

## Newer Paradigms in Renal Replacement Therapy: Will They Alter Cardiovascular Outcomes?

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Cardiovascular disease remains the leading cause of death in patients with end-stage renal disease (ESRD) [1]. Etiologic factors include persistent myocardial injury exacerbated by volume and pressure overload as well as endothelial dysfunction [2,3]. Impaired endothelial-dependent dilation is becoming recognized as an early dysfunction in both non-ESRD and uremic populations [4,5] and has been associated with traditional cardiovascular risk factors such as insulin resistance [6], hypertension [7], and hyperlipidemia [8]. Patients receiving conventional hemodialysis (4 hours/session, three treatments/week) have impaired endothelial responsiveness, decreased vascular compliance, and activated vasoconstrictor systems [5,9]. Patients with severe endothelial dysfunction and vascular stiffness tend to also have left ventricular hypertrophy (LVH), impaired left ventricular systolic function, and accelerated atherosclerosis. These conditions are known to be independent risk factors for cardiac death in ESRD [10]. Indeed, in patients undergoing conventional hemodialysis, poor uremic control, hypertension, LVH, and impaired systolic function are markers for adverse cardiovascular events [3,11–13].

In addition, hyperphosphatemia and hyperparathyroidism have been shown to be independent cardiovascular risk factors in ESRD [14].

Elevated phosphate levels may contribute to the development of uremic calcific vasculopathy [15,16]. Furthermore, recent evidence suggests that hyperparathyroidism may cause interstitial cell activation, thereby leading to cardiac fibrosis [17]. It can be postulated that myocardial fibrosis reduces cardiac compliance, resulting in an increased tendency for arrhythmias.

To date, conventional hemodialysis has not significantly altered the aforementioned markers for adverse cardiovascular events. Patients with ESRD continue to suffer an astonishingly high annual mortality rate, approximately 20% [1].

Other alternatives to conventional hemodialysis include short daily hemodialysis (2 hours/session, six sessions/week) and nocturnal home hemodialysis (6 hours/session, five to six sessions/week). Short daily hemodialysis was first described in 1968 by DePalma et al [18]. The rationale for short daily hemodialysis is that it provides enhanced hemodynamic stability and increases solute removal by delivering dialysis when the plasma–dialysate gradient is highest. Nocturnal home hemodialysis was described in 1996 by Uldall et al [19]. It is delivered at home, 5 to 6 nights/week, at variable blood and dialysate flow rates. One of the rationales for the preference of nocturnal home hemodialysis is that it increases middle molecule clearance because of the increased frequency and length of dialysis treatments [20–22]. Increased middle molecule clearance has been associated with higher patient survival [23,24].

Both short daily hemodialysis and nocturnal home hemodialysis have been associated with significant clinical benefits. Specifically, nocturnal

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home hemodialysis has been associated with improved solute removal [20–22], increased quality of life [23–26], and improved anemia control with decreasing erythropoietin requirements [27–29]. In addition, recent studies have demonstrated improvement in sleep disorders, as evidenced by an improvement in the number of apnea-hypopnea episodes [30], as well as reduced overall costs because of lowered fixed modality expenditures [31,32].

Furthermore, nocturnal hemodialysis has been associated with significant benefits in cardiovascular parameters. This article (1) reviews the documented effects of intensive hemodialysis on blood pressure control, cardiac geometry and left ventricular systolic function, lipid profiles, calcium-phosphate metabolism and parathyroid hormone (PTH) levels, homocysteine levels, and sleep apnea and autonomic modulation of heart rate, and (2) provides possible mechanistic explanations to account for these observed changes.

### Blood pressure

Hypertension related to ESRD has been recently reviewed [33]. From a simplified hemodynamic standpoint, elevated arterial pressure may be caused by either extracellular volume expansion or increased total peripheral resistance. Volume and pressure overload have been classically associated with the development of hypertension [34]. Volume overload is usually attributed to sodium and water retention [35], whereas pressure overload is attributed to increased peripheral resistance and increased arterial stiffness [36]. Renal replacement therapy improves volume overload by removing excess extracellular fluid and thus lowering blood pressure.

Both short daily hemodialysis and nocturnal hemodialysis have been shown to result in improved blood pressure control in ESRD. In 1999, Woods et al [37] reported in a retrospective review that 75% of patients receiving short daily hemodialysis had normal blood pressure values without the concomitant use of antihypertensive agents [37]. Likewise, Fagugli et al [38] reported in their cross-over prospective design that short daily hemodialysis resulted in improvements in blood pressure control and decreased antihypertensive requirements. Systolic blood pressures fell from  $148 \pm 19$  mm Hg to  $128 \pm 12$  mm Hg ( $P < 0.01$ ). Similarly, diastolic blood pressures fell from  $73 \pm 5$  mm Hg to  $67 \pm 8$  mm Hg ( $P = 0.01$ ). Both investigators measured the change in extracellular fluid content and attributed

the reductions in blood pressure to a decrease in extracellular fluid volume.

