HEMODIALYSIS OF THE FUTURE: PROLONGED AND/OR FREQUENT DIALYSIS

SUNG-FENG WEN

Despite recent advances in hemodialysis (HD) technology, the overall outcome of patients on conventional HD remains miserably unsatisfactory with a 5-year patient survival rate of 30% in the United States. In search of better HD modalities, a number of investigators in Europe and North America have reported greatly improved outcome with prolonged and/or frequent HD. These include 8h, 3-times-weekly HD from Tassin, France, every-other-day or 4-times-weekly HD from Lecce, Italy, short daily HD (SDHD) from Perugia, Italy, and nocturnal HD (NHD) from Toronto, Canada, with increasing number of other SDHD and NHD programs reported in recent years. The prolonged and/or frequent HD allows better clearance of solutes, smooth ultrafiltration with good control of hypertension, avoidance of solute rebound and disequilibrium symptoms, liberalization of diet with improved nutrition, and better neuro-cognitive function. In addition, NHD is associated with correction of hyperphosphatemia without the use of phosphate binders, improved removal of middle molecules such as β2 microglobulin, and effective control of sleep apnea. Above all, in all of these HD modalities, patient survival is remarkably improved with reduction in hospitalization, and the better quality of life leads to good rehabilitation. Although these reports are based on anecdotal experiences, many with selected groups of patients, the impressive improvement in patient outcome makes it worthwhile to further pursue large scale controlled studies for confirmation as well as for the future guide to improve HD modalities (Acta Nephrologica 2002; 16: 1-11).

Key words: hemodialysis, prolonged hemodialysis, frequent hemodialysis, daily hemodialysis, nocturnal hemodialysis

INTRODUCTION

Hemodialysis (HD) is an epoch-making medical technology introduced clinically in the early 1960’s which made it possible to prolong the lives of patients with end-stage renal disease (ESRD).¹ There have been a number of advances made in recent years to improve the efficiency and prevent the complications of HD, including the development of high-flux membranes for more efficient dialysis,² the designing of computerized ultrafiltration profiling to rigidly control fluid removal, and the use of bicarbonate buffer in the dialysate to avoid the adverse effects of acetate buffer.³ Urea kinetic modeling has also been devised to quantitate and improve dialysis delivery.⁴ Despite these advances in HD technology, the outcome of dialysis patients, who rely on dialysis for survival, remains miserably unsatisfactory. The average rate of 5 year survival of ESRD patients in the United States has been about 30%, and the overall annual mortality rate for dialysis patients in 1990 was 25% and improved only slightly over the succeeding years to 22.4% in 1997.⁵ Thus, a recent United States Renal Data System (USRDS) indicates that ESRD patients aged 50-54 have a life expectancy of only 5-7 years, a grim prospect akin to that of patients with colon cancer or other malignancies.⁶ In view of the unfavorable prognosis for patients who are undergoing conventional HD (CHD), a number of dialysis centers in Europe and North America have initiated trials of drastically revised HD schedules to improve morbidity and mortality of HD patients.⁶-¹¹ In this review, we will discuss the reported experiences of prolonged and/or frequent HD modalities in these centers where remarkable improvements in patient out-
come have been achieved.

**Shortcomings of Conventional Hemodialysis**

CHD is typically carried out 3 times weekly, usually 3-4 hours each time. In the place of cellulosic membranes, which are associated with more episodes of untoward reactions such as complement fixation and release of cytokines, more biocompatible synthetic membranes have become popular and are associated with improved morbidity and mortality.\(^2\) The performance of dialyzers has also improved by the use of high efficiency and high-flux dialyzers.\(^{13}\) However, because of the limited time and frequency of CHD schedule, not only the clearance of uremic toxins can be generally inadequate, but also the rapid and sometimes drastic changes in extracellular fluid (ECF) volume and dialyzable solutes may lead to significant complications during and after dialysis. As intravascular refilling during the process of ultrafiltration is limited to 300-400 ml/h, ultrafiltration exceeding this rate may result in vasoconstriction to guard against hypotension.\(^6,14\) However, in some patients, this compensatory vasoconstriction may be defective, leading to intradialytic hypotension. In addition, resultant vasoconstrictive response to hypotension may reduce the rate of solute clearance from the extracellular compartments. On the other hand, inadequate ultrafiltration relative to interdialytic fluid accumulation may lead to ECF volume expansion, hypertension and congestive heart failure. Also, rapid removal of solutes from one compartment will result in solute disequilibrium between compartments (such as extracellular vs. intracellular compartments) and may induce disequilibrium symptoms such as postdialysis fatigue, weakness, nausea and vomiting. It also causes postdialysis urea rebound and overestimation of dialysis efficiency when single-pool fractional urea clearance, \(\text{spKt/V} = (K \times t) / V\) (K, urea clearance; t, time of dialysis; V, urea distribution volume),\(^4\) is used. Urea rebound can be corrected by the use of \(e\text{Kt/V}\) (equilibrated fractional urea clearance).\(^{15}\) The inadequate removal of phosphate by CHD is also related in part to the compartment effects of phosphate which are more pronounced due to its slower intercompartmental clearance.\(^{16}\) Therefore, hyperphosphatemia is one of the common complications of patients on CHD and plays an important role in the morbidity and mortality of ESRD patients.\(^{17}\)

