

Will Incremental Hemodialysis Preserve Residual Function and Improve Patient Survival?

Andrew Davenport

University College London Center for Nephrology, Royal Free Hospital, University College London Medical School, London, United Kingdom

ABSTRACT

The progressive loss of residual renal function in peritoneal dialysis patients is associated with increased mortality. It has been suggested that incremental dialysis may help preserve residual renal function and improve patient survival. Residual renal function depends upon both patient related and dialysis associated factors. Maintaining patients in an over-hydrated state may be associated with better preservation of residual renal function but any benefit comes with a significant risk of cardiovascular

consequences. Notably, it is only observational studies that have reported an association between dialysis patient survival and residual renal function; causality has not been established for dialysis patient survival. The tenuous connections between residual renal function and outcomes and between incremental hemodialysis and residual renal function should temper our enthusiasm for interventions in this area.

Most patients embark on hemodialysis with some degree of residual renal function. Its preservation is strongly associated with patient and technique survival for peritoneal dialysis patients. Comparative studies have suggested that initiating treatment with peritoneal dialysis offers patients a survival advantage over hemodialysis in the short term (1). In most centers, patients treated by hemodialysis lose residual renal function more rapidly than those on peritoneal dialysis, and as such there has been renewed interest in how patients initiate hemodialysis and whether practice techniques influence loss of residual renal function.

In the United States, payment for chronic hemodialysis treatments are linked to achieving a defined dose of dialysis, in terms of urea clearance (Kt/V), and this has led to the practice of starting patients on thrice weekly treatments designed to achieve the target Kt/V , irrespective of residual renal function.

It has been questioned as to whether this approach might lead to a more rapid loss of residual renal function by reducing the drive to hyperfiltration of the remaining functioning nephrons (2). As such there has been renewed interest in initiating hemodialysis as an adjuvant to residual renal function, akin to incremental peritoneal dialysis.

Although a practitioner of incremental hemodialysis, I believe there are a number of factors that need some consideration. Firstly, the greatest risk for death for hemodialysis patients is in the first 90 days after transition from nondialysis dependent chronic kidney disease (CKD) to dialysis (3). Indeed, mortality in this period can be much greater for those initiating hemodialysis compared to stage 5 CKD patients opting for conservative nondialysis care (4). The majority of studies which have investigated transitioning to dialysis have shown that mortality is predominantly associated with underlying patient co-morbidity and lack of predialysis specialist nephrological care (3). This would suggest that the patient trajectory is an important determinant of outcome, as patients starting hemodialysis precipitously following an acute deterioration in renal function on a background of CKD—(such as following an acute coronary syndrome or development of cast nephropathy) have much higher mortality rates than those with slower progressive trajectories (5). The alternative scenario, CKD patients attending specialist nephrology clinics, shows no benefit from earlier compared to later initiation of dialysis (6).

On the other hand, earlier initiation of dialysis in the IDEAL trial did not disadvantage patients, suggesting that a planned start of dialysis in patients

Address correspondence to: Andrew Davenport, UCL Centre for Nephrology, Royal Free Hospital, London NW3 2QG, UK, Tel.: +44-2074726457, Fax: 44-2073178591, or e-mail: andrewdavenport@nhs.net.

Conflict of interest: The author has no conflict of interest.

Seminars in Dialysis—Vol 28, No 1 (January–February) 2015 pp. 16–19

DOI: 10.1111/sdi.12320

© 2014 The Authors. *Seminars in Dialysis* published by Wiley Periodicals, Inc.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

benefiting from prior specialist nephrology care did not have increased mortality during the transition phase. As such the introduction of thrice weekly HD in this group of patients with a lower CKD trajectory did not result in excessive mortality, suggesting that hemodialysis per se may not carry a major mortality risk. However, these patients predominantly dialyzed using arterio-venous fistulae, rather than catheter access, whereas CKD patients who have a sudden rapid deterioration in renal function requiring dialysis, invariably dialyze using catheters with increased risk for systemic bacteremia and mortality (7).

