



# Prognostic indicators of cardiovascular risk in renal disease

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Although the annual mortality rate for end-stage renal disease (ESRD) is decreasing, likely due to an increase in kidney transplantation rate, the survival probability for ESRD patients from day one of dialysis has not changed, and is still poor with a 5-year survival rate of approximately 34%. This is contributed to by a high prevalence of cardiovascular disease, which is the leading cause of death in ESRD patients. In order to improve survival outcomes, patients at high risk of cardiovascular related mortality need to be identified. Heart rate variability (HRV), baroreceptor sensitivity, and baroreceptor reflex effectiveness index can be used to assess heart rate control and may predict cardiovascular mortality. This paper will discuss how HRV, baroreceptor sensitivity, and baroreceptor reflex effectiveness index are altered in renal disease and the utility of these indices as markers of cardiac risk in this patient population.

**Keywords:** baroreceptor reflex sensitivity, heart rate variability, end-stage renal disease

## INTRODUCTION

Cardiovascular disease is highly prevalent chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients, and occurs due to the development of vasculopathies, e.g., atherosclerosis or arteriosclerosis, or cardiomyopathy, resulting in ischemic heart disease or heart failure (Parfrey and Foley, 1999; Shamseddin and Parfrey, 2011). The high incidence of cardiovascular disease in CKD/ESRD patients is due to a greater prevalence of traditional cardiovascular risk factors, e.g., hypertension, hyperlipidemia, and diabetes, and risk factors associated with a chronic uremic state, e.g., volume overload, anemia, and oxidative stress (Parfrey and Foley, 1999). Consequently, cardiovascular disease is the leading cause of death in ESRD patients, accounting for ~40% of deaths in dialysis patients (U.S. Renal Data System, 2011).

Sudden cardiac death is the major cause of cardiac mortality in ESRD (Herzog, 2003; U.S. Renal Data System, 2011). The incidence of sudden cardiac death increases as the stage of kidney disease increases. In a retrospective study of renal disease patients with coronary artery disease, the incidence of sudden cardiac death was 3.8 events per 1000 patient-years in patients with an estimated glomerular filtration rate (eGFR)  $\geq 60$  ml/min, 7.3 in patients with an eGFR between 15–59 ml/min, and 24.2 in dialysis patients (Pun et al., 2009). The prognosis for ESRD patients who have been resuscitated following a cardiac arrest is abysmal, with 60% of patients dying in the first 48-h (Karnik et al., 2001), and a 30-day and 1-year survival rate of only 32 and 15%, respectively (Herzog, 2003). Nevertheless, despite these disturbing statistics, the high cardiovascular mortality rate in ESRD patients may be reduced, as the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers, independent of any antihypertensive effect, is associated with a lower risk of mortality (Efrati et al., 2002; Fang et al., 2008). In order to reduce the cardiac mortality rate in ESRD, however, CKD or ESRD patients at a high risk of cardiac death need to be identified early, to allow appropriate clinical intervention.

Abnormalities in autonomic function, namely sympathetic overdrive and parasympathetic insufficiency, play a key role in the susceptibility to sudden cardiac death (Schwartz and Stone, 1980; Schwartz et al., 1988, 1992). There is now an overwhelming amount of evidence showing the involvement of the autonomic nervous system in the genesis of cardiovascular disease in CKD. This includes sympathetic overactivity, as muscle (Converse et al., 1992; Hausberg et al., 2002; Klein et al., 2003), but not skin (Park et al., 2008; Grassi et al., 2009), sympathetic nerve activity is elevated. The increase in muscle sympathetic nerve activity occurs early in the disease progression (Grassi et al., 2011) and likely increases the risk of mortality, as elevated plasma noradrenaline levels are associated with both an increased risk of all-cause mortality and cardiovascular events in ESRD patients without heart failure (Zoccali et al., 2002). Conversely, parasympathetic nerve activity is reduced, evidenced by reduced heart rate (HR) responses to deep breathing, valsalva maneuver, and standing up (Agarwal et al., 1991; Sahin et al., 2006). This sympatho-vagal imbalance undoubtedly contributes to the increased risk of sudden cardiac death in CKD/ESRD.

Heart rate variability (HRV) and baroreceptor reflex sensitivity (BRS) can be used to examine autonomic regulation of HR. In myocardial infarction survivors, reduced HRV and BRS have been shown to be highly predictive of an increased risk of cardiac mortality (La Rovere et al., 1998, 2001). This review will discuss how HRV, BRS, and an additional measure of baroreflex function, baroreceptor effectiveness index (BEI), are altered in renal disease, and their utility in predicting cardiac risk in ESRD patients.

## HEART RATE VARIABILITY

Heart rate variability reflects the ability of the sinoatrial node to adaptively alter HR in response to sympathetic and parasympathetic inputs, respiration, circadian rhythm, and hormonal and thermoregulatory influences (Stauss, 2003). In many disease states, the sinoatrial node is less able to alter HR, and instead the heart beats like a metronome. Irrespective of the underlying cause, a

reduction in HRV may predict sudden cardiac death (Molgaard et al., 1991; La Rovere et al., 2003; Kataoka et al., 2004).