**Rationale for Frequent and/or Prolonged Dialysis**

Urea has traditionally been used as a marker for low-molecular-weight uremic toxins even though urea itself is not considered the toxin. Therefore, Gotch and Sargent\(^4\) proposed a urea kinetic modeling to quantify the efficiency of removal of low-molecular-weight toxins by HD, using a single-pool formula \(\text{spKt/V}\). During a standard 4-hour HD, removal of urea occurs very rapidly during the first 2 hours amounting to 60-75% of total urea removal.\(^{18}\) This is due to the initially high blood urea concentration and high permeability of the dialyzer membrane to urea. However, as the dialysis is continued, urea removal rate progressively declines owing to the rapid fall in blood urea levels. Therefore, dialysis efficiency is much higher during the first 2 hours compared with that of the second 2 hours. For a total of 12-hour weekly HD, 2-hour daily HD (DHD) performed for 6 days weekly will provide more efficient urea removal (an increase of 20-50%) than that by 4-hour, 3 times weekly schedule of CHD.\(^{19}\) If the total hours of weekly HD is increased to more than 12 hours in DHD, the efficiency of dialysis can be further enhanced. In addition, frequent HD allows more smooth removal of fluid with ultrafiltration by not drastically changing ECF volume during single HD, thereby preventing intradialytic hypotension, and also improves control of hypertension by shortening interdialytic intervals.

Although small-molecular-weight toxins are generally accepted as the likely cause of uremia, additional role of middle-molecular-weight toxins has been proposed.\(^{19}\) The “middle molecule theory” is based on the observations in 1970’s that ESRD patients on peritoneal dialysis had lower incidence of uremic neuropathy compared with those on intermittent HD. It is thought that the higher permeability of peritoneal membrane than HD membranes as well as the prolonged duration of peritoneal dialysis may account for the better clearance of middle molecules which could be responsible for uremic neuropathy. Although the advent of high-flux dialyzers has improved the clearance of middle molecules such as ß2-microglobulin,\(^20\) their limited permeability necessitates longer duration of HD for better clearance of middle molecules. Unlike small-molecular-weight toxins, the concentration gradient of middle molecules across the dialyzer membranes is well maintained during HD because of their slow removal and, therefore, their effective removal becomes time-dependent. Thus, the efficiency of middle molecule removal has been related to square-meter hour (\(M^2 \times h\)) which is the product of surface area of the dialyzer multiplied by hours of dialysis.\(^{21}\) For comparison with a control value, dialysis index (DI) is calculated using the weekly amount of a middle-molecular-weight marker (usually vitamin B\(_6\)) removed, which is divided by the minimum weekly amount of the marker needed to be removed.\(^{22}\) The latter is the least amount of middle molecule removal required to maintain a satisfactory clinical condition based on published clinical experience. A DI of less than 1.0, therefore, indicates inadequate

---

\(^2\) S. F. WEN Vol. 16, No. 1, 2002
removal of middle molecules.