Although there are many reported benefits for preserving residual renal function in hemodialysis patients (8), it is unclear whether its loss is a major driver for the increased mortality observed during the dialysis transition phase. Indeed, the Tassin center approach, associated with one of the highest reported survival rates for hemodialysis patients, renders more than 90% of patients initiating dialysis anuric within the first 90 days (9). There are no prospective trials reporting that preservation of residual renal function improves survival for hemodialysis patients.

Preserving Residual Function in Hemodialysis Patients

The majority of hemodialysis patients are volume overloaded prior to their dialysis session, and loose both extracellular and intracellular fluid during treatment (10). Bioimpedance devices have been recently introduced into dialysis centers to aid clinical decision making assessing fluid status in dialysis patients (11). Cross-sectional and longitudinal observational studies have reported that overhydrated dialysis patients do not have greater or better preservation of residual renal function (12,13). So, simply keeping patients overhydrated does not appear to preserve residual function, but risks hypertension and left ventricular hypertrophy.

On the other hand too rapid a removal of fluid during hemodialysis risks hypotension (14), and repetitive hypotensive episodes may potentially lead to renal ischemia and premature loss of residual renal function. Intradialytic hypotension is more common in centers which target lower pre and post-dialysis blood pressures (15), and patients attending for dialysis at, or close to their target weight (16,17). Although this approach risks anuria, blood pressure is lowered and left ventricular hypertrophy regresses.

As most dialysis centers do not regularly measure residual function, it remains to be established whether preventing intradialytic hypotension by using bioimpedance and dialysis machine technology (18), can preserve residual renal function. However, observational studies have shown that patients with more intradialytic hypotensive episodes (19), and those deliberately dialyzed to achieve lower bioimpedance targets (20) lost residual renal function quicker. The more frequent nocturnal hemodialysis

trial reported faster loss of residual renal function with more frequent and longer dialysis sessions (21). Whether this was due to achieving greater clearances or more hypotensive episodes remains unclear.

In contrast, a Spanish study reported better preservation of residual renal function in patients hemodialyzed twice weekly compared to thrice weekly, with a similar loss of residual renal function to peritoneal dialysis patients (22). However, this study was confounded by lead time bias, as patients with greater residual renal function initiating dialysis were dialyzed twice weekly, whereas those with lower residual renal function were dialyzed thrice weekly. Similarly other studies advocating twice weekly hemodialysis are also confounded by retrospective analysis, no propensity matching with differences in lead time and patient co-morbidity (23,24).

If twice a week hemodialysis were to offer an advantage in terms of preserving residual renal function, then it may do so by keeping patients volume expanded and reducing episodes of intradialytic hypotension (25). However, this practice risks worsening blood pressure control and left ventricular hypertrophy (25). Supplemental thrice weekly hemodialysis would potentially control over-hydration better than twice weekly treatments, and also, by reducing the amount of fluid to be removed during any one session, would potentially reduce the risk of intradialytic hypotension. This is supported by recent prospective trial using incremental dialysis which reported very few intradialytic hypotensive episodes and observed that residual renal function was better preserved than that reported from historic series but this study (26).

However, it must be recognized that factors other than hypovolemia and episodes of intradialytic hypotension determine the loss of residual renal function. Due to the paucity of prospective studies in hemodialysis patients, most of the information on residual renal function emanates from peritoneal dialysis patients. These studies have consistently reported that the loss or residual renal function depends upon the original renal disease, typically faster loss for cystic and diabetic kidney disease compared to glomerulonephritis (27). Similarly, those with proteinuric renal diseases are more likely to have a faster loss of RRF (28), as are those with peripheral and cardiovascular disease (29). Residual renal function tends to be lost earlier in those patients initiating dialysis with lower residual renal function, but this could be confounded by lead time bias. Although angiotensin enzyme converting enzyme inhibitors and angiotensin receptor blockers have been associated with preservation of residual renal function, they have not been shown to have any protective effect in hemodialysis patients (26,30).