In a similar fashion, nocturnal home hemodialysis has been consistently associated with improved blood pressure control along with decreased antihypertensive requirements. Raj et al [39] described superior blood pressure control coincident with a decrease in the number of antihypertensive agents in patients switching from conventional hemodialysis to nocturnal home hemodialysis. In a controlled cohort design, investigators at the University of Toronto studied 28 patients undergoing nocturnal home hemodialysis for a minimum of 2 years and compared these patients with 13 self-care conventional hemodialysis patients [40]. Systolic blood pressures fell from  $145 \pm 20$  mm Hg to  $122 \pm 13$  mm Hg ( $P < 0.001$ ), and diastolic pressures fell from  $84 \pm 15$  mm Hg to  $74 \pm 12$  mm Hg ( $P = 0.02$ ). These decreases occurred even though the use of antihypertensive medications was reduced (from 1.8 per patient to 0.3 per patient;  $P < 0.05$ ). Unlike the studies of short daily hemodialysis, the Toronto experience did not find significant changes in extracellular volume. Similar results were reported by Nesrallah et al [41] at the University of Western Ontario. They found that both short daily hemodialysis and nocturnal hemodialysis resulted in blood pressure normalization, but extracellular fluid control was significant only in short daily hemodialysis. This finding suggests that short daily hemodialysis improves blood pressure through improved control of extracellular volume, whereas other mechanisms, such as enhanced solute removal or decreased neurohormonal factors, may be involved in the nocturnal home hemodialysis cohort. Chan and colleagues [42] tested this hypothesis by studying 18 consecutive patients who switched from conventional to nocturnal home hemodialysis. They found that as the dialysis dose per session (Kt/V) increased after 2 months, mean arterial pressure decreased from  $102 \pm 3$  to  $90 \pm 2$  mm Hg. There was an associated decrease in total peripheral resistance (from  $1967 \pm 235$  to  $1499 \pm 191$  dyne.s.cm<sup>-5</sup>;  $P < 0.01$ ) and in plasma norepinephrine levels (from  $2.66 \pm 0.4$  to  $1.96 \pm 0.2$  nmol;  $P = 0.04$ ). Although endothelium-dependent vasodilation could not be elicited during conventional hemodialysis, it was restored after a 2-month period of nocturnal hemodialysis. In addition, brachial artery responsiveness to nitroglycerin improved from  $6.9 \pm 2.8\%$  to  $15.7 \pm 1.6\%$  ( $P < 0.05$ ). No

significant change in weight and extracellular volume was demonstrated.

### Cardiac geometry and systolic function

As with hypertension, volume and pressure overload has been associated with the development of LVH [34,43–45] and with increased cardiovascular mortality in patients with ESRD [46]. Volume and pressure overload is characterized by a generalized increase in left ventricular mass, enlargement in left ventricular end-diastolic diameters, or an increase in left ventricular wall thickness [43,44]. These factors culminate in a combination of eccentric and concentric LVH. Although ventricular hypertrophy is an initial beneficial adaptive response, continuous hemodynamic overload leads to a maladaptive hypertrophic phenotype that results in congestive heart failure [13,47,48]. At the cellular level, there is a demonstrable increase in myocardial size, mass, and interstitial collagen content. At the molecular level, fetal gene expression occurs along with abnormal protein production. Hence, congestive heart failure is the end result of LVH progression, as systolic and diastolic dysfunction develops. Patients with congestive heart failure benefit from volume removal through renal replacement therapy. Their ventricular preload is decreased, resulting in improved left ventricle filling, and stroke volume is decrease because of diastolic ventricular interaction [49].

Similar to the beneficial antihypertensive outcomes, the Toronto experience demonstrated a significant regression in left ventricular mass index (LVMI) from  $147 \text{ g/m}^2$  to  $122 \text{ g/m}^2$  when patients switched from conventional hemodialysis to nocturnal home hemodialysis [40]. A consistent finding was the positive correlative between systolic blood pressure and LVMI.