Prolonged HD also allows slower and more gentle removal of fluid and solutes without compromising dialysis efficiency. Thus, slow dialysis not only controls hypertension well with more smooth ultrafiltration but also facilitates solute equilibration between compartments so that symptoms of disequilibrium can be avoided. Longer duration of HD also substantially improves dialysis delivery and efficiency. With nocturnal HD (NHD) which combines both frequent and prolonged HD, the advantage on the removal of both small and middle molecules is further magnified.\textsuperscript{11} Unique to this HD modality is the greatly enhanced clearance of phosphate so that the use of phosphate binders is not required to correct hyperphosphatemia.\textsuperscript{23}

**Examples of Prolonged Hemodialysis**

The most widely hailed example of the benefit of prolonged HD has been reported from Tassin, France by Charra et al. (THD)\textsuperscript{8}. They used Kiil flat-plate or hollow-fiber dialyzers with cellulose membranes (surface area 1.1–1.7 M\textsuperscript{2}). The patients were dialyzed for 8 hours, 3 times weekly in-center or at home, using slow blood flow rate (BFR) of 200-220 ml/min and dialysate flow rate (DFR) of 500 ml/min. They achieved a mean spKt/V of 1.71±0.41 and DI of 1.53±0.45. Their survival rates were reported to be the best in the world at the time, with 83% at 5 years, 69% at 10 years and 49% at 15 years (Fig. 1). Charra et al. has had more than 28 years of experience with 769 patients on THD (Tables 1 and 2).

More recently, prolonged nightly HD (NHD) has been reported by Pierratos et al. from Toronto, Canada.\textsuperscript{11} They performed home HD for 8-10 hours at night during sleep, 6-7 times weekly (Table 1). The rationale for NHD is that it can be performed during the unused time and a large dose of HD can be delivered with its long duration and high frequency. Polysulfone dialyzers with the surface area of 0.7–1.8 M\textsuperscript{2} were used with the BFR of 250-300 ml/min and the DFR of 100-200 ml/min for the slow but prolonged HD. Initially, Ul-dall-Cook internal jugular venous catheters were used with a locking connection (InterLink system) to prevent accidental separation of the catheter. Later they were able to use native arteriovenous fistulae with a buttonhole technique (to puncture the same site) along with the band-fixed needles to ensure its safety. An enuresis alarm system was also added to detect extravasation of blood. A remote monitoring system using the Internet was employed but this was not considered to be critical. Pierratos et al. reported an annual crude mortality rate of 4.4% (vs. about 20% of USRDS) after 5 years of observation in 37 patients on NHD.\textsuperscript{7,40} The mean per-session spKt/V was 1.00±0.23 and the extrapolated weekly spKt/V reached 6 to 7\textsuperscript{11,40} (Table 2). Using dialyzers with a large surface area, O’Sullivan et al. reported weekly spKt/V as high as 13.84±2.12 in 5 patients on NHD.\textsuperscript{24}

**Examples of Frequent Hemodialysis**

The 3-times-weekly schedule of CHD currently adopted by most HD centers is based largely on constraints of time and cost rather than scientific evidence. The Lecce group from Italy (LHD) has reported their experience of 17 years in 224 patients with an every-other-day in-center HD schedule in which the extra off-dialysis day on weekends is avoided\textsuperscript{7} (Table 1). For those patients with large size who tend to be underdialyzed, 4-times-weekly HD was performed. With the increase in the frequency of HD, the authors obtained the mean weekly spKt/V of 4.62±0.76 compared with that of CHD at about 3.6 (Table 2). The patient survival was excellent with 75% at 5 years, 60% at 10 years and 48% at 15 years (Fig. 1). An annual mortality rate was 1.85%.

Buoncristiani et al. from Italy has reported 69 patients with short daily HD (SDHD) at home observed over a period of 15 years\textsuperscript{10} (Table 1). Relatively small polyacrylonitrile dialyzers with the surface area of 1.0–1.5 M\textsuperscript{2} were used with the BFR of 275 ml/min and dialysis duration of 90-120 minutes, 5-7 times weekly. The mean per-session spKt/V was 0.4–0.6 and the extrapolated weekly spKt/V was 2.4–3.6, similar to that of CHD (Table 2). However, solute clearance rate improved when the patients changed from CHD to SDHD as evidenced by a fall in predialysis serum creatinine levels\textsuperscript{7,9,25}. The overall 2 year survival in 72 patients on SDHD compiled from 9 centers in Europe and the United States was 93% with a crude annual mortality of 3.5%\textsuperscript{26} (Fig. 1).

