Blood Purification

Blood Purif 2007;25:90–98
DOI: 10.1159/000096403

Published online: December 14, 2006

Treatment Time and Ultrafiltration Rate Are More Important in Dialysis Prescription than Small Molecule Clearance

Zbylut J. Twardowski

Department of Medicine, Division of Nephrology, University of Missouri, Columbia, Mo., USA

Key Words
Dialysis duration · Ultrafiltration · Sodium profiling · Hypotension, intradialytic · Hypertension · Kt/V_{urea} · Lag phenomenon

Abstract
Chronic hemodialysis sessions, as developed in Seattle in the 1960s, were long procedures with minimal intra- and interdialytic symptoms. Over the next three decades, dialysis duration was shorten to 4, 3, even 2 h in thrice weekly schedules. This method spread rapidly, particularly in the United States, after the National Cooperative Dialysis Study suggested that the time of dialysis is of minor importance as long as urea clearance multiplied by dialysis time and scaled to total body water (Kt/V_{urea}) equals 0.95–1.0. This number was later increased to 1.3, but the assumption that hemodialysis time is of minimal importance remained unchanged. However, Kt/V_{urea} measures only the removal of low molecular weight substances and does not consider the removal of larger molecules. Nor does it correlate with the other important function of hemodialysis, namely ultrafiltration. Rapid ultrafiltration is associated with cramps, nausea, vomiting, headache, fatigue, hypotensive episodes during dialysis, and hangover after dialysis; patients remain fluid overloaded with subsequent poor blood pressure control leading to left ventricular hypertrophy, diastolic dysfunction, and high cardiovascular mortality. Kt/V_{urea} should be abandoned as a measure of dialysis quality. The formula suggests that it is possible to decrease t as long as K is proportionately increased, but this is not true. Time of dialysis should be adjusted in such a way that patients would not suffer from symptoms related to rapid ultrafiltration, would not have other uremic symptoms and most patients would have blood pressure controlled without antihypertensive drugs.

The evolution of hemodialysis duration and various measures of dialysis adequacy has recently been reviewed [1–3]. This article will provide a synopsis of these reviews, updated with recent Dialysis Outcomes and Practice Patterns Study (DOPPS) data, strengthening the notion that longer hemodialysis duration and slower ultrafiltration is associated with reduced mortality and better treatment tolerance of hemodialysis patients [4]. A short discussion of volume-dependent hypertension and the ‘lag phenomenon’ will be also included.

Evolution of Dialysis Duration

In the early 1960s chronic hemodialyses were long procedures, usually 20–40 h/week on standard Kiil dialyzers in-center [5] or 8–10 h three times weekly at home [6]. The first trials of shorter dialysis duration were at-

KARGER

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

0253–5068/07/0251–0090$23.50/0

Accessible online at:
www.karger.com/bpu

Zbylut J. Twardowski, MD
Dialysis Clinic, Inc.
3300 LeMone Industrial Blvd
Columbia, MO 65201 (USA)
E-Mail Twardowskiz@health.missouri.edu

tempted in the late 1960s. Schupak and Merrill [7] indicated that shorter dialysis sessions (total duration of 12–16 h/week with the use of coil dialyzers) achieved biochemical control similar to that achieved on Kiil dialyzers with longer dialysis durations.

The tendency to shorten dialysis duration continued in the 1970s. The major incentive was the need of more intensive utilization of dialysis centers because the number of candidates for chronic dialysis markedly exceeded the availability of treatment facilities [8, 9]. In the late 1970s, an increasing number of centers in Europe and in the US followed this trend. Short dialysis had a tremendous appeal to the patients once they were told that the results were not worse than those with long dialysis.

Justification for Short Dialysis

Three factors were necessary for the widespread acceptance of short dialysis: economic incentives, technical feasibility, and medical/scientific justification [10]. Economic incentives were demonstrated by early proponents of short dialysis. In the meantime, very efficient dialyzers had been designed and their values demonstrated in short-term studies [11, 12]. Nevertheless, short-term studies would not be sufficient for the widespread use of short dialysis. Some scientific support and a mathematical formula were needed to define an adequate dose of dialysis and justify short treatment duration.

Square Meter-Hour Hypothesis and Dialysis Index

The first such formula was developed in the early 1970s. Uremic peripheral neuropathy was a common complication of hemodialysis and very resistant to treatment. This complication was not dependent on urea and creatinine concentrations, but was rare with 24–27 h weekly hemodialysis on standard Kiil dialyzers and in patients on peritoneal dialysis. Based on these observations, Babb et al. [13] first proposed the idea that toxins responsible for neuropathy might be in the molecular weight range of 2,000–5,000 Daltons. They originated the term 'middle molecules' (MMs) and calculated that their clearance is the product of the overall mass transfer coefficient and the membrane area. This hypothesis led to the 'square meter-hour hypothesis', which implied that by doubling the surface area of a hemodialyzer the time of dialysis could be halved for equivalent MM removal [13–15]. This was an important step in the justification of high efficiency, short time dialysis. Ultimately 'a dialysis index', the first quantitative description of adequacy of dialysis, was developed [15]. The formula takes into consideration residual renal function, which was omitted in formulas developed later.