Measurement of Residual Renal Function

Incremental dialysis depends on the ability to measure residual renal function and then adjusting

the dose of dialysis accordingly. Unfortunately there is no simple blood test to readily assess residual renal function; the obvious measure, urine volume, is an inaccurate assessment. The “gold” standards of inulin, ⁵¹chromium ethylenediaminetetra-acetic acid (EDTA), and iothalamate radiocontrast clearance are more accurate for determining residual renal function in dialysis patients than urine collections but are impractical in clinical practice. As such, 24 hour urine collections remain the standard method, with clinical guidelines recommending calculating the mean of both creatinine and urea clearance, as urea underestimates and creatinine overestimates inulin clearance, and then adjusting clearance to a body surface area of 1.73 m² (31).

Putting aside the problems of reliably collecting 24 hour urine collections, both serum urea and creatinine are affected by dietary protein intake, and creatinine also depends upon muscle mass and physical activity, and changes in intestinal bacteria flora alter urea and creatinine gastrointestinal losses. In addition, there is the effect of chromagens which accumulate in CKD and interfere with the standard laboratory colorimetric Jaffe reaction (32). Another confounder is the timing of the urine collection in relation to dialysis sessions, especially when patients are dialyzed twice or thrice weekly. The composite urea and creatinine clearance then has to be adjusted to body size. It is many years since the original equations linking anthropomorphic measurements to body surface area were made, and over time populations have changed, with increasing body fat (33). As such the original link between body surface area and muscle mass, particularly in the dialysis population, with an increased risk of sarcopenia may no longer hold (34,35).

As such, although 24 hour urine collections underpin measuring residual renal function in dialysis patients, one has to appreciate the limitations of the measurements and confounding errors. The final difficulty is then equating this measured residual renal clearance with a dialysis derived urea clearance, based on an estimate of total body water (36,37).

Summary

Although there is a marked increased risk of mortality as CKD5 patients transition to hemodialysis, it is most likely that this is due to patient co-morbidity and unplanned dialysis starts, rather than simply the loss of residual renal function. Maintaining residual renal function potentially allows the patient a better quality of life with more liberal diet and fluid intake. However, there is no definitive evidence that preserving residual renal function improves patient survival. Loss of residual renal function is predominantly determined by the primary renal disease and patient co-morbidity. However, hypovolemia, and repetitive episodes of hypotension are associated with faster loss of residual renal function, and as such incremental dialysis

may help to preserve residual renal function. As dialysis dosing is not simply a matter of small solute clearance, and dialysis should also be prescribed to achieve volume control and maintain electrolyte and acid base balance. Although there are financial and patient benefits for twice weekly incremental dialysis, it is more likely that a thrice weekly approach will better preserve residual renal function.

Funding

Royal Free Hospital.