**Comparison of Dialysis Efficiency**

Efficiency of CHD is usually determined by the urea kinetic modeling using per-session spKt/V based on 3-times-weekly HD schedule.\textsuperscript{4} For SDHD, the extrapolated weekly spKt/V is in the range of 2.4–3.6 (0.4–0.6 multiplied by 6)\textsuperscript{10}, which is similar to that of CHD, extrapolated to 3.6 (1.2 x 3). However, as the small-molecular-weight solutes are cleared faster during the first 2 h of HD than those during the second 2 h, actual solute clearance is more efficient with SDHD than that of CHD even though the total weekly HD duration may be the same.\textsuperscript{10,27} This is reflected in the lower predialysis plasma levels of these solutes when the patients change from CHD to SDHD.\textsuperscript{7} During the first 2 to 3 weeks on SDHD, the predialysis solute levels will fall to a low steady-state level and the advantage of increased solute removal may be lost. However, the
new low predialysis solute levels at equilibrium are more advantageous to the patients because of the favorable internal milieu created by the frequent HD.\textsuperscript{27}

In LHD where HD frequency is increased to every other day or 4 times weekly without shortening dialysis time, weekly sp\textit{Kt/V} is significantly increased to 4.62\ ±\ 0.76.\textsuperscript{8} With THD\textsuperscript{8}, the corresponding weekly sp\textit{Kt/V} will be (1.71\ ±\ 0.41) \times 3, and for NHD\textsuperscript{11}, (1.00\ ±\ 0.23) \times 6 (Table 2). However, such extrapolation of weekly sp\textit{Kt/V} for comparison of dialysis adequacy among HD with different frequency is probably invalid. Gotch proposed the standard Kt/V model using a derivative of urea clearance to compare the dialysis efficiency between intermittent and continuous dialysis\textsuperscript{28}. Instead of the mean blood urea nitrogen (BUN), the average predialysis BUN is used in the denominator for clearance calculation\textsuperscript{29}. Because the predialysis BUN is higher than the mean BUN, std\textit{Kt/V} will be lower than sp\textit{Kt/V} except for in continuous dialysis. Thus, weekly std\textit{Kt/V} is about 2.0 for CHD, a value similar to that of continuous ambulatory peritoneal dialysis (CAPD)\textsuperscript{28}. For SDHD,\textsuperscript{7} despite a low per-session sp\textit{Kt/V} of 0.5, weekly std\textit{Kt/V} will reach 2.1–2.5. If per-session sp\textit{Kt/V} can be increased to 1.2 performed 5 times weekly, or 0.9 performed 6 times weekly, it is possible to reach a weekly std\textit{Kt/V} of 3.0 for SDHD\textsuperscript{7}. Lindsay et al. have shown that weekly std\textit{Kt/V} in their SDHD group reached 2.9\ ±\ 0.9 compared with 2.4\ ±\ 0.2 for their control CHD group (P<0.05) during 18 months of observation\textsuperscript{27}. With NHD, because of the combined frequent and prolonged HD, much higher weekly std\textit{Kt/V} of 4.3 can be achieved\textsuperscript{7,11} (Table 2).

The information on middle molecule clearance by various HD modalities is very limited in the literature. Charra et al. reported that THD yielded a mean square-meter hour of 23.8\ ±\ 2.3 Mf/hwk and a DI of 1.53\ ±\ 0.45, indicating highly improved removal of middle molecules by the prolonged HD as compared with CHD\textsuperscript{8} (Table 2). Similar data are not available for NHD but higher values are expected because of its prolonged as well as frequent HD.

Dialysis-related amyloidosis (DRA) is thought to be caused by the accumulation of β2-microglobulin (β2-M) in patients on long-term dialysis and includes the
Table 1. Examples of Hemodialysis Modalities

<table>
<thead>
<tr>
<th>HD Type</th>
<th>THD</th>
<th>LHD</th>
<th>SDHD</th>
<th>NHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Place)</td>
<td>(In-center)</td>
<td>(In-center)</td>
<td>(Home)</td>
<td>(Home)</td>
</tr>
<tr>
<td>No. of Patients</td>
<td>769</td>
<td>224</td>
<td>69</td>
<td>37</td>
</tr>
<tr>
<td>Dialyzer</td>
<td>Cellulose</td>
<td>Cuprophane, AN69, PMMA, polysulfone</td>
<td>Polycryliconitrile</td>
<td>Polysulfone</td>
</tr>
<tr>
<td>S.A. (M²)</td>
<td>1.1 – 1.7</td>
<td>1.2 – 2.02</td>
<td>1.0 – 1.5</td>
<td>0.7 – 1.8</td>
</tr>
<tr>
<td>HD Time</td>
<td>8 h</td>
<td>3 h</td>
<td>90-120 min</td>
<td>8-10 h</td>
</tr>
<tr>
<td>BFR (ml/min)</td>
<td>200 - 220</td>
<td>300 - 500</td>
<td>250 - 300</td>
<td>250 - 300</td>
</tr>
<tr>
<td>DFR (ml/min)</td>
<td>500</td>
<td>500 - 800</td>
<td>500</td>
<td>100 - 200</td>
</tr>
<tr>
<td>Experience (yr)</td>
<td>28</td>
<td>17</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Reference</td>
<td>Charra et al.⁸</td>
<td>Mastrangelo et al.⁹</td>
<td>Buoncristiani et al.¹⁰,²⁵</td>
<td>Pierratos et al.¹¹,⁴⁰</td>
</tr>
</tbody>
</table>