Urea Kinetics

In the late 1970s and early 1980s, short dialysis received support from a new measure of dialysis adequacy based on urea kinetics. Gotch and Sargent [16] recommended that the minimum dose of dialysis (dialyzer urea clearance, treatment time and frequency) should be sufficient to result in mean predialysis blood urea nitrogen (BUN) values of 80 mg/dl in patients with documented protein intakes of at least 1.0 g/kg/day. It is worth noting that, unlike the MM clearance, the urea clearance is significantly influenced by blood and dialysate flow rates, because urea molecules diffuse rapidly through the membrane and from red blood cells to the plasma. Therefore, to maintain a high concentration gradient of urea between blood and dialysate, high blood and dialysis solution flow rates are required. The National Institutes of Health (NIH) sponsored the National Cooperative Dialysis Study (NCDS) to establish the objective, quantitative criteria for the adequate dose of dialysis [17]. Urea kinetics coupled with the monitoring of nutrition was chosen as the criterion of dialysis dose [18]. It was accepted that the single measure of dialysis dose should be Kt/V_{urea}: the amount of urea clearance (K) multiplied by time (t) and divided by urea distribution volume (V). Morbidity was used to judge the quality of dialysis. Patients with high BUNs and short hemodialysis durations were hospitalized more often compared to the group with high BUN but longer dialysis; however, this was statistically insignificant and in the final recommendations, the length of dialysis was considered as only marginally important [19]. It is amazing that the length of dialysis was rejected as an important factor on the basis that p was <0.06 instead of the sacrosanct 0.05. It was forgotten that absence of evidence is not evidence of absence. However, it was recommended that 'short dialysis should be prescribed with caution in patients who are likely to suffer cardiovascular complications' [20]. In later analysis of the NCDS, Gotch and Sargent [21] concluded that 'normalized protein catabolic rate over 1.0 g/kg/day and Kt/V_{urea} over 1.0 per treatment in hemodialysis is of no apparent clinical value with the cellulosic dialyzers in thrice-weekly treatment schedule'.

The results of this study spurred other studies to demonstrate that dialysis time could be halved by doubling blood flow and dialyzer surface area [22, 23]. Although clearances of small molecular substances did not differ significantly, the tolerance of dialysis was worse and hypotensive episodes were more frequent with shorter dialysis sessions particularly in patients without residual urine output [24]. It is worth mentioning that early studies indicating benefits of short dialysis were carried out in patients starting chronic hemodialysis and *eo ipso* with substantial residual urine output. In the NCDS study, residual renal function was not taken into account, but most patients were of short dialysis vintage, so it is likely that their residual renal function was significant.

Problems with Short Dialysis (Small t)

Early Reports

In the first paper on shorter dialysis duration, Schupak and Merrill [7] reported a markedly higher rate of hypertension problems than in the early reports with longer dialysis [5, 6]. The French Dialysis Registry reported a gradual decrease in hemodialysis duration during the 1970s and a higher rate of hypotensive episodes [25]. In 1983, the European Dialysis and Transplant Association reported 'the proportion of deaths in the Federal Republic of Germany was twice as high in short dialysis' [26].

An early warning that a short duration of dialysis was associated with multiple problems related to water and sodium retention came in the report by Sellars et al. [27]. Exchangeable sodium was significantly increased with short dialysis, and more patients required antihypertensive drugs. Another warning came from Germany in the report by Wizemann and Kramer [28] in 1987. They did not observe any significant differences in serum biochemistry between short (2.5 h) and long dialysis (4 h), except for serum phosphate, which was lower during longer dialysis. However, weight gains were higher, blood pressure control was worse, and hypotensive episodes were markedly more frequent with shorter dialysis [28].

High Mortality

In the US, the relative mortality risk was about 20% higher in patients receiving a dialysis duration of <3.5 h compared to those with treatment for >3.5 h [29, 30]. The annual mortality in US patients has increased from 10 to 25% over the last three decades, but has remained stable at around 10% in Japan [31]. During the period 1982–1987, hemodialysis mortality in the US was found to be 22% higher than in Europe and 40% higher than in Japan [32] and the duration of dialysis was 23.5% shorter in the USA than in Europe and 40% shorter than in Japan [33]. The experience in Tassin, France, clearly indicates that longer dialysis (8 h thrice weekly) than is usual in the US improves patient survival [34]. When comparing the survival of US patients to those dialyzed in Tassin, it is in the older age group that the difference is particularly pronounced. While the risk of death is two times higher in the US in the patients younger than 45 years, it is 12 times higher in patients older than 65 years [34, 35]. This finding is thus similar to the Japan-US comparison, where the relative risk of death in the US also markedly increases with the age of the patients [32].

The results from the Japanese dialysis registry [36, 37] showed that shorter dialysis increases death rates. In Europe, Valderrábano [38] reported a lower gross mortality rate in patients who were dialyzed for more than 12 h/week as compared to those dialyzed for ≤12 h/week; the difference in mortality was particularly considerable in patients over 65 years old.

A recent DOPPS [4] showed reduced mortality with longer treatment time. Statistical adjustments were made for patient demographics, comorbidities, dose of dialysis (Kt/V), and body size. Every 30 min longer on hemodialysis was associated with a 7% reduced relative risk of mortality. The association was present in USA, Europe, and Japan, but was most pronounced in Japan. A synergistic interaction occurred between Kt/V and treatment time ($p = 0.007$) toward a mortality reduction. An ultrafiltration rate of >10 ml/h/kg was associated with 9% increased mortality risk.

Intradialytic Hypotension and Duration of Dialysis

Intradialytic hypotension (IDH) occurs in 25–50% of short, thrice weekly hemodialysis treatments in the US. The detrimental effect of IDH is being increasingly recognized as an important factor in the increased relative risk of death due to acute coronary syndrome, and arrhythmias [39–41]. Dialysis hypotension occurs because a large volume of blood water and solutes are removed over a short period, exceeding the plasma-refilling rate and the reduction of venous capacity [42, 43]. Short dialysis is associated with high-speed ultrafiltration and rapid removal of small molecules, thus swiftly depleting plasma volume. In a study by Ronco et al. [44] ultrafiltration rates of 0.3, 0.4, 0.5, and 0.6 ml/min/kg were associated with approximate rates for IDH of 8, 15, 26, and 60%, respectively. In addition to an increased mortality with rapid ultrafiltration, a recent DOPPS [4] also showed markedly higher odds of IDH episodes in patients with an ultrafiltration rate of >10 ml/h/kg.

