (diabetes mellitus, systemic diseases, nephrosclerosis and malignant diseases), the etiology was unknown in almost 15% of the cases. The mean (SD) age at initiation of HD was 48.4 (14.3); 19% of patients started after age 60. The average age at start of treatment has increased from 36 years in 1969 to 55 years in 1989. The Table 2 shows the calendar evolution of the age at start of dialysis and of the proportion of different etiologies of CRF; age and proportion of high risk etiologies have been steadily increasing along years. Almost all patients were anuric after six months of dialysis. Eleven patients were anephric, their mean hematocrit was 21.3 (3.1) but none of them was regularly transfused. Nineteen patients had been formerly living with a transplanted kidney for more than two months (mean duration 22.2 ± 15.3 months). The transplantation time has not been taken into account in the survival data.

All patients received the same treatment: 24 hours/week on

flat plate dialyzers (Meltec® Multipoint Kiil of 1 square meter area) with cuprophane membrane (11.5 μ). The blood flow was kept at 200 ml/min or more. The dialysate, used single pass (500 ml/min), had the following composition (in mmol/liter): Na = 138, K = 1.5, Ca = 1.75, Mg = 0.75, Cl = 106, acetate = 35. The diet was low salt (no added salt) with a mean protein intake >1 g/kg body weight. Out of exceptional cases of severe bleeding, the patients received no blood transfusion.

The KT/V index was retrospectively determined using averaged mean pre- and post-dialysis urea (12 measures per year), weight loss, and dry weight using the formula suggested by Daugirdas [4]:

$$KT/V = -\ln(R - 0.03 - UF/DW)$$

where R = pre- to post-dialysis urea ratio, UF = ultrafiltration rate, DW = dry weight. It was calculated for each patient and for each year of HD. The mean pre-dialysis urea was 25.2 (5.8) mmol/liter, the mean post-dialysis urea was 6.4 (2.2) mmol/liter. The mean KT/V for the 445 patients was 1.67 (0.41). Since all patients received the same 24 square meter hours per week of dialysis irrespective of their body weight, there was a strong negative correlation ($r = -0.60$, $P < 0.001$) between dry weight and KT/V. Because of this, female patients received a significantly ($P < 0.001$) larger dialysis dose (mean KT/V = 1.92 ± 0.40) than male (mean KT/V = 1.55 ± 0.33). For subsequent survival comparison two equal numbered ($N = 222$ and 223) subgroups of patients were designed as a function of KT/V: a "low" (mean KT/V = 1.35 ± 0.16) and a "high" (mean KT/V = 1.97 ± 0.35) subgroup. These two groups differed (Table 3) in terms of mean arterial pressure but included the same proportion of high risk etiologies of CRF. Their age at the start of HD was not significantly different. A total of 80.3% of the female patients belonged to the high KT/V subgroup (vs. only 36% of the male patients).

The pre dialysis mean arterial pressure (MAP) was calculated [$MAP = \text{diastolic} + (\text{systolic} - \text{diastolic})/3$] for each patient and each year of treatment (from average value of all sessions of the year). Two equal number subgroups of patients were designed as a function of MAP, a "low" (mean MAP = 89.5 ± 8.3 mm Hg) and a "high" (mean MAP = 109.0 ± 8.3 mm Hg) subgroup. These two subgroups differed (Table 3) in terms of age at start, proportion of high risk etiologies of CRF, mean KT/V, and sex ratio. For further analysis of effect of sex, KT/V and MAP, survival at up to 15 years was calculated separately for male and female patients: each gender group was split into two equal numbered subgroups as a function of KT/V and MAP.

The protein catabolic rate (PCR) of our pts was prospectively evaluated by indirect determination using the Gotch and Sargent formula [5]:

$$PCR \text{ (g/kg/day)} = 9.35G + 0.00028 V$$

(where G = net urea generation rate in mg/min and V = urea distribution volume in ml) beginning in 1989 for the current population of the unit.

When starting dialysis, each new patient's dry weight was determined and maintained by carefully controlled ultrafiltration. At the same time, a moderate sodium restriction was advocated, that is, no added salt, and antihypertensive drugs were progressively withdrawn. The mean interdialytic weight gain of the population was 1.90 (0.61) kg. It was less than 5% of

Table 3. Features of the 2 urea kinetics (KT/V) and of the 2 mean arterial pressure (MAP) subgroups of patients

	Age at start of HD	High risk causes of CRF	Mean arterial pressure	Female ratio (overall = 31.2%)
KT/V < 1.60 (N = 222)	47.0 (±12.9)	21.2%	100.4 (±11.4)	12.6%
KT/V > 1.60 (N = 223)	44.4 (±15.5)	17.0%	97.6 (±13.8)	51.1%
<i>P</i> ^a	NS	NS	<0.02	<0.0001
	Age at start of HD	High risk causes of CRF	Mean KT/V	Female ratio (overall = 31.2%)
MAP < 99 mm Hg (N = 222)	42.9 (±14.9)	12.1%	1.72 (±0.37)	44.0%
MAP > 99 mm Hg (N = 223)	48.5 (±13.1)	26.1%	1.60 (±0.40)	19.8%
<i>P</i> ^a	<0.001	<0.001	<0.001	<0.0001