Abbreviations: HD, hemodialysis; THD, Tassin hemodialysis; LHD, Lecce hemodialysis; SDHD, short daily hemodialysis; NHD, nocturnal hemodialysis; S.A., surface area; BFR, blood flow rate; DFR, dialysate flow rate; PMMA, polymethylmethacrylate.

Table 2. Dialysis Efficiency and Nutrition of Patients for the Hemodialysis Modalities

<table>
<thead>
<tr>
<th>HD Type</th>
<th>Per-Session</th>
<th>Weekly</th>
<th>Weekly</th>
<th>DI</th>
<th>DPI</th>
<th>Salb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>spKt/V</td>
<td>stdKt/V</td>
<td>g/kg/d</td>
<td></td>
<td>g/dl</td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>1.2</td>
<td>3.6</td>
<td>2.0</td>
<td>1.0</td>
<td>1.0±0.3</td>
<td>3.8±0.3</td>
</tr>
<tr>
<td>THD</td>
<td>1.71±0.41</td>
<td>5.13</td>
<td>2.5</td>
<td>1.53±0.32</td>
<td>1.33±0.42</td>
<td>4.16±0.48</td>
</tr>
<tr>
<td>LHD</td>
<td>1.22±0.24</td>
<td>4.62±0.76</td>
<td>2.5</td>
<td>NA</td>
<td>1.3±0.3</td>
<td>4.04±0.55</td>
</tr>
<tr>
<td>SDHD</td>
<td>0.4–0.6</td>
<td>2.4–3.6</td>
<td>2.1–2.5*</td>
<td>NA</td>
<td>1.3**</td>
<td>4.35</td>
</tr>
<tr>
<td>NHD</td>
<td>1.00±0.23</td>
<td>6–7</td>
<td>4.3*</td>
<td>NA</td>
<td>1.44±0.20</td>
<td>4.12±0.26</td>
</tr>
</tbody>
</table>

Abbreviations: sp, single-pool; std, standard; K, urea clearance; t, dialysis time; V, urea distribution volume; DI, dialysis index; DPI, dietary protein intake based on protein catabolic rate (PCR); Salb, serum albumin; CHD, conventional hemodialysis; NA, not available; others as in Table 1.

*Data estimated by Lacson and Diaz-Buxo⁷ based on SDHD and NHD reports in the literature.

**Data from Lindsay et al.²⁷.

Development of carpal tunnel syndrome, arthropathy and bone cysts⁹⁰. Removal of β2-M is enhanced by the use of high-flux membrane dialyzers³¹, especially with prolonged and frequent HD. Raj et al. have shown that NHD removed significantly greater amount of β2-M than CHD (585±309 vs. 127±48 mg/wk) using a polysulfone high-flux dialyzer³². Predialysis serum β2-M level decreased from 27.2±11.7 mg/dl to 13.7±4.4 mg/dl by 9 months of NHD and remained stable thereafter. On the other hand, Charra et al. reported 50% incidence of arthropathy in their patients who had been on THD for 165 months using the cellulosic membrane dialyzers³³. The mean predialysis serum β2-M level declined from 60 mg/dl to 40 mg/dl but still remained high, indicating the need to use high-flux membranes as well as more frequent dialysis for more efficient removal of β2-M. Another group of middle molecules, advanced glycation end products (AGE), are also considered as the potential candidates for uremic toxins and have been implicated in the morbidity of dialysis patients including hypertension, atherogenesis, platelet dysfunction and DRA³⁴³⁵. Buoncristiani et al. have shown that predialysis AGE-related total fluorescence was lower after 6 months of SDHD than the corresponding value for CHD control (201.3±36.4 vs. 267.5±141.4 AU/ml, P=0.03)³⁰. However, these values are still 20-fold higher than normal values and not different from those of CAPD patients. Use of the superflux membranes appears to lower serum AGE levels better than the high-flux membranes³⁷. No data are available on the efficacy of AGE removal by NHD but it is expected to be better than SDHD because of longer duration of dialysis.