Stratagems to Reduce IDH without Prolonging Dialysis Duration

Although the K/DOQI Guidelines [45] and others [39, 42, 43] admit that to avoid IDH the ultrafiltration rate should not exceed the refilling rate, there is no stress on the lengthening of dialysis sessions, the simplest way to avoid the problem. Instead, multiple maneuvers have been applied to increase the plasma-refilling rate and decrease venous capacity such as: isolated ultrafiltration [46], high dialysate osmolality [24, 47], dialysate bicarbonate instead of acetate [48, 49], lowered dialysate temperature [50], and higher dialysate ionized calcium [51]. Rapid lowering of serum potassium during dialysis and high dialysate magnesium were also considered as factors augmenting hypotensive episodes [43]. Finally, predialysis withdrawal of blood pressure medications and/or use of blood pressure-rising drugs, such as ephedrine, fludrocortisone, caffeine, and midodrine have been recommended [52].

The most popular recent method of preventing IDH was ultrafiltration and sodium profiling. Although a multitude of approaches has been tried [53], the most common was application of a high ultrafiltration rate and high sodium concentration at the beginning of dialysis with a gradual or stepwise decrease in dialysate sodium concentrations and ultrafiltration rates throughout the dialysis session [54]. Whereas short-term studies showed improvement in the incidence of hypotensive episodes, a careful study of sodium balance showed that improvement was related to a positive sodium balance, leading to chronic volume overload, hypertension, myocardial hypertrophy, and increased cardiovascular mortality [55, 56].

Hypertension in Hemodialysis Patients

Hypertension occurs in 90% of patients starting hemodialysis and persists in 70–90% of hemodialysis patients in the US [57]. In the large, multicenter Hemodialysis (HEMO) Study, more than 70% of patients were hypertensive by JNC VI guidelines, and almost 75% required antihypertensive medications [58]. This is contrary to the situation in the late 1960s, when strict control of true dry body weight was practiced and the majority of patients did not require antihypertensive agents [59]. There is a consensus that most patients on dialysis have volume-dependent hypertension. Only a small proportion of patients have vasoconstrictive hypertension requiring bilateral nephrectomy in the past [59] or blood pressure medications at present. The problem is how to achieve normovolemia and control blood pressure without medications.

Blood Pressure Control by Dietary Measures and Low Dialysate Sodium

The possibility of controlling blood pressure in a renoprival state by drastic reduction in dietary salt intake was first shown by Kempner [60, 61] in the 1940s. It was subsequently shown that the beneficial effect of the 'rice diet' on hypertension was related to the lowering of plasma volume and extracellular fluid space [62]. In the 1960s it was considered as mandatory to restrict dietary salt intake in hemodialysis patients to control blood pressure. This restriction was combined with long dialysis sessions and relatively low dialysate sodium. The achievement of blood pressure control was very gradual. It was not surprising for the hemodialysis pioneers as this phenomenon was already observed by Kempner [60, 61] in the 1940s. In the first patient on a 'rice diet' containing less than 500 mg of salt, blood pressure was lowered gradually from 230/145 to 135/90 mm Hg in 8 weeks [60]. Even achievement of dry body weight does not lead immediately to controlling blood pressure because the relationship between extracellular volume status and blood pressure is not simple and linear, but complex because of a lag of several weeks between the normalization of the time-averaged extracellular volume and the decrease in blood pressure ('lag phenomenon') [63]. The exact pathomechanism of the lag phenomenon is not clear. It is likely that this may be caused by the retention of circulating factors, such as asymmetric dimethyl-L-arginine, a potent inhibitor of nitric oxide synthesis and Na^+,K^+-ATPase inhibitors that may remain elevated because of a large volume of distribution and ineffective removal [64]. Elevated sodium may remain in the arterial smooth muscles and be responsible for vasoconstriction. It may take several weeks of normovolemia for the intracellular sodium to escape. Regardless of the mechanism, the normalization of blood pressure by volume control is tricky, requires patience and a good understanding of the problem [56, 63, 64]. Several groups have tried to lower extracellular volume and blood pressure without lengthening dialysis duration by dietary measures and low dialysate sodium [65]. In 8 patients Krautzig et al. [66] tried a regime of gradual lowering of the dialysate sodium concentration from 140 to 135 mEq/l at a rate of 1 mEq/l every 3–4 weeks and restricting dietary salt intake while maintaining dialysis duration of 4–5 h/session. It is worth stressing that dialysis duration was longer that practiced in the US.

The authors reported lowering blood pressure in these patients with a possibility of stopping blood pressure medications in 4 patients and only a moderate increase in the frequency of cramps during dialysis. The control of extracellular volume by a low sodium diet without prolongation of dialysis duration and low dialysate sodium is difficult; it increases intradialytic symptoms and requires a very strict adherence to an unpalatable diet.