References

- Liem YS, Wong JB, Hunink MG, de Charro FT, Winkelmayer WC: Comparison of hemodialysis and peritoneal dialysis survival in The Netherlands. *Kidney Int* 71(2):153–158, 2007
- Bricker NS, Morrin PA, Kime SW Jr: The pathologic physiology of chronic Bright's disease. An exposition of the “intact nephron hypothesis”. *Am J Med* 28:77–98, 1960
- Foley RN, Chen SC, Solid CA, Gilbertson DT, Collins AJ: Early mortality in patients starting dialysis appears to go unregistered. *Kidney Int* 86(2):392–398, 2014
- Carson RC, Juszcak M, Davenport A, Burns A: Is maximum conservative management an equivalent treatment option to dialysis for elderly patients with significant comorbid disease? *Clin J Am Soc Nephrol* 4(10):1611–1619, 2009
- Rosansky SJ: Renal function trajectory is more important than chronic kidney disease stage for managing patients with chronic kidney disease. *Am J Nephrol* 36(1):1–10, 2012
- Cooper BA, Branley P, Bulfone L, Collins JF, Craig JC, Fraenkel MB, Harris A, Johnson DW, Kesselhut J, Li JJ, Luxton G, Pilmore A, Tiller DJ, Harris DC, Pollock CA: IDEAL Study: A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med* 363(7):609–619, 2010
- Li PK, Chow KM: Infectious complications in dialysis—epidemiology and outcomes. *Nat Rev Nephrol* 8(2):77–88, 2011
- Vilar E, Farrington K: Emerging importance of residual renal function in end-stage renal failure. *Semin Dial* 24(5):487–494, 2011
- Chazot C, Wabel P, Chamney P, Moissl U, Wieskotten S, Wizemann V: Importance of normohydration for the long-term survival of haemodialysis patients. *Nephrol Dial Transplant* 27(6):2404–2410, 2012
- Papakrivopoulou E, Booth J, Pinney J, Davenport A: Comparison of volume status in asymptomatic haemodialysis and peritoneal dialysis outpatients. *Nephron Extra* 2(1):48–54, 2012
- Davies SJ, Davenport A: The role of bioimpedance and biomarkers in helping to aid clinical decision-making of volume assessments in dialysis patients. *Kidney Int* 86(3):489–496, 2014
- Davenport A, Sayed RH, Fan S: Is extracellular volume expansion of peritoneal dialysis patients associated with greater urine output? *Blood Purif* 32(3):226–231, 2011
- McCafferty K, Fan S, Davenport A: Extracellular volume expansion, measured by multifrequency bioimpedance, does not help preserve residual renal function in peritoneal dialysis patients. *Kidney Int* 85(1):151–157, 2014
- Davenport A: Intradialytic complications during hemodialysis. *Hemodial Int* 10(2):162–167, 2006
- Davenport A, Cox C, Thuraisingham R: Achieving blood pressure targets during dialysis improves control but increases intradialytic hypotension. *Kidney Int* 73(6):759–764, 2008
- Booth J, Pinney J, Davenport A: Do changes in relative blood volume monitoring correlate to hemodialysis-associated hypotension? *Nephron Clin Pract* 117(3):c179–c183, 2011
- Kumar S, Khosravi M, Massart A, Potluri M, Davenport A: Are serum to dialysate sodium gradient and segmental bioimpedance volumes associated with the fall in blood pressure with hemodialysis? *Int J Artif Organs* 37(1):21–28, 2014
- Davenport A: Can advances in hemodialysis machine technology prevent intradialytic hypotension? *Semin Dial* 22(3):231–236, 2009
- FHN Trial Group; Chertow GM, Levin NW, Beck GJ, Depner TA, Eggers PW, Gassman JJ, Gorodetskaya I, Greene T, James S, Larive B, Lindsay RM, Mehta RL, Miller B, Ornt DB, Rajagopalan S, Rastogi A, Rocco MV, Schiller B, Sergeyeva O, Schulman G, Ting GO, Unruh ML, Star RA, Klinger AS: In-center hemodialysis six times per