NUTRITION

It has been well established that nutrition plays an important role in determining the morbidity and mortality of dialysis patients³⁸³⁹. Serum albumin levels have been shown to correlate inversely with the mortality of the dialysis population⁹⁰. In addition to acute phase re-
action including inflammation which may affect serum albumin levels, malnutrition is a major cause for hypoalbuminemia. Therefore, low dietary protein intake (DPI) based on the determination of protein catabolic rate (PCR) is an important predictor of high mortality in ESRD patients on dialysis. THD and LHD patients were able to maintain relatively high DPI at 1.33±0.42 g/kg/d and 1.3±0.3 g/kg/d, respectively. Similarly, Pierratos et al. demonstrated that DPI improved from 1.0±0.3 g/kg/d to 1.44±0.2 g/kg/d following conversion from CHD to NHD (Table 2). Normal mean serum albumin levels were maintained in most of the prolonged and/or frequent HD modalities with 4.2±0.5 g/dl for THD, 4.04±0.6 g/dl for LHD, and 4.1±0.3 g/dl for NHD, compared with 3.8±0.3 g/dl for CHD (Table 2). In 5 reports on SDHD, mean serum albumin levels increased by 2-22% within 6-12 months, and in 4 reports on NHD, the values increased by 0.4-20.5% in 2-12 months. In NHD, despite substantial loss of amino acids by the prolonged dialysis (10-15 g/d), total body nitrogen (TBN) as measured by neutron activation analysis increased in 75% of the 24 patients on NHD, indicating anabolic state of these patients. There were increases in total, essential and branched-chain amino acid concentrations after one year on NHD. However, abnormal ratios of essential/non-essential amino acids, tyrosine/phenylalanine, and valine/glycine were not corrected. In patients on SDHD or NHD, after the initial weight loss from ultrafiltration, typically there would be a progressive increase in dry weight, indicating improvement in the nutritional status as the results of improved appetite, freedom of diet choices and general feeling of well-being.

**Control of Blood Pressure and Cardiovascular Disease**

Cardiovascular disease is the most important cause of mortality in ESRD patients on dialysis with the incidence reaching 20 times of the general population. Hypertension is an important cause of cardiovascular disease and is seen in up to 90% of patients reaching ESRD. Of the many causes of hypertension, ECF volume expansion is the most important factor in ESRD patients and ultrafiltration during dialysis to correct the volume excess is efficacious in controlling hypertension. Both prolonged HD and frequent HD allow smooth fluid removal to achieve the “dry weight” without the intradialytic complications such as hypotension or muscle cramps. THD group reported that less than 3% of their patients required antihypertensive medications after 3 months on dialysis. LHD group showed that hypertension was satisfactorily controlled in 85% of patients with 39% requiring drugs. Vascular instability during ultrafiltration occurred in only 7%. Pierratos reported that blood pressure control in their NHD patients was impressive with most patients achieving the “dry weight” without significant symptoms. Only 6 out of 30 patients required a small dose of a beta-blocker. In 7 reports on SDHD collected by Lacson and Diaz-Buxo, systolic blood pressure fell by 10-33 mmHg after conversion from CHD to SDHD, with the mean systolic blood pressure controlled at 127-141 mmHg, indicating efficient control of hypertension and universal decline in the use of antihypertensive medications (Table 3).

Left ventricular hypertrophy (LVH) has been recognized as a major risk factor of mortality in ESRD patients. Hypertension and impaired arteriolar compliance play an important role in the development of LVH.

<table>
<thead>
<tr>
<th>Table 3. Morbidity of Patients for the Hemodialysis Modalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD Type</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>CHD</td>
</tr>
<tr>
<td>THD</td>
</tr>
<tr>
<td>LHD</td>
</tr>
<tr>
<td>SDHD</td>
</tr>
<tr>
<td>NHD</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; LVH, left ventricular hypertrophy; rHEPO, recombinant human erythropoietin; pt-yr, patient-year; USRDS, United States Renal Data System; others as in Tables 1 and 2.