Blood Pressure Control and Duration of Dialysis

Hypertension is less frequent in Europe and Japan where dialysis time is longer. The lowest mortality related to cardiovascular causes is reported from the Centre de Rein artificial, Tassin, France [56], where long duration hemodialysis is practiced. Long-term mortality in this center is lower in patients with lower mean blood pressures. In addition, gentle ultrafiltration and proper estimation of dry body weight allows the achievement of good blood pressure control in the majority of patients [56]. Hypotension, in patients dialyzed thrice weekly for 8 h, is a strong indicator that the patient weight dropped below the true dry body weight [56]. With rapid ultrafiltration, hypotension is dependent mostly on hypovolemia, which occurs long before the dry body weight is achieved. In spite of clear evidence that short dialysis is associated with poor blood pressure control, the blame is commonly put on suboptimal drug therapy, excessive interdialytic weight gains ('patient noncompliance'), and the practice of withholding antihypertensive medications before dialysis [67].

With long-duration hemodialysis sessions, blood pressure could be controlled without antihypertensive therapy in 90–95% of patients [56, 68]. These patients have volume-dependent hypertension. The remaining 5–10% of patients has 'refractory' hypertension, treated with bilateral nephrectomy in the past, but nowadays these patients respond to antihypertensive therapy with converting enzyme inhibitors [69]. The originator of chronic dialysis is Belding H. Scribner, who practiced long-duration dialysis sessions in the 1960s, and in recent years advocated forcefully departure from short dialysis and better attention to volume management for blood pressure control [63, 70–72]. Other groups also advocate longer dialysis sessions for better blood pressure control [73–75]. A recent randomized crossover study of long (6–8 h) dialysis thrice weekly at home and short (3.5–4.5 h) thrice weekly in the dialysis center showed much better control of blood pressure and a reduction in hypotensive episodes with longer dialysis sessions [76]. Even moderate prolongation of dialysis sessions from 253 ± 15 to 273 ± 25 min together with strict control of sodium balance over 3–4 months allowed control of blood pressure in 10 of 16 patients with 'dialysis-resistant' hypertension [77].

The K/DOQI guidelines do not recommend the duration of dialysis as an independent measure of dialysis adequacy. After discussing all arguments for and against the importance of dialysis duration, the work group could not reach a consensus on this subject and did not include it in the final recommendations [45]. Some work group members felt strongly that the time of dialysis should not fall below 2.5 h, but a duration of dialysis of >4 h was not recommended [45]. However, I see no good explanation for why duration of dialysis is dismissed as unimportant.

Problems with High Small Solute Clearances (Large K)

Blood Flow and Efficiency of Dialysis

Short dialysis with fixed Kt/V_{urea} leads to maximization of dialysis efficiency by using higher efficiency dialyzers and high blood and dialysate flows; however, the influence of blood flow on the efficiency of dialysis is markedly lower than dialysis time. Removal of MMs (including phosphorus) is only slightly dependent on blood and dialysate flows [13], so compensating shortened dialysis time by increasing blood flow is not effective. This is not only related to the slow diffusion of these molecules through the membrane, but also to multicompartmental behavior, i.e., slow diffusion from the extravascular space to the plasma [78]. This process may be compared to the poor 'plasma-refilling rate' of water and sodium in high ultrafiltration rate hemodialysis. It is worth realizing that even for removal of small molecules, an increased time of dialysis is more effective than increased blood and dialysate flows, because $spKt/V_{urea}$ (single pool) is directly proportional to dialysis time, but K is exponentially, not linearly, proportional to blood and dialysate flows.

High Blood Flow Rates and Retrofiltration

The introduction of ultra-short dialysis treatments with high blood flow and high flux dialyzers brought other unexpected, undesirable effects, namely back filtration or retrofiltration of dialysate to the blood compartment [79, 80]. Ronco [81] explained that back filtration (retrofiltration) is particularly pronounced with long dialyzer and the high flows of blood and dialysate. The consequence of bacterial product delivery from the dialysate to the blood stream is an acute phase reaction with consequent chronic inflammation, protein-energy malnutrition, and accelerated arteriosclerosis constituting the well-described malnutrition-inflammation-arteriosclerosis syndrome [82, 83].

High Blood Flow Rates and Blood Access Problems
According to the DOPPS, in the US the mean dialysis duration of 213 min is the lowest of the seven nations participating in the study and the prescribed blood flow rate of 401 ml/min is the highest [84]. The requirement of high blood flow increases demand on blood access. There are major differences in blood access use between Europe and the US in both genders, in all age groups, and in patients with and without diabetes. In addition, survival of arteriovenous fistulas is better in Europe than in the US [85]. It is my strong suspicion that the differences are related, at least in part, to the differences in required blood flow. For instance, primary arteriovenous wrist fistulae providing blood flows of 300 ml/min may be considered adequate in Europe where the mean prescribed flow is 300 ml/min, but are considered inadequate in the US where the prescribed blood flow is over 400 ml/min [86]. Such fistulae are abandoned and other blood accesses are created instead in the US. Even fistulae providing blood flows of 350 ml/min are in jeopardy because of repeated attempts to achieve higher blood flows using tourniquets and other maneuvers. With these attempts, the intima of the fistula is damaged by suction of the inflow needle, and the survival of the fistula is shortened. Finally, hypotensive episodes suddenly reduce fistula blood flow and predispose to clotting. If intravenous catheters are used as blood accesses, large catheter lumens are required to achieve high blood flows. The large diameter catheter fits the vein too tightly and predisposes to damage of the vein wall, vein thrombosis and stenosis [87]. Thus, the requirement of very high blood flow may be a contributing factor to poor blood access results in the US.