In addition to the beneficial changes in blood pressure control and LVMI regression, the Toronto experience has also demonstrated the positive impact of nocturnal home hemodialysis on impaired left ventricular ejection fraction [50]. In a cohort study, six ESRD patients with coexistent congestive heart failure switched from conventional hemodialysis to nocturnal home hemodialysis. Along with a significant decrease in systolic blood pressure (from  $138 \pm 10 \text{ mm Hg}$  to  $120 \pm 9 \text{ mm Hg}$ ;  $P = 0.04$ ), these patients had a significant increase in their left ventricular ejection fraction (from  $28 \pm 12\%$  to  $41 \pm 18\%$ ;  $P = 0.01$ ). These changes occurred even though the number of

vasoactive medications was decreased (from 2.2 to 0.7/patient;  $P = 0.02$ ) and without a change in extracellular fluid volume. These findings show that, for improved cardiovascular indices, enhanced uremic clearance and hemodynamic effects are more important than decreased extracellular volume content.

### Lipid profile

In the general population, a low high-density lipoprotein (HDL) level and a high triglyceride level are independent risk factors for the development of atherosclerosis and coronary artery disease [51–54]. More than 90% of hemodialysis patients have a characteristic dyslipidemia that includes increased concentrations of triglyceride-rich apolipoprotein B-containing lipoproteins, very-low-density lipoproteins, and intermediate-low-density lipoproteins and decreased HDL [55]. These changes promote atherosclerosis [56,57]. Bugeja and Chan [58] conducted a prospective study in a cohort of 11 patients with ESRD, studying their lipid profiles before and after conversion from conventional hemodialysis to nocturnal home hemodialysis [58]. They found a significant decrease in triglyceride concentrations (from  $2.05 \pm 0.30$  to  $1.01 \pm 0.14 \text{ mmol/L}$ ;  $P < 0.001$ ), a significant increase in HDL concentrations (from  $1.17 \pm 0.13$  to  $1.65 \pm 0.14 \text{ mmol/L}$ ;  $P < 0.001$ ), and a significant increase in the HDL/triglyceride ratio (from  $0.26 \pm 0.03$  to  $0.35 \pm 0.02$ ;  $P < 0.001$ ). Although the exact mechanisms for these changes are unknown, the authors postulated that superior uremic clearance allowed the restoration of lipase function and modification of lipoprotein composition by removing uremic inhibitors such as pre-B-HDL.

### Calcium–phosphate metabolism and hyperparathyroidism

An elevated calcium–phosphate product and hyperphosphatemia can contribute to cardiovascular disease in ESRD patients through vascular calcifications and hardening. Increasing evidence suggests that improving phosphate control reduces the incidence in vascular calcifications [59]. Conventional hemodialysis results in suboptimal removal of phosphate because phosphate is mobilized slowly from the deep tissues during dialysis. This slow mobilization results in an early decline in the serum phosphate levels during dialysis and subsequent loss of the serum–dialysate concentration gradient. During the last hour of dialysis and

after its termination, serum phosphate levels rebound [60]. Although high-flux dialyzers and the convective process can increase phosphate removal, the main determinant of phosphate removal is the duration of dialysis. High-frequency dialysis likewise increases phosphate removal because it allows daily equilibration of serum phosphate levels, thereby restoring the blood–dialysate gradient [22]. Nocturnal home hemodialysis has been shown to double the weekly phosphate removal as compared with conventional hemodialysis. In fact, many patients are able to discontinue phosphate binders within 1 week after initiating nocturnal home hemodialysis and can take an unrestricted-phosphate diet [61]. Dissolution of tumoral extraosseous calcifications has been reported in one patient receiving nocturnal hemodialysis every 24 hours [62].

Because patients receiving nocturnal home dialysis no longer require calcium-containing phosphate binders, they are typically in a negative calcium balance and often require a higher dialysate calcium level than patients receiving conventional hemodialysis [63,64]. Dialysate calcium levels can be adjusted by adding powdered calcium chloride into the acid concentrate to achieve the desired pre- and postdialysis calcium and PTH levels. The average dialysate calcium level was  $1.6 \pm 0.1$  mmol/L at one center [63]. This relatively increased calcium bath led to a significantly lower PTH level after 6 months (from  $580 \pm 590$  ng/mL to  $228 \pm 295$  ng/mL).

### Homocysteine levels

Hyperhomocysteinemia is a documented risk factor for atherosclerotic outcomes, and homocysteine level have been shown to be elevated in more than 85% of hemodialysis patients. High-flux or super-flux hemodialysis has consistently failed to normalize total homocysteine (tHcy) levels. There are limited data examining the effects of nocturnal home hemodialysis on tHcy levels. Friedman et al [65] compared predialysis plasma tHcy levels in 23 patients undergoing nocturnal home hemodialysis with those of 31 patients undergoing conventional hemodialysis [65]. The tHcy levels for the nocturnal home hemodialysis patients were significantly lower ( $12.7$  versus  $20.0$   $\mu\text{M}$ ,  $P < 0.0001$ ), as was the prevalence of mild-to-moderate hyperhomocysteinemia ( $>12$   $\mu\text{M}$ ; nocturnal home hemodialysis, 57%; conventional hemodialysis, 94%;  $P = 0.002$ ). The authors concluded that tHcy levels are significantly lower

among nocturnal home hemodialysis patients than in patients receiving conventional dialysis. Similarly, a study conducted by Nesrallah and colleagues [66] found that patients who underwent either short daily hemodialysis or nocturnal home hemodialysis had significantly lower homocysteine levels than patients receiving conventional dialysis [66].