*Data from Lindsay, et al. 27.

**Data from Lockridge 74 and Pierratos 40.
Although prolonged HD with 8h, 3-times-weekly schedule provided good control of blood pressure, Covic et al. reported that LVH was seen in 76% of patients after 10 or more years. Luik et al. also showed that a similar prolonged HD for 5.9±6.6 years did not prevent an increased stiffening of smooth muscles of the femoral artery. In contrast, Buoncrristiani et al. reported that SDHD was associated with significant regression of LV mass and LV end-diastolic diameter which correlated with the reduction in ECF volume. Similarly, Chan et al. demonstrated that reduction in blood pressure achieved by conversion from CHD to NHD was associated with regression of LVH during the period of observation for at least 2 years. However, they failed to confirm the role of changes in ECF volume in the regression of LVH. Thus, it appears that frequent HD, either SDHD or NHD, is required for the regression of LVH to occur.

Cardiovascular morbidity may be improved by either prolonged or frequent HD through correction of excessive ECF volume and hypertension, improved dialysis efficiency with better clearance of atherogenic factors (such as homocysteine, dimethylarginine, AGEs), correction of anemia, improved nutrition and modification of sleep apnea. SDHD and NHD appear to be more advantageous in the prevention or regression of LVH than the prolonged but less frequent HD (such as THD), suggesting the need for shortening interdialytic period for further cardioprotection.

Anemia and Erythropoietin Requirements

The majority of ESRD patients on dialysis requires the use of exogenous recombinant human erythropoietin (rHEPO) to alleviate anemia. It has been shown that increasing hematocrit (or hemoglobin) to the target levels is associated with improvement in physical performance and quality of life as well as morbidity and mortality in dialysis patients. As the dialyzable uremic toxins are thought to interfere with the erythropoietic response to rHEPO, improved dialysis efficiency may reduce the requirement for rHEPO. In conversion from CHD to prolonged or frequent HD, significant improvements in hematocrit (or hemoglobin) have been reported with increases of 20% for THD, 7.5–70% for SDHD and 9.9% for NHD. LHD patients showed 21% higher hematocrit than that of CHD in the same region. It is estimated that about 20–50% reduction in rHEPO doses can be achieved with SDHD as well as NHD resulting in significant financial savings. In the initial report on NHD, however, the reduced requirement of rHEPO doses could not be demonstrated due to the development of deficiency in iron, vitamin B12, folate and phosphate from prolonged and frequent HD. When these compounds were supplemented, rHEPO requirement was significantly reduced by 40% (Table 3).

Mineral Metabolism

One of the difficulties in correcting abnormal mineral metabolism in ESRD patients on dialysis is related to the inadequate removal of phosphate by CHD leading to positive phosphate balance and hyperphosphatemia. Hyperphosphatemia results in increased Ca x P product, secondary hyperparathyroidism, renal osteodystrophy, metastatic calcifications, and in severe cases, calciphylaxis. Very high incidence of calcifications in the cardiovascular system has been implicated in the increased mortality of ESRD patients on dialysis. CHD is inefficient in phosphate removal in part due to slow equilibration between compartments resulting in prominent postdialysis rebound. As the weekly removal of phosphate by CHD is less than the weekly intestinal phosphate absorption, positive phosphate balance and hyperphosphatemia are fairly common and the majority of HD patients require phosphate binders to restrict phosphate absorption. Although phosphate clearance is said to be improved in SDHD, most patients still require the use of phosphate binders probably at lower doses. NHD is unique in that normalization of serum phosphate without the use of phosphate binders can be achieved within 4 months after starting NHD. In these patients, bone density is maintained or improved and alkaline phosphatase normalized. Disappearance of extraosseous calcifications has also been noticed.