Advantages of Long Dialysis (Large T)

From the above discussion, the advantages of long dialysis to the patients are obvious: better tolerance of dialysis, better control of blood pressure, better removal of MMs, better rehabilitation, and longer survival. The average ratio of patients to dialysis personnel is 3–4 to 1 in the US. Because of better tolerance of dialysis with fewer hypotensive episodes, the same ratio in Tassin is 6 to 1 [56]. Thus, the financial disadvantage of longer dialysis may be blunted by a reduced staff requirement. Long dialysis sessions may be performed at home without increased cost to the providers.

Kt/V_{urea} Should Be Abandoned as a Measure of Dialysis Quality
The acceptance of this index was based on insufficient data and their false interpretation. In the NCDS study the tendency toward lower morbidity with longer dialysis duration was rejected as statistically insignificant because p was 0.06 instead of 0.05 (sic!). However, the power of this study was low because of an insufficient number of patients, short study duration (52 weeks) and disregard of residual renal function, which must have been substantial as many patients were of short vintage. It is worth repeating that the absence of evidence is not the evidence of absence. Combining dialyzer urea clearance (K), dialysis duration (t) and urea distribution volume (V) in one formula and accepting this formula as a measure of dialysis adequacy has brought disastrous consequences. The formula suggests that it is possible to decrease t as long as K is proportionately increased, but this is not true. For instance, increasing dialyzer urea clearance (K) may compensate for shorter dialysis time (t) regarding urea removal, but it cannot compensate for the dialysis tolerance depending on the rate of ultrafiltration, nor has it reflected removal of bigger molecules. A very small urea distribution volume (V) will provide large Kt/V_{urea} in malnourished patients, even if their dialysis duration is short and dialyzer clearances are low. One can imagine that following only Kt/V_{urea}, patients loosing appetite, poorly nourished, may maintain this index of dialysis adequacy continuously loosing weight and urea distribution volume (V) until their demise. The Kt/V formula is misleading and should be abandoned as a measure of dialysis quality. Would any aircraft pilot use an altimeter showing the wrong altitude?

Clinical Assessment of Dialysis Quality

One may ask what index of dialysis adequacy should be used instead of Kt/V_{urea}. It is tempting to give a simple formula, easy to implement and easy for bureaucrats to control. If such a formula were really developed, nephrologists would not be needed in dialysis centers – computer programs and dialysis technicians would suffice. I do not believe that such a formula will be developed any time soon as dialysis is a very complex procedure. The use of rigid, quantitative guidelines (e.g., $spKt/V_{urea}$ of 1.3 per dialysis) assumes that all patients behave identically in response to therapeutic maneuvers, like the mean of the group, but this is not true [88]. Medicine is still an art, not exclusively science; the individual approach assumes that there are differences among patients which require adjustment of the dialysis prescription for each patient based on clinical symptoms and signs. It is better to use clinical judgment instead of misleading formulae.

During the early years of chronic hemodialysis, the definition of adequate dialysis was based on the two essential goals of dialysis: eradication of signs and symptoms of uremia, and rehabilitation [5]. In the early 1970s, the definitions were based on a mixture of resolution of clinical symptoms and laboratory data [68, 89, 90]. This approach of assessing adequacy is subjective, requires very careful monitoring of patients, and is time-consuming, but it is relevant for the individual patient. In this context I would like to cite Ronco's [91] formula for a general approach to dialysis, MDt/P, where MD is the doctor and t/P is the time spent with the patient.

In the 1970s it was considered obvious that an absence of uremic symptoms predicted low morbidity and mortality. Does it hold true in the 2000s? The DOPPS found a strong association between lower scores for the three major components of health-related quality of life and higher risk of death and hospitalizations in hemodialysis patients [92]. In another DOPPS report, physical functioning was better in Japan and Europe than in the US, where there is the highest mortality. Particularly striking was the high percent of comorbidities related to hypervolemia, such as hypertension, congestive heart failure, and dyspnea in patients dialyzed in the US, where the duration of dialysis is the shortest [93].

Conclusions

Kt/V_{urea} is a poor measure of dialysis quality because it combines three unrelated variables into one formula. These variables influence the clinical status of the patient independent of each other. It is impossible to compensate short dialysis duration (t) with the increased clearances of small molecular substances (K), because the tolerance of ultrafiltration depends on the plasma-refilling rate, which has nothing in common with urea clearances. Clinical assessment is the best criterion of dialysis quality. Longer dialysis provides better tolerance of ultrafiltration, less frequent intradialytic hypotensive episodes, better control of blood pressure, and lower mortality.