^a Using unpaired *t*-test or chi square test

Table 4. Demographic factors and patient survival at 5, 10, 15 and 20 years of hemodialysis

Initial age years	# pts	% Patient survival, years			
		5	10	15	20
<35	112	93	88	80	71
35-44	84	92	79	62	39
45-54	111	89	76	54	—
55-64	98	83	62	23	—
>64	40	67	59	—	—
Total	445	87	75	55	43
Etiology					
Chronic GN	138	93	85	76	66
Interstitial N	98	95	84	67	—
Polycystic KD	60	88	78	50	—
Nephrosclerosis	44	81	60	23	—
DM/system D	40	65	58	—	—
Unknown	65	84	66	50	33
Total	445	87	75	55	43
Sex					
Female	142	94	90	67	64
Male	303	85	69	54	38
Total	445	87	75	55	43

the body weight in all but 18 patients. Using the above regimen, satisfactory control of BP was obtained within six months, at which point all antihypertensive medication had been stopped. There were only seven exceptions (1.6%).

The comparisons of incidence were made using the chi square test, the comparisons of means using the unpaired *t*-test. Actuarial survival rates were determined by the Kaplan-Meier method [6]. Log-rank test was used to compare the different survival curves. The limit of significance was set at 5%.

Results

The survival rates as a function of demographic factors are presented on Table 4. The overall population half life was 17 years but the survival rate decreased significantly for patients who were older at initiation of HD. There was no survival difference (log-rank test: NS) between patients whose CRF was due to chronic glomerulonephritis, interstitial nephritis or polycystic kidney disease. On the other hand, patients with diabetes mellitus, systemic diseases, nephrosclerosis or malignant dis-

eases had a significantly lower survival rate (log-rank = 33.7, *P* < 0.001). Female patient survival was superior to male (log-rank = 9.7, *P* < 0.01).

Our five year survival for different age cohorts is presented in Figure 1 in comparison to similar age groups in three major national registries: Japan [7] US Medicare [8] and EDTA [9]. The results appear better in our series. The difference is more obvious for older age groups. In Figure 2 our long term survival of the 35 to 44 year cohort is compared to available data for similar age patients from EDTA [9] and two US centers [10, 11].

The effects on patient survival of the dose of dialysis as measured by KT/V and of the MAP are shown in Table 5. The patient survival in the high dose and in the low MAP cohorts are significantly better. Survival rates as a function of the same two parameters are presented separately for male and female patients on Table 6.

The mean measured PCR in the population was 1.26 (0.52) g/kg/day. The serum albumin was 4.19 (0.47) g/dl, cholesterol was 229 (38) mg/dl. The mean pre-dialysis values were: creatinine 10.1 (1.6) mg/dl; BUN 70.6 (15.1) mg/dl; potassium 5.1 (1.2) mEq/liter, calcium 9.6 (0.7) mg/dl, phosphorus 5.0 (1.8) mg/dl. The mean hematocrit before session was 28.1 (5.8).

The causes of death, expressed in number per 1000 patient-years, are reported on Table 7. A high incidence of deaths due to car crash is to be noticed, only in one case was the patient himself driving the car. Cardiovascular deaths, including sudden deaths of unknown origin, represent the major cause of mortality. Cardiovascular mortality was significantly higher (*P* < 0.001) in the subset of patients whose MAP was higher than 99 mm Hg. This difference existed despite the fact that both subgroups were in fact normotensive.

Discussion

Figures 1 and 2 demonstrate clearly that survival in our series of 445 patients is better than any other published series, and in certain respects remarkably so. We offer the hypothesis that the major factor responsible for our longer survival is the prevention of uremia induced acceleration of atherosclerosis by adequate control of blood pressure.