- week versus three times per week. *N Engl J Med* 363(24):2287–2300, 2010
20. Davenport A: Dialysis: bioimpedance spectroscopy for assessment of fluid overload. *Nat Rev Nephrol* 9(5):252–254, 2013
 21. Daugirdas JT, Greene T, Rocco MV, Kaysen GA, Depner TA, Levin NW, Chertow GM, Ornt DB, Raimann JG, Larive B, Klinger AS; FHN Trial Group: Effect of frequent hemodialysis on residual kidney function. *Kidney Int* 83(5):949–958, 2013
 22. Teruel-Briones JL, Fernández-Lucas M, Rivera-Gorriñ M, Ruiz-Roso G, Díaz-Domínguez M, Rodríguez-Mendiola N, Quereda-Rodríguez-Navarro C: Progression of residual renal function with an increase in dialysis: haemodialysis versus peritoneal dialysis. *Nefrología* 33(5):640–649, 2013
 23. Lin YF, Huang JW, Wu MS, Chu TS, Lin SL, Chen YM, Tsai TJ, Wu KD: Comparison of residual renal function in patients undergoing twice-weekly versus three-times-weekly haemodialysis. *Nephrology* 14(1):59–64, 2009
 24. Lin X, Yan Y, Ni Z, Gu L, Zhu M, Dai H, Zhang W, Qian J: Clinical outcome of twice-weekly hemodialysis patients in Shanghai. *Blood Purif* 33(1–3):66–72, 2012
 25. Liu S, Diao Z, Zhang D, Ding J, Cui W, Liu W: Preservation of residual renal function by not removing water in new hemodialysis patients: a randomized, controlled study. *Int Urol Nephrol* 46(1):83–90, 2014
 26. Kjaergaard KD, Peters CD, Jespersen B, Tietze IN, Madsen JK, Pedersen BB, Novosel MK, Laursen KS, Bo Bibby BM, Strandhave C, Jensen JD: Angiotensin blockade and progressive loss of kidney function in hemodialysis patients: a randomized controlled trial. *Am J Kidney Dis* doi: 10.1053/j.ajkd.2014.05.011, 2014
 27. Haynes R, Staplin N, Emberson J, Herrington WG, Tomson C, Agodoa L, Tesar V, Levin A, Lewis D, Reith C, Baigent C, Landray MJ; SHARP Collaborative Group: Evaluating the contribution of the cause of kidney disease to prognosis in CKD: results from the study of heart and renal protection (SHARP). *Am J Kidney Dis* 64(1):40–48, 2014
 28. Szeto CC, Kwan BC, Chow KM, Chung S, Yu V, Cheng MS, Leung CB, Law MC, Li PK: Predictors of residual renal function decline in patients undergoing continuous ambulatory peritoneal dialysis. *Perit Dial Int* doi: 10.3747/pdi.2013.00075, 2014
 29. Palomo-Piñón S, Mora-Villalpando CJ, Del Carmen Prado-Urbe M, Ceballos-Reyes GM, De Jesús Ventura-García M, Avila-Díaz M, Rodríguez OO, Paniagua-Sierra JR: Inflammation and myocardial damage markers influence loss of residual renal function in peritoneal dialysis patients. *Arch Med Res* 45(6):484–488, 2014
 30. Davenport A: Maintaining residual kidney function in dialysis patients – is there a role for angiotensin converting enzyme inhibitors or receptor blockers? *Am J Kidney Dis* 2014 (in press)
 31. Peritoneal Dialysis Adequacy Work Group: NKF-K/DOQI Clinical Practice Guidelines for peritoneal dialysis adequacy: update 2006. *Am J Kidney Dis* 48(Suppl. 1):S98–S129, 2006
 32. Davenport A, Cholongitas E, Xirouchakis E, Burroughs AK: Pitfalls in assessing renal function in patients with cirrhosis – potential inequity for access to treatment of hepatorenal failure and liver transplantation. *Nephrol Dial Transplant* 26(9):2735–2742, 2011
 33. Davenport A, Hussain Sayed R, Fan S: The effect of racial origin on total body water volume in peritoneal dialysis patients. *Clin J Am Soc Nephrol* 6(10):2492–2498, 2011
 34. Fürstenberg A, Davenport A: Assessment of body composition in peritoneal dialysis patients using bioelectrical impedance and dual-energy x-ray absorptiometry. *Am J Nephrol* 33(2):150–156, 2011
 35. Fürstenberg A, Davenport A: Comparison of multifrequency bioelectrical impedance analysis and dual-energy X-ray absorptiometry assessments in outpatient hemodialysis patients. *Am J Kidney Dis* 57(1):123–129, 2011
 36. Davenport A: Differences in prescribed Kt/V and delivered haemodialysis dose – why obesity makes a difference to survival for haemodialysis patients when using a ‘one size fits all’ Kt/V target. *Nephrol Dial Transplant* 28(Suppl. 4):iv219–iv223, 2013
 37. Kumar S, Khosravi M, Massart A, Potluri M, Davenport A: The effects of racial differences on body composition and total body water measured by multifrequency bioelectrical impedance analysis influence delivered Kt/V dialysis dosing. *Nephron Clin Pract* 124(1–2):60–66, 2013