References

1 Twardowski ZJ: We should strive for optimal hemodialysis: a criticism of the hemodialysis adequacy concept. Hemodial Int 2003;7:5–16.
2 Twardowski ZJ: Fallacies of high-speed hemodialysis. Hemodial Int 2003;7:109–117.
3 Twardowski ZJ: Short, thrice-weekly hemodialysis is inadequate regardless of small molecule clearance. Int J Artif Organs 2004; 27:452–466.
4 Saran R, Bragg-Gresham JL, Levin NW, Twardowski ZJ, Wizemann V, Saito A, Kimata N, Gillespie BW, Combe C, Bommer J, Akiba T, Mapes DL, Young EW, Port FK: Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the DOPPS. Kidney Int 2006;69:1222–1228.
5 Pendras JP, Erickson RV: Hemodialysis: a successful therapy for chronic uremia. Ann Intern Med 1966;64:293–311.
6 Eschbach JW Jr, Barnett BM, Cole JJ, Daly S, Scribner BH: Hemodialysis in the home. A new approach to the treatment of chronic uremia. Ann Intern Med 1967;67:1149–1162.
7 Schupak E, Merrill JP: Experience with long-term intermittent hemodialysis. Ann Intern Med 1965;62:509–518.
8 Cambi V, Arisi L, Buzio C, Rossi E, Savazzi G, Migone L: Intensive utilisation of a dialysis unit. Proc Eur Dial Transplant Assoc 1973;10:342–348.
9 Cambi V, Savazzi G, Arisi L, Bignardi L, Bruschi G, Rossi E, Migone L: Short dialysis schedules (SDS) – finally ready to become a routine? Proc Eur Dial Transplant Assoc 1975;11:112–120.
10 Barth RH: Short hemodialysis: big trouble in a small package; in Friedman EA (ed): Death on Hemodialysis: Preventable or Inevitable. Dordrecht, Kluwer Academic, 1994, pp 143–157.
11 Stewart RD, Lipps BJ, Baretta ED, Piering WR, Roth DA, Sargent JA: Short-term hemodialysis with the capillary kidney. Trans Am Soc Artif Intern Organs 1968;14:121–125.
12 Ari JB, Oren A, Berlyne GM: Short duration-high area regular dialysis using two UF 2 coils in series. Nephron 1976;16:74–79.
13 Babb AL, Popovich RP, Christopher TG, Scribner BH: The genesis of the square meter-hour hypothesis. Trans Am Soc Artif Intern Organs 1971;17:81–91.
14 Scribner BH: A personalized history of chronic hemodialysis. Am J Kidney Dis 1990;16:511–519.
15 Babb AL, Strand MJ, Uvelli DA, Milutinovic J, Scribner BH: Quantitative description of dialysis treatment: a dialysis index. Kidney Int Suppl 1975;2:23–29.
16 Gotch FA, Sargent JA: A theoretical definition of minimal acceptable dialysis therapy. Kidney Int Suppl 1978;8:S108–S111.
17 Lowrie EG: History and organization of the National Cooperative Dialysis Study. Kidney Int Suppl 1983;13:S1–S7.
18 Sargent JA: Control of dialysis by a single-pool urea model: the National Cooperative Dialysis Study. Kidney Int Suppl 1983;13: S19–S25.
19 Parker TF, Laird NM, Lowrie EG: Comparison of the study groups in the National Cooperative Dialysis Study and a description of morbidity, mortality, and patient withdrawal. Kidney Int Suppl 1983;13:S42–S49.
20 Harter HR: Review of significant findings from the National Cooperative Dialysis Study and recommendations. Kidney Int Suppl 1983;13:S107–S112.