That dialysis patients, like diabetics, are prone to develop atherosclerosis (whether accelerated or not) has been well

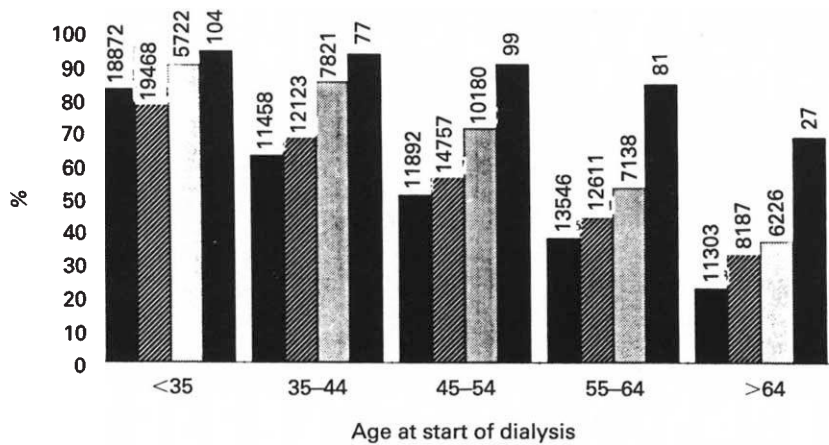


Fig. 1. Five year survival (%) for different age cohorts in four different series. The number of patients remaining alive at the end of each interval is shown over the bar. Symbols are: () US registry; () EDTA; () Japan; () Tassin.

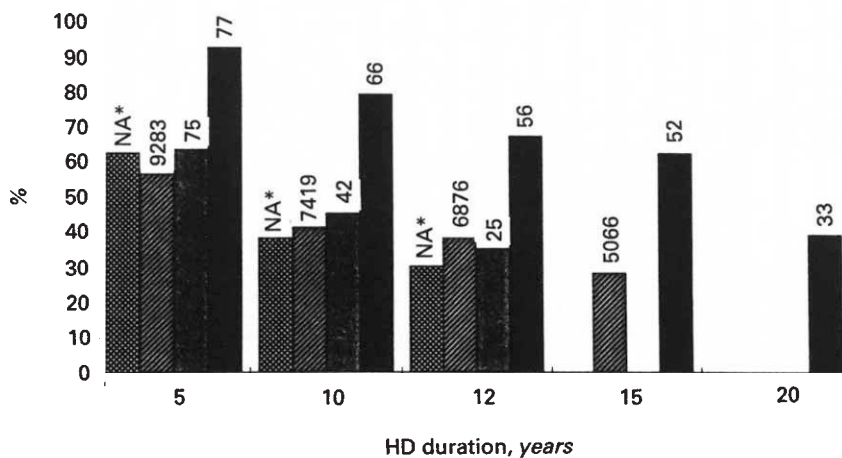


Fig. 2. Long-term survival (%) of patients (35 to 44 years old cohort) in four series. The number of patients remaining alive at the end of each interval is shown over the bar (NA* = not available). Symbols are: () Philadelphia; () EDTA; () Seattle NWKC; () Tassin.

Table 5. Survival rates at 5, 10, 15 and 20 years of HD as a function of KT/V and mean arterial pressure (MAP)

		% Patient survival, years				
	# pts	5	10	15	20	P
KT/V ^a						
<1.60	222	85	71	50	33	<0.005
≥1.60	223	91	82	63	57	
Total	455	87	75	55	43	
MAP ^b						
<99 mm Hg	222	93	85	67	53	<0.001
≥99 mm Hg	223	81	65	43	—	
Total	445	87	75	55	43	

^a KT/V was estimated using the formula: $KT/V = -\ln(R - 0.03 - UF/DW)$ where: R = pre- to post-dialysis urea ratio, UF = ultrafiltration rate, DW = dry weight

^b MAP: pre-dialysis mean arterial pressure = $[\text{diastolic} + (\text{systolic} - \text{diastolic}/3)]$

Table 6. Survival rates (%) of KT/V and mean arterial pressure (MAP) subgroups of patients

	<i>N</i>	% Patient survival, years			<i>P</i>
		5	10	15	
Male patients					
KT/V < 1.45	(151)	83	68	47	NS
KT/V > 1.45	(151)	87	74	55	
MAP < 101 mm Hg	(151)	88	80	65	
MAP > 101 mm Hg	(151)	81	60	33	
Female pts					
KT/V < 1.85	(71)	91	85	48	NS
KT/V > 1.85	(72)	93	88	71	
MAP < 94 mm Hg	(71)	96	80	75	
MAP > 94 mm Hg	(72)	88	76	38	

documented [12–14]. That it often can be prevented by normalizing blood pressure was established by us in 1983 [15, 16].

A striking feature of our series is that the five year survival difference with the other series (Fig. 1) becomes more evident when the age of the compared cohorts gets older. Since older patients are more likely to die of complications of atherosclerosis than younger patients, prevention of this complication by

controlling blood pressure is a likely explanation for the differences observed.

The results shown in Figure 2 provide even stronger support for our hypothesis. Although selection bias may explain in part the differences in patient survival at five years, the far superior results at 10 years and beyond are best explained by the lack of deaths from the complications of atherosclerosis in our series.

