The natural history of symptomatic cardiac conduction-system disease in end-stage renal disease

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Among patients with end-stage renal disease (ESRD) treated with renal replacement therapy, cardiovascular disease is a leading cause of morbidity and mortality. Although the incidence and outcomes of congestive heart failure, strokes, myocardial infarction and other atherosclerotic complications among dialysis patients have been well characterized, scant attention has been paid to cardiac conduction system diseases. Sudden death is the direst manifestation of such a disease and is now eminently treatable with the use of permanent pacemakers (PPMs) and automatic intracardiac defibrillator devices [1]. Nonetheless, few studies have evaluated the magnitude of this problem.

In this issue of Nephrology Dialysis Transplantation, Wang et al. [2] report the incidence of cardiac conduction system disorders that are severe enough to lead to implantation of a PPM utilizing the large Taiwan National Health Insurance Database. Between 2000 and 2010, the investigators identified over 28,000 newly diagnosed ESRD patients [9700 on peritoneal dialysis (PD) and 18,771 on hemodialysis (HD)] and 113,769 controls randomly selected without clinical kidney disease to evaluate the incidence of PPM implantation through 31 December 2011. Control subjects were matched to the ESRD group by age sex and index year. There were 143 PPM implantations in the control group (n = 113,769) and 139 in the ESRD group (n = 28,471). The incidence rate of PPM implantation per 1000 patient years was 0.25 in controls and 1.27 among those with ESRD. The incidence rate of PPM implantation was 0.88 in PD patients and 1.46 in HD patients. Compared with the control group, the crude hazard ratio adjusted for age and sex was 5.1 for ESRD. The crude hazard ratio among PD patients was 3.5 and among HD patients 5.8. The higher incidence rate among HD patients was not surprising given that HD patients had a greater age, and higher incidences of coronary artery disease, diabetes mellitus, stroke, dyslipidemia and congestive heart failure, and they also used more antiplatelet agents. Adjusting for the baseline differences revealed that the adjusted hazard ratio among PD patients was 2.4 compared with 3.2 among HD patients. In propensity-matched analyses, the two adjusted hazard ratios were not statistically different. Accordingly, compared with PD, HD per se was not associated with increased risk of pacemaker implantation.

Compared with the control group, the crude hazard ratio of pacemaker implantation was 5.1 in ESRD. Adjusted for various comorbidities such as diabetes, previous coronary artery disease, stroke, etc., the hazard ratio fell to 2.9 [95% confidence interval (CI) 2.22–3.89]. Thus, it appears that ESRD is strongly associated with conduction system disease and not simply related to conditions such as the presence of diabetes or coronary artery disease. ESRD is plausibly related to accelerated conduction system disease for several reasons [3]. It has now long been recognized that chronic kidney disease is associated with cardiomyocyte capillary mismatch [4]. Ischemia to the conduction system is therefore a real possibility in ESRD. Enhanced myocardial fibrosis may promote the substrate for arrhythmogenesis in this vulnerable population. Like the propensity for vascular calcification, it is possible that the cardiac conduction system is also vulnerable to calcify [5]. This may further worsen the cardiac conduction system disease. Volume overload and therefore cardiac chamber dilatation are common in this population and may predispose to arrhythmias. ESRD is a state of enhanced sympathetic activation, which may further promote arrhythmias [6].

An interesting observation made in this cohort is that the tempo of disease among the PD and HD patients was quite different. The incidence rate of PPM implantation (per 1000 patient-years) was 0.54 in the PD group and 1.99 HD group in the first year of follow-up. In an analysis that was propensity score matched, the adjusted hazard ratio was 3.81 (95% CI 1.41–10.3). When the follow-up time was 1–3 years, the incidence rate in the PD group was 0.68 versus 1.32 in the HD group. When the follow-up time was >3 years, the incidence rate of PPM implantation was 1.30 in the PD group and 1.28 in the HD. Thus, it appears that there is an accelerated rate of conduction system disease among HD patients. However, if ESRD patients lived >3 years, PD patients ultimately had the same degree of conduction system disease as those on HD.
Among those on PD, 8.3% of the patients had a kidney transplant compared with 4% on HD. Mortality among PD patients was 27% compared with 30% in HD.

Thus, HD patients were a sicker group. The accelerated senescence of the conduction system disease among HD patients may simply be due to them being older, and more coronary artery disease, more diabetes and more cardiovascular risk factors that were present in this cohort. We can only speculate that larger excursions in electrolytes and volume may be causally related to accelerated conduction system senescence among patients on HD. The loss of residual renal function among PD patients is an important reason for failure of the modality in the long term. It is possible that among PD patients this may also promote the senescence of the cardiac conduction system and an accelerated rate of PPM implantation later in the course of illness.

Sudden cardiac death (SCD) is the unexpected natural death from a cardiac cause generally ≤1 h from the onset of symptoms, in a person without any current medical condition that would appear immediately fatal [7]. Patients with known coronary artery disease and chronic kidney disease were found in the Duke Databank for Cardiovascular Disease to have an 11% increase in the risk of SCD for every 10 mL/min decrement in estimated glomerular filtration rate, with HD patients having the highest risk at 24.2 SCDs per 1000 patient-years [8]. This is compared with 1.9 deaths due to SCD per 1000 patient-years in the general population [9]. HD patients have also been found to have a high incidence of appropriate shocks when implanted with a cardioverter-defibrillator, with one study finding the incidence of first appropriate ICD shock at 1 year to be 10.7% for non-dialysis patients versus 37.5% for patients on dialysis (P < 0.0001) [10]. Furthermore, a recent study found that in 50 HD patients with implantable cardiac monitoring devices undergoing thrice weekly HD, 8 experienced SCD over a mean follow-up of 18 ± 4 months. All eight SCD patients developed severe bradycardia and asystole as their terminal event, and all SCDs occurred during the long 72-h inter-dialyses period [11]. This calls into question whether we should continue to dialyze patients three times a week [12]. The contemporary management strategy for patients with traditional risk factors for an increased risk of SCD, such as a history of aborted SCD or heart failure with a left ventricular ejection fraction of ≤35%, is the implantation of an ICD [1]. All modern transvenous ICDs also have a right ventricular pacing function and protect against bradyarrhythmias as well as ventricular tachyarrhythmias.