21 Gotch FA, Sargent JA: A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). Kidney Int 1985;28:526–534.
22 von Albertini B, Miller JH, Gardner PW, Shinaberger JH: High-flux hemodiafiltration: under six hours/week treatment. Trans Am Soc Artif Intern Organs 1984;30:227–231.
23 Rotellar E, Martinez E, Samso JM, Barrios J, Simo R, Mulero JF, Perez D, Bandrès S, Piñol J: Why dialyze more than 6 hours a week? Trans Am Soc Artif Intern Organs 1985;31: 538–545.
24 Rotellar E: Why dialyze more than 6 hours a week?. Trans Am Soc Artif Intern Organs 1985;31:538–545.
25 Degoulet P, Rach I, Rozenbaum W, Aime F, Devries C, Berger C, Rojas P, Jacobs C, Legrain M: Société de Néphrologie. Commission informatique. Programme Dialyse-Informatique. J Urol Nephrol (Paris) 1979; 85:909–962.
26 Kramer P, Broyer M, Brunner FP, Brynger H, Donckerwolcke RA, Jacobs C, Selwood NH, Wing AJ: Combined report on regular dialysis and transplantation in Europe, XII, 1981. Proc Eur Dial Transplant Assoc 1983;19:4–59.
27 Sellars L, Robson V, Wilkinson R: Sodium retention and hypertension with short dialysis. Br Med J 1979;1:520–521.
28 Wizemann V, Kramer W: Short-term dialysis – long-term complications. Ten years experience with short-duration renal replacement therapy. Blood Purif 1987;5:193–201.
29 Held PJ, Levin NW, Bovbjerg RR, Pauly MV, Diamond LH: Mortality and duration of hemodialysis treatment. JAMA 1991;265:871–875.
30 Berger EE, Lowrie EG: Mortality and the length of dialysis. JAMA 1991;265:909–910.
31 Kjellstrand CM, Blagg CR: Differences in dialysis practice are the main reasons for the high mortality rate in the United States compared to Japan. Hemodial Int 2003;7:67–71.
32 Held PJ, Brunner F, Odaka M, Garcia JR, Port FK, Gaylin DS: Five-year survival for end-stage renal disease patients in the United States, Europe, and Japan, 1982 to 1987. Am J Kidney Dis 1990;15:451–457.
33 Held PJ, Blagg CR, Liska DW, Port FK, Hakim R, Levin N: The dose of hemodialysis according to dialysis prescription in Europe and the United States. Kidney Int Suppl 1992;38:S16–S21.
34 Innes A, Charra B, Burden RP, Morgan AG, Laurent G: The effect of long, slow hemodialysis on patient survival. Nephrol Dial Transplant 1999;14:919–922.
35 US Renal Data System, USRDS 2002 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2002.
36 Shinzato T, Nakai S, Akiba T, Yamazaki C, Sasaki R, Kitaoka T, Kubo K, Shinoda T, Kurokawa K, Marumo F, Sato T, Maeda K: Survival in long-term haemodialysis patients: results from the annual survey of the Japanese Society of Dialysis Therapy. Nephrol Dial Transplant 1997;12:884–888.
37 Shinzato T, Nakai S: Do shorter hemodialyses increase the risk of death? Int J Artif Organs 1999;22:199–201.
38 Valderrábano F: Weekly duration of dialysis treatment – does it matter for survival? Nephrol Dial Transplant 1996;11:569–572.
39 Schreiber MJ Jr: Setting the stage. Am J Kidney Dis 2001;38(suppl 4):S1–S10.
40 Tislér A, Akócsi K, Borás B, Fazakas L, Ferenczi S, Görögh S, Kulcsár I, Nagy L, Sámik J, Szegedi J, Tóth E, Wágner G, Kiss I: The effect of frequent or occasional dialysis-associated hypotension on survival of patients on maintenance haemodialysis. Nephrol Dial Transplant 2003;18:2601–2605.
41 Brunet P, Saingra Y, Leonetti F, Vacher-Coponat H, Ramananarivo P, Berland Y: Tolerance of haemodialysis: a randomized crossover trial of 5-hour vs. 4-hour treatment time. Nephrol Dial Transplant 1996;11 (suppl 8):46–51.
42 Daugirdas JT: Pathophysiology of dialysis hypotension: an update. Am J Kidney Dis 2001;38(suppl 4):S11–S17.
43 Sherman RA: Modifying the dialysis prescription to reduce intradialytic hypotension. Am J Kidney Dis 2001;38(suppl 4):S18–S25.
44 Ronco C, Feriani M, Chiaramonte S, Conz P, Brendolan A, Bragantini L, Milan M, Fabris A, Dell'Aquila R, Dissegna D, Crepaldi C, Agazia B, Finochi G, De Dominicas E, La Greca G: Impact of high blood flows on vascular stability in haemodialysis. Nephrol Dial Transplant 1990;5(suppl 1):109–114.
45 National Kidney Foundation: K/DOQI clinical practice guidelines for hemodialysis adequacy, 2000. Am J Kidney Dis 2001;37 (suppl 1):S7–S64.
46 Bergström J, Asaba H, Fürst P, Oulès R: Dialysis, ultrafiltration, and blood pressure. Proc Eur Dial Transplant Assoc 1976;13: 293–305.
47 Locatelli F, Costanzo R, Di Filippo S, Pedrini L, Marai P, Pozzi C, Ponti R, Sforzini S, Redaelli B: Ultrafiltration and high sodium concentration dialysis: Pathophysiological correlation. Proc Eur Dial Transplant Assoc 1978;15:253–259.
48 Graefe U, Follette WC, Vizzo JE, Goodisman LD, Scribner BH: Reduction in dialysis-induced morbidity and vascular instability with the use of bicarbonate in dialysate. Proc Clin Dial Transplant Forum 1976;6:203–209.
49 Graefe U, Milutinovich J, Follette WC, Vizzo JE, Babb AL, Scribner BH: Less dialysis-induced morbidity and vascular instability with bicarbonate in dialysate. Ann Intern Med 1978;88:332–336.
50 Maggiore Q, Pizzarelli F, Zoccali C, Sisca S, Nicolo F, Parlongo S: Effect of extracorporeal blood cooling on dialytic arterial hypotension. Proc Eur Dial Transpl Assoc 1981; 18:597–602.
51 Henrich WL, Hunt JM, Nixon JV: Increased ionized calcium and left ventricular contractility during hemodialysis. N Engl J Med 1984;310:19–23.
52 Perazella MA: Pharmacologic options available to treat symptomatic intradialytic hypotension. Am J Kidney Dis. 2001;38(suppl 4): S26–S36.
53 Stiller S, Bonnie-Schorn E, Grassmann A, Uhlenbusch-Körwer I, Mann H: A critical review of sodium profiling for hemodialysis. Semin Dial 2001;14:337–347.
54 Stefanidis I, Stiller S, Ikonomov V, Mann H: Sodium and body fluid homeostasis in profiling hemodialysis treatment. Int J Artif Organs 2002;25:421–428.
55 Iselin H, Tsinalis D, Brunner FP: Sodium balance-neutral sodium profiling does not improve dialysis tolerance. Swiss Med Wkly 2001;131:635–639.
56 Charra B, Jean G, Hurot J-M, Terrat J-C, Vanel T, VoVan C, Maazoun F, Chazot C: Clinical determination of dry body weight. Hemodial Int 2001;5:42–50.
57 Salem M: Hypertension in the hemodialysis population? High time for answers. Am J Kidney Dis 1999;33:592–594.
58 Rocco MV, Yan G, Heyka RJ, Benz R, Cheung AK; HEMO Study Group: Risk factors for hypertension in chronic hemodialysis patients: baseline data from the HEMO study. Am J Nephrol 2001;21:280–288.
59 Vertes V, Cangiano JL, Berman LB, Gould A: Hypertension in end-stage renal disease. N Engl J Med 1969;280:978–981.
60 Kempner W: Treatment of kidney disease and hypertensive vascular disease with rice diet. NC Med J 1944;5:125–133.
61 Kempner W: Treatment of heart and kidney disease and of hypertensive and arteriosclerotic vascular disease with the rice diet. Ann Intern Med 1949;31:821–856.
62 Murphy RJF: The effect of 'rice diet' on plasma volume and extracellular fluid space in hypertensive patients. J Clin Invest 1950;29: 912–917.
63 Charra B, Bergstrom J, Scribner BH: Blood pressure control in dialysis patients: Importance of the lag phenomenon. Am J Kidney Dis 1998;32:720–724.
64 Khosla UM, Johnson RJ: Hypertension in the hemodialysis patient and the 'lag phenomenon': insights into pathophysiology and clinical management. Am J Kidney Dis 2004;43:739–751.
65 Tuccillo S, De Nicola L, Minutolo R, Scigliano R, Trucillo P, Avino D, Venditti G, De Luca A, Tirino G, Mascia S, Laurino S, Conte G: Hypertension in patients on hemodialysis: the role of salt intake. (in Italian). G Ital Nefrol 2005;22:456–465.