Table 7. Causes of death (in number of deaths per 1000 patient-yr) among 445 patients as a function of dialysis dose (KT/V) and pre-dialysis mean arterial pressure (MAP mm Hg)

	KT/V < 1.6	KT/V ≥ 1.6	P	MAP < 99	MAP ≥ 99	P
N patients	222	223		222	223	
Years at risk	1858.2	1832.2		2165.6	1524.8	
Car crash	2.15	2.18	NS	1.39	3.26	NS
Cardiovascular	15.14	10.82	NS	9.70	17.71	<0.001
Infection	8.61	6.46	NS	6.08	9.84	NS
Postsurgery	2.15	1.64	NS	2.77	4.69	NS
Cancer	6.92	1.09	<0.01	1.39	2.62	NS
Other causes	6.46	4.37	NS	3.69	7.87	<0.02
Unknown	1.61	0.55	NS	0.00	2.62	NS
Total	36.94	30.17	<0.01	24.02	48.61	<0.001

As a matter of fact, the mortality analysis (Table 7) shows that the cardiovascular mortality, by far the first cause of death, is significantly ($P < 0.001$) correlated with a higher MAP, but not with a lower KT/V.

Tassin's artificial kidney center's experience is unique in that the old fashioned slow Kiil dialysis technique using on average eight hours of dialysis three times a week has been maintained unchanged for over 20 years. This regimen allows for a good nutritional state and hematocrit control which may enhance survival. Beyond that, it provides more than enough time for ultrafiltration to maintain dry weight and control blood pressure so effectively that antihypertensive medications are very seldom needed. This feature of our program is perhaps the most important factor contributing to our survival results.

As time on dialysis is made shorter and shorter, it becomes more and more difficult to achieve adequate blood pressure control even with the addition of antihypertensive medications [17]. Failure to control blood pressure when dialysis time is shortened should be regarded as an absolute contraindication to continuing that regimen. Dialysis time should be increased along with more aggressive ultrafiltration to the point where blood pressure is normalized.

Decreasing time on dialysis might also maintain the patient in subclinical uremia resulting in decreased appetite. This can cause serious protein malnutrition [18] because the dialysis procedure itself results in increased protein catabolism [19, 20]. In the case of this series, caloric and protein nutrition was maintained as evidenced by the average serum levels of BUN, creatinine, potassium, albumin and cholesterol. It is noteworthy that this biological profile of our pts fits with a decreased mortality risk in Lowrie and Lew analysis [18], each of these parameters is within the limits of the value cited as "reference" in their study.

The higher than usual dose of dialysis (average KT/V = 1.67) may have contributed to our lower mortality. The significantly better survival in our high dose subgroup (mean KT/V = 1.97) would seem to support this conclusion. However, since the high dose subset contained many more female patients and had a significantly lower average blood pressure (Table 3), these factors rather than dialysis dose may have had the major effect on mortality difference. The same line of reasoning applies to the large risk factor differences between the two MAP subgroups. Nevertheless, when male and female patients were considered separately (Table 6), there was in both groups no

significant survival difference up to 15 years between the Kt/V subgroups but a clear cut survival difference between MAP subgroups. This would support the hypothesis that blood pressure control is a more significant determinant of survival than small molecule diffusion. What can be concluded with confidence from our data, is that the ill effect of too much dialysis simply does not exist.

What our higher dose of dialysis did accomplish was to provide a large margin of safety that insured that our patients were seldom if ever underdialyzed. That chronic underdialysis can cause significant morbidity (and by implication increased mortality in the long run) is clearly established by the results of the US cooperative study [21]. More recently, chronic underdialysis due to shortening dialysis time without increasing dialysis efficiency has been implicated as a cause of increasing mortality in the United States [3]. Which brings us to a brief discussion of the increasing popularity, especially among patients, of high efficiency shortened time dialysis.

To increase the efficiency of a hemodialysis system in order to shorten dialysis time pushes every operational aspect of that system toward its maximum capacity. That in turn increases exponentially the chances for malfunction, error or abuse. For example, pushing up the blood flow greatly increases the chance of recirculation in the fistula. Therefore, it is not surprising that, unless great care is taken, the chance for underdialysis is increased as time is shortened, which may well explain why Gotch, Yarian and Keen [22] found among 101 visitors to San Francisco that 45% were underdialyzed, especially those on shortened time dialysis.

We don't want to leave the reader under the impression that it takes anywhere near eight hours of dialysis to achieve sufficient ultrafiltration to control blood pressure. What we do believe though, is that sometimes it takes longer to remove enough fluid to control blood pressure than it does to provide an adequate dose of dialysis.

In summary, we believe that the definition of adequate dialysis should include at least three components: 1) adequate control of blood pressure mainly by use of carefully adjusted ultrafiltration, 2) adequate energy and protein intake with a PCR of at least 1.20 [23], and 3) a dose of dialysis that is high enough to provide a margin of safety. A minimum dose equivalent to a KT/V of 1.6 is suggested, especially if dialysis time is shortened.

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