In the HD patient, infectious complications from implanted cardiac devices are relatively high compared with the general population [13] and can be an area of concern for both the referring and implanting physicians. In general, this increased risk of infectious complications should not sway the referring or implanting physician from implanting potentially lifesaving cardiac devices in the otherwise appropriate ESRD patient given their increased risk of appropriate pacing indications as described by Fung-Chang Sung et al., their increased risk of SCD [8] and their increased rate of appropriate ICD shocks after ICD implantation [10]. It should be kept in mind that in any patient being considered for an ICD, with ESRD or otherwise, life expectancy must be ≥1 year [1].

Because we know that incidence of conduction system disease is high in HD population, and it can lead to SCD, the main question is that how to prevent these? The main symptoms are syncope, pre-syncope or dizziness; however, these patients have many other causes of these symptoms including orthostatic hypotension during and after HD, autonomic neuropathy and drug-induced hypotension. Careful monitoring of some of these high-risk patients for conduction system disease with long-term ECG monitoring with an event monitor or implantable loop recorder may be beneficial. Intracardiac leadless pacemakers are now available and should be studied in the ESRD population as they may provide a decreased infectious risk in this vulnerable population [14]. Retrieval of these pacemakers has not been a major issue so far. In ESRD patients who have an ICD indication, subcutaneous implantable cardioverter-defibrillators (S-ICD) are currently available to avoid hardware in the intravascular space. Currently, S-ICDs have no pacing capability however, and cannot protect against potentially symptomatic or deadly bradyarrhythmias. Because of this and the high incidence of brady-arrhythias or asystolic cardiac arrest in the HD patient [11], S-ICDs should not be preferentially chosen in the dialyses patient over transvenous ICDs simply to avoid potential infectious issues unless there are other compelling reasons. In the future, S-ICDs may be a more reasonable option for the ESRD patient as they will be able to communicate remotely with a leadless pacemaker for a device that can both pace and defibrillate the heart as needed with a minimal intracardiac presence [15].

(See related article by Wang et al. Permanent cardiac pacing in patients with end-stage renal disease undergoing dialysis. *Nephrol Dial Transplant* 2016; 31: 2115–2122)

**REFERENCES**

Exercise limitation in chronic kidney disease: deep seas and new shores

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Among their many burdens, patients with chronic kidney disease (CKD) live with both a reduction in physical strength and a diminished capacity for exercise—they struggle to do what their healthy, age-matched counterparts take for granted. Understanding the cause of their functional impairment has proved both elusive and difficult to interpret. Early studies had to contend with comorbidities ranging from systemic acidosis and inflammation to muscle wasting and malnutrition, often compounded for those with end-stage kidney disease often by inadequate dialysis. Despite these complexities, before 1990 many considered the predominant cause of exercise limitation in CKD to be related to the associated anaemia. This was not an unreasonable hypothesis: the primary focus of study in these patients was usually aerobic exercise and, without the means to correct the deficiency in their oxygen-carrying capacity, patients’ limited functional ability was considered most closely related to the prevailing, and often severe, anaemia. As a story it made sense and, for marked anaemia, it probably still does, but the theory lacked an appreciation of the largely irrelevant effects of milder degrees of anaemia on exercise limitation in CKD. After epoetin became a clinical reality in the late 1980s, it slowly became apparent that even near-normal haemoglobin concentrations were at best only partially successful in addressing patients’ limited well-being and functional capacity [1].

In the post-epoetin era, the complexities of functional limitations in CKD were gradually accepted by researchers and clinicians alike as studies identified that elements such as muscle bulk and isometric strength determined functional capacity more than reduced oxygen delivery. In fact, oxygen delivery for the degree of exercise performed was probably sufficient [2]. However, concerns were also raised that such changes were both permanent and progressive, with evidence offibrotic change and fibre atrophy on muscle specimens. One study identified little improvement in exercise capacity or peak oxygen consumption between paediatric haemodialysis patients following transplantation, and a continued decline in exercise capacity over 2 years was found in another longitudinal study of non-dialysis CKD patients as renal function decreased, despite a stable haemoglobin concentration [3, 4]. Additional contributory factors were also identified: myocytic anomalies and enzymatic dysfunction (especially Na⁺-K⁺ATPase), subclinical systemic inflammation and mitochondrial dysfunction all became recognized as contributing to patients’ limited exercise potential [5]. Such studies, however, were exacting as well as difficult to perform, they usually comprised a limited number of patients and, most telling, often produced conflicting findings. It became evident that the truth of exercise limitation in CKD was far more complex than anyone had envisaged only two decades earlier.

Perhaps partly because of such difficulties, the focus in recent years has shifted to some extent to the pragmatic recognition that patients with CKD can both feel and perform better by adopting simple exercise regimens. Dialysis patients in particular have been studied, with demonstrably improved muscle function and exercise capacity following regular training. Such efforts are both laudable and necessary; yet, if we do not resolve the interplay behind the reality, our progress will remain limited.

In this issue of *Nephrology Dialysis Transplantation*, Van Craenenbroek et al. [6] present the results of an observational,