Heart rate variability in patients with end-stage renal disease: an emerging predictive tool for sudden cardiac death?

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Patients with end-stage renal disease (ESRD) have an elevated cardiovascular mortality. Although much interest has been focused on the understanding of the accelerated nature of their coronary artery disease, sudden cardiac death (SCD) has emerged as the single largest cause of cardiac death in our patient population. Multiple traditional and novel cardiovascular risk factors contribute to the particular vulnerability of dialysis patients towards SCD, including myocardial ischaemia, left ventricular hypertrophy/dilatation, electrolytes abnormalities, volume overload, sleep apnoea and sympathetic overactivity [1]. Despite our best efforts with revascularization and medical therapy, the risk of arrhythmically mediated death remains elevated and uncorrected in ESRD [2]. Careful examination of the impairments in heart rate variability (HRV) may allow for better insights into the ‘non-ischemic’ contributors of SCD and may have the potential to serve as both a monitoring and a prognostic tool in the ESRD population.

There are multiple validated methods in quantifying HRV, which have been reviewed previously [3–5]. Commonly used techniques include time domain and spectral or frequency domain analysis of HRV. Basic pharmacological studies using animals and humans have formed the rationale for identifying high frequency (HF) power [0.15 Hz] as an indicator of parasympathetic modulation of heart rate given that the administration of atropine or other blockers of the parasympathetic nervous system was able to abolish the HF component of HRV. Similarly, classical manoeuvres in augmenting central sympathetic outflow (e.g. tilt, lower body negative pressure) have resulted in increases in low frequency (LF) [0.05–0.15 Hz] power of HRV [6]. Further refinements of normalized ratios such as LF/HF have been used to estimate the sympathetic/vagal influence of HRV. It is important to note that most of the validation studies were performed in normal subjects using a before and after design, which should be considered within the limitations of this technique [4].

Notwithstanding these limitations of HRV methodologies, abnormalities of HRV have been reported in multiple disease states [5]. ESRD patients have consistently been demonstrated to have a withdrawal in parasympathetic modulation of heart rate in conjunction with an increase in the sympathetic input to the sino-atrial node [7–9]. In addition, changes in HRV during dialysis treatments have been used to predict haemodynamic instability [10]. Moreover, anomalies in HRV were associated with a higher likelihood of co-existing left ventricular hypertrophy [11]. Importantly, impairments in HRV derived from 24-h ambulatory electrocardiography recording in 383 chronic haemodialysis patients were independently associated with the incidence of all cause and cardiovascular death after adjustment for traditional cardiovascular risk factors [12]. Larger prospective cohort studies will be required to determine the sensitivity, specificity and predictive value of HRV for relevant clinical adverse events and cardiovascular mortality in the ESRD population.

Why would HRV be uniquely suited for the prognostication of ESRD patients? From a simplistic viewpoint, abnormalities in HRV provide insights into the neurohormonal milieu and the mechanical strain exerted on to the sino-atrial node. ESRD patients are known to have sympathetic overactivity. Because central sympathetic outflow to skeletal muscle is increased in patients with native kidneys in situ but not after bilateral nephrectomy, sympathetic activation in ESRD has been attributed to a chemosensitive excitatory reflex arising from the failing kidney [13]. One of the common denominators of disease states characterized by sustained elevation in systemic levels of catecholamines is SCD. In addition to the arrhythmogenicity of sympathetic overactivity, myofibrillar degeneration, wall motion abnormalities and free radical release are now recognized as part of the ‘neurocardiac’ lesions of sympathetic overload [14]. Indeed, elevated circulating levels of plasma norepinephrine have been associated with the development of left ventricular hypertrophy [15] and incident cardiovascular events [16] in ESRD. Intriguingly, where SCD has been
used as a clinical endpoint in these relevant disease states (e.g., chronic heart failure), alterations in HRV, in particular, LF and LF:HF to be independent predictors [17]. Other than the neurohormonal milieu, mechanical stretch of the sino-atrial node directly reduces HRV in animal models. Horner et al. used a specially designed piston device to mechanically stretch the sino-atrial node in a pig heart model. These investigators were able to demonstrate that the stretch of the sino-atrial node reduces the HF power of HRV [18]. The clinical implication of this finding is particularly relevant in patients with recurrent fluid overload, which may explain in part the withdrawal of parasympathetic modulation of heart rate seen in ESRD.

SCD is a major challenge in the care of patients with ESRD, which will require further innovative therapeutic strategy to be tested. The prognostic value of reductions in HRV for sudden death and major arrhythmic events in the non-ESRD literature has been substantiated [19,20]. The examination of HRV in ESRD is particularly relevant given the altered neurohormonal milieu and the repetitive insult of fluid overload especially seen in the conventional haemodialysis population. The predictive accuracy and the risk stratification potential of abnormal HRV in ESRD merit further examination in a large prospective ESRD cohort.

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References


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