Hospitalization

The average hospitalization rate for CHD patients in the United States is 14.2 hospital days per patient-year. For SDHD, Mohr et al. reported 30% reduction in hospitalization in 18 patients after one year, and Lindsay et al. showed average admission rate of 0.46/patient/yr (control 1.08) and average hospitalization days of 1.54/patient/yr (control 5.25) in 10 patients after 18 months of observation. For NHD, Lockridge et al. reported 68% reduction in hospitalization from 8.9 to 2.8 days per patient-year in 15 patients after 3 years. Similarly, Pierratos showed only 3.5 hospital days per patient-year in 30 NHD patients after 18 months of observation.
Quality of Life
The quality of life assessment of HD patients involves medical, social and psychological factors. Short form-36 (SF-36)47,61,62, Kidney Disease Quality of Life (KDQOL)77,78, Nottingham Health Profile70, Sickness Impact Profile (SIP)79, Choice Health Experience Questionnaire (CHEQ)79, etc. have been used as a measure of quality of life. The areas of medical improvement in quality of life observed in prolonged and/or frequent HD include intradialytic symptomatology (such as muscle cramps, hypotension, lightheadness), postdialysis fatigue, fluid overload, uremic symptoms and time for full recovery from dialysis treatments8,77-79. In most patients, there is a distinct feeling of well-being which is generally related to the slow and more gentle removal of solutes and fluid by the prolonged HD6,80 or the shorter but more frequent HD which is better tolerated than CHD due to the shorter interdialytic periods with less accumulation of solutes and fluid for removal27,77,78,81. There are also improvements in cognitive function80,82 and psychological stress scores76,83. One drawback of SDHD is related to the social isolation from increased time requirements for the frequent HD sessions7,84. This can be prevented in NHD as HD is performed at night during sleep. In NHD, there is increased autonomy of the patients to control treatment, enabling them to seek employment and plan for their life, so that many of them resume their previous job or obtain a new job61. Also in NHD, those patients with fragmented uremic sleep, frequently associated with sleep apnea, will show improved apnea-hypopnea index with normalization of the sleep pattern59. There appears to be a preference for NHD over SDHD for those who temporarily switch to SDHD but become anxious to return to NHD later40,85.

Cost and Finances
Charra et al. reported that their THD program was most cost effective in France due to improved morbidity of the patients6,30. The operating cost of NHD in Canada is similar to that of CAPD and slightly less than that of in-center HD6,11,40. The increase in direct costs (supplies and labor) of SDHD is off-set by savings from decreased use of drugs and lower number of hospitalizations78,86. The doses of rHEPO and antihypertensive medications can be substantially reduced93,86 and reuse of dialyzers in the home settings60 can also add to the cost savings. Obviously home HD will provide more economic benefit than in-center HD. The improved quality of life with successful rehabilitation will eventually determine the economic contribution to both the patients and the society6,11,78,86. In the United States, the current reimbursement system of capitation by the Medicare Administration will increase the direct costs for SDHD and NHD and become a disincentive to the establishment of these HD modalities. The economic and logistic feasibility of SDHD and NHD in the United States is currently being evaluated7,86.

Concerns and Prospects
Human errors and mechanical failures in SDHD and NHD are said to be rare6. However, the increased frequency and duration of HD raise the concern of potential increase in accidental bleeding, air emboli and other complications6,87. Also, prolonged HD may remove not only uremic toxins but also essential plasma components such as vitamins, amino acids, minerals and trace metals6,23,88-90. Pierratos et al. reported that NHD was associated with vitamin B12 and folate deficiency and phosphate depletion requiring replacement of these compounds11. There are also concerns about increased exposure to dialyzer materials and endotoxins91 as well as the prolonged effects of dialysis-related catabolism caused by the release of inflammatory mediators such as cytokines92. Another concern is related to the durability of vascular access which needs to be used frequently for SDHD and NHD, and, therefore, access complications and failure may increase. However, this has not been borne out with the use of either central catheters with the InterLink system11 or arteriovenous fistulae with the buttonhole cannulation technique10,93, both showing the access problem rate not worse than that of CHD10,27,87,84. Little information is available on the use of synthetic graft in frequent HD.

The overall favorable reports on the benefits and outcome of the prolonged and/or frequent HD are derived from the anecdotal experiences in the selected groups of patients (in SDHD and NHD) without the objective and controlled comparison with those of CHD. The patients selected for SDHD and NHD tend to be younger and highly motivated with less comorbidity11,37. Thus, the selection bias may contribute to the observed favorable outcome6 and may also limit the feasibility of these HD modalities to a defined group of dialysis population. Nevertheless, the reported improvements in patient survival and quality of life are so impressive and remarkably different from those of CHD population that both SDHD and NHD deserve recognition and further evaluation10,27. Both modalities are well tolerated and can be accepted at least by certain groups of HD population10,27,40. More systematic and well designed, prospective controlled studies in large groups of patients are needed to determine the feasibility of...
these new HD modalities to be carried out as a standard form of HD in ESRD population.

REFERENCES