66 Krautzig S, Janssen U, Koch KM, Granolleras C, Shaldon S: Dietary salt restriction and reduction of dialysate sodium to control hypertension in maintenance haemodialysis patients. Nephrol Dial Transplant 1998;13:552–553.
67 Rahman M, Dixit A, Donley V, Gupta S, Hanslik T, Lacson E, Ogundipe A, Weigel K, Smith MC: Factors associated with inadequate blood pressure control in hypertensive hemodialysis patients. Am J Kidney Dis 1999;33:498–506.
68 Twardowski Z: The adequacy of haemodialysis in treatment of chronic renal failure. Acta Med Pol 1974;15:227–243.
69 Dorhout Mees EJ: Volaemia and blood pressure in renal failure: Have old truths been forgotten? Nephrol Dial Transplant 1995;10:1297–1298.
70 Scribner BH: Chronic renal disease and hypertension. Dial Transplant 1998;27:702–704.
71 Scribner BH: Can antihypertensive medications control BP in haemodialysis patients: yes or no? Nephrol Dial Transplant 1999;14:2599–2601.
72 Fishbane SA, Scribner BH: Blood pressure control in dialysis patients. Semin Dial 2002;15:144–145.
73 Hörl MP, Hörl WH: Hemodialysis-associated hypertension: pathophysiology and therapy. Am J Kidney Dis 2002;39:227–244.
74 Locatelli F, Manzoni C: Duration of dialysis session – was Hegel right? Nephrol Dial Transplant 1999;14:560–563.
75 Covic A, Goldsmith DJ, Venning MC, Ackrill P: Long-hours home haemodialysis – the best renal replacement therapy method? QJM 1999;92:251–260.
76 McGregor DO, Buttimore AL, Lynn KL, Nicholls MG, Jardine DL: A comparative study of blood pressure control with short in-center versus long home hemodialysis. Blood Purif 2001;19:293–300.
77 Katzarski KS, Divino Filho JC, Bergström J: Extracellular volume changes and blood pressure levels in hemodialysis patients. Hemodial Int 2003;7:135–142.
78 Vanholder RC, Glorieux GL, De Smet RV: Uremic toxins: removal with different therapies. Hemodial Int 2003;7:156–161.
79 Stiller S, Mann H, Brunner H: Backfiltration in hemodialysis with highly permeable membranes; in Streicher E, Seyffart G (eds): Highly Permeable Membranes. Contrib Nephrol. Basel, Karger, 1985, 46, pp 23–32.
80 Montagnac R, Schillinger F, Milcent T, Croix JC: Hypersensitivity reactions during hemodialysis. Role of high permeability, retrofiltration and bacterial contamination of the dialysate (in French). Nephrologie 1988;9:29–32.
81 Ronco C: Backfiltration: a controversial issue in modern dialysis. Int J Artif Organs 1988;11:69–74.
82 Panichi V, Migliori M, De Pietro S, Taccola D, Andreini B, Metelli MR, Giovannini L, Palla R: The link of biocompatibility to cytokine production. Kidney Int Suppl 2000;76:S96–S103.
83 Kalantar-Zadeh K, Stenvinkel P, Pillon L, Kopple JD: Inflammation and nutrition in renal insufficiency. Adv Ren Replace Ther 2003;10:155–169.
84 Goodkin DA, Young EW: An update on the Dialysis Outcomes and Practice Patterns Study (DOPPS). Contemp Dial Nephrol 2001;22:36–40.
85 Pisoni RL, Young EW, Dykstra DM, Greenwood RN, Hecking E, Gillespie B, Wolfe RA, Goodkin DA, Held PJ: Vascular access use in Europe and the United States: results from the DOPPS. Kidney Int 2002;61:305–316.
86 Allon M, Robbin ML: Increasing arteriovenous fistulas in hemodialysis patients: problems and solutions. Kidney Int 2002;62:1109–1124.
87 Davenport A: Central venous catheters for hemodialysis: how to overcome the problems. Hemodial Int 2000;4:78–82.
88 Bommer J: If you wish to improve adequacy of dialysis, urea kinetics, such as Kt/V, may be the wrong parameter to study. ASAIO J 2001;47:189–191.
89 De Palma JR, Abukurah A, Rubini ME: 'Adequacy' of haemodialysis. Proc Eur Dial Transplant Assoc 1972;9:265–270.
90 Twardowski Z: Significance of certain measurable parameters in the evaluation of haemodialysis adequacy. Acta Med Pol 1974;15:245–254.
91 Ronco C: On-line monitors in hemodialysis: tools or toys. Hemodialysis Today 2001;3:13.
92 Mapes DL, Lopes AA, Satayathum S, McCullough KP, Goodkin DA, Locatelli F, Fukuhara S, Young EW, Kurokawa K, Saito A, Bommer J, Wolfe RA, Held PJ, Port FK: Health-related quality of life as a predictor of mortality and hospitalization: the Dialysis Outcomes and Practice Patterns Study (DOPPS). Kidney Int 2003;64:339–349.
93 Fukuhara S, Lopes AA, Bragg-Gresham JL, Kurokawa K, Mapes DL, Akizawa T, Bommer J, Canaud BJ, Port FK, Held PJ; Worldwide Dialysis Outcomes and Practice Patterns Study: Health-related quality of life among dialysis patients on three continents: the Dialysis Outcomes and Practice Patterns Study. Kidney Int 2003;64:1903–1910.