### Nocturnal hypoxemia

Nocturnal hypoxemia is a known trigger of the sympathetic nervous system, which is in turn associated with the development of concentric LVH [67]. Zoccali and colleagues [68] recently postulated that nocturnal hypoxemia may be an overlooked cardiovascular risk factor linked to mortality in ESRD. The correction of sleep apnea is yet another modality that may lower cardiovascular mortality risk in ESRD patients [69]. Sleep studies were performed on 14 subjects who were enrolled in the first nocturnal hemodialysis project in Toronto [30]. Seven of these patients had sleep apnea as defined by the apnea–hypopnea index of more than 15 episodes/h. The apnea–hypopnea index in these patients decreased from  $46 \pm 19$  to  $9 \pm 9$  per hour ( $P = 0.006$ ). There was an associated increase in the minimal oxygen saturation from  $89.2 \pm 1.8\%$  to  $94.1 \pm 1.6\%$  ( $P = 0.005$ ). There was no effect on daytime sleepiness when measured before and after conversion to nocturnal hemodialysis.

Decreased heart-rate variability has been correlated with cardiovascular mortality in healthy subjects and following myocardial infarction [70]. ESRD patients have been shown to have decreased heart variability and increased sympathetic activity, factors that are correlated with increased mortality [71]. Chan et al [72] analyzed heart-rate variability during stage II sleep in nine ESRD patients when receiving conventional hemodialysis and 6 to 15 months after conversion to nocturnal hemodialysis. Patients receiving nocturnal hemodialysis had a significantly reduced duration of nocturnal hypoxemia and increased heart-rate variability during sleep. At present, it is unclear how these observations may affect clinical outcomes.

### Cardiovascular events and survival outcomes

Because nocturnal home hemodialysis is a relatively new modality, few outcome studies examining cardiovascular events and survival outcomes are available; in fact, no hard data are available to date. Patient survival in 83 patients at the Humber

River Regional Hospital has been reported to be 81% over a 5-year period [73]. One retrospective study reported lower hospitalization rates in patients receiving daily hemodialysis than in patients receiving conventional hemodialysis [74]. Similar findings were found in a prospective study comparing two cohorts of patients receiving conventional and nocturnal hemodialysis [75]. One should be careful in interpreting these results, because the higher-than-expected survival rates and the lower-than-expected hospitalization rates may be related to a case-mix bias.

### Physiologic link between nocturnal home hemodialysis and cardiovascular improvements

Both short daily hemodialysis and nocturnal home hemodialysis improve blood pressure readings. The mechanism for short daily hemodialysis seems to be related primarily to improved removal of extracellular volume achieved through more frequent renal replacement therapy.

Nocturnal home hemodialysis, however, has not been shown to decrease extracellular volume significantly. Its superior effects may be attributed to improved clearance of uremic solute through the greater frequency and duration of renal replacement therapy. The physiologic impact of nocturnal home hemodialysis on cardiovascular outcomes is being actively investigated at the University of Toronto. Conventional hemodialysis creates tremendous fluctuations in extracellular volume and biochemical status [76]. Nocturnal home hemodialysis more closely approximates the natural physiology of the kidneys than do other modalities of renal replacement therapy, and this closer approximation of natural function may be an important factor [77]. Indeed, beneficial effects have been described in improved endothelial-dependent and -independent vasodilation, decreased total peripheral resistance, decreased plasma norepinephrine levels, correction of sleep apnea, improved autonomic modulation of heart rate during sleep, and normalization of calcium-phosphate-PTH balance.

### Future directions

A randomized, controlled trial is currently underway through the National Institute of Health-sponsored Frequent Hemodialysis Network trial. Patients enrolled in this trial will be randomly assigned to receive nocturnal home hemodialysis, short daily dialysis, or conventional hemodialysis

in accordance with the current Kidney/Dialysis Outcome Quality Initiative adequacy guidelines. The cardiovascular effects of intensive hemodialysis modalities will be compared with standard therapy. This study, and others, are required to understand more clearly the impact of frequent intensive hemodialysis on cardiovascular event rates in ESRD patients.

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