Heart rate variability can be assessed in a variety of ways: time-domain analysis (statistical or geometrical), frequency-domain analysis, or non-linear methods (Task Force of the ESC and NASPE, 1996). Statistical time- and frequency-domain analyses of HRV are the most commonly used methods. Statistical time-domain parameters of HRV include SD of all normal R–R intervals (SDNN), SD of the average R–R interval in all 5-min segments (SDANN), square root of the mean squared differences of successive R–R intervals (RMSDD), and the proportion of adjacent R–R intervals that are more than 50 ms apart (pNN50). Frequency-domain indices of HRV include total (TP), high frequency (HF), low frequency (LF), and very low frequency (VLF) power. Total power and SDNN correlate, reflecting overall HRV. HF power, RMSDD, and pNN50 are analogous and reflect vagal and respiratory mediated changes in HR. LF power reflects the capacity of both the parasympathetic and sympathetic nervous systems to alter HR, and cardiovascular reflexes, such as the, baroreceptor reflex to buffer changes in HR. VLF and SDANN reflect long-term changes in HR (Task Force of the ESC and NASPE, 1996; Zaza and Lombardi, 2001; Guzik et al., 2007). A summary of how the various HRV indices are altered in CKD/ESRD is presented in **Table 1**.

The Renal Research Institute-CKD study, a four center prospective cohort study of adults with moderate to severe CKD (stages 3–5), demonstrated that HRV decreased as renal disease severity increased. In this study, SDNN, SDANN, VLF, and LF:HF power was lower in stage 5 non-dialysis CKD patients compared with stage 3 and 4 CKD patients (Chandra et al., 2011). Furthermore, in type 1 diabetics with overt nephropathy, SDNN, RMSDD, pNN50, SDANN, and LF power are positively related to creatinine clearance, such that a decline in creatinine clearance is associated with a diminution of HRV (Burger et al., 2002). Thus, the progressive decline in renal function that occurs in renal disease alters autonomic and long-term regulation of HR, resulting in a reduction in HRV.

Few studies have examined the difference in HRV parameters between stage 4/5 non-dialysis CKD and dialysis patients. Those that have demonstrate no difference in the spectral indices (i.e., TP, HF, and LF) between stage 4/5 non-dialysis CKD and dialysis patients (Mylonopoulou et al., 2010; Roumelioti et al., 2010), while time-domain indices (e.g., SDNN and SDANN) may increase in dialysis patients (Mylonopoulou et al., 2010). The lack of difference in spectral HRV indices may indicate that the inhibitory effect of renal disease on HRV has reached maximal levels prior to the need for renal replacement therapy.

Several co-variables affect HRV estimates in ESRD/CKD patients, the most significant of which is diabetes. Regardless of disease stage, diabetic CKD patients have lower HRV indices (Yamanaka et al., 2005; Mylonopoulou et al., 2010; Chandra et al., 2011). The combination of renal disease and diabetes has a greater inhibitory effect on HRV than the presence of renal disease or diabetes alone, with non-diabetic ESRD and diabetic patients having similar HRV estimates (Mylonopoulou et al., 2010). The only exception is HF power, which is comparable in diabetic and non-diabetic ESRD patients (Mylonopoulou et al., 2010). High resting

HR, older age, elevated serum phosphorus levels, anemia, high cholesterol levels, increased left ventricular mass index, and/or use of beta-blockers are also associated with reduced HRV in CKD and ESRD (Steinberg et al., 1998; Furland et al., 2008; Chandra et al., 2011).

One of the hypothesized causes for autonomic dysfunction, which can result in reduced HRV and an increased risk of cardiac mortality (La Rovere et al., 1998), in ESRD is a uremia driven excitation of the renal afferent nerves. Accordingly, muscle sympathetic nerve activity is lower in nephrectomized versus non-nephrectomized ESRD patients (Converse et al., 1992). Furthermore, conversion from conventional to nocturnal hemodialysis, which allows for a more aggressive correction of uremia, reduces plasma noradrenaline levels (Chan et al., 2003). Uremic excitation of renal afferents may also underlie reduced HRV. Acutely, hemodialysis increases SDNN, SDANN and reduces the ratio of LF to HF power (Giordano et al., 2001; Tong and Hou, 2007; Mylonopoulou et al., 2010; Celik et al., 2011); whereas, conversion from chronic to nocturnal hemodialysis increases HF power and normalizes LF to HF ratio (Chan et al., 2004). Following renal transplantation, there is an eventual improvement in HRV. At 1 month post-transplantation, HRV parameters are similar to pre-transplantation levels (Yang et al., 2010), while from 5 to 12 months post-transplantation, LF, HF, TP, and SDNN are similar to healthy control levels (Yildiz et al., 1998; Rubinger et al., 2009; Yang et al., 2010). Nevertheless, such improvements are not always reported (Kurata et al., 2004; Parisotto et al., 2008); whether this reflects an insufficient post-surgical recovery time (recovery time 1–4+ months) or other causes for reduced HRV in ESRD is unknown.

The Renal Research Institute-CKD study concluded that a low LF to HF ratio was associated with a higher risk of progression to ESRD (Chandra et al., 2011) and the Atherosclerosis Risk in Communities study highlighted the association between low LF and HF power and the subsequent development of renal impairment, even after correction for classical risk factors such as diabetes, hypertension, and low baseline renal function (Brotman et al., 2010). On the basis of this alone, reduced HRV values are predictive of a greater risk of mortality, whether cardiac related or not, due to a higher risk of developing ESRD. Reduced HRV can also predict an increased risk of cardiac mortality, with retrospective evidence existing that ESRD or CKD patients that died of coronary artery disease, peripheral artery disease, congestive heart failure, acute myocardial infarction, or a cardiac arrest, had reduced HRV, notably low VLF, LF, and LF to HF ratio values, compared with survivors (Fukuta et al., 2003a; Chandra et al., 2011). Interestingly, ultra LF power, a rarely reported frequency-domain parameter that reflects circadian rhythm changes in HR (Stauss, 2003), is a highly sensitive parameter in predicting cardiac related deaths (e.g., acute myocardial infarction, heart failure, sudden cardiac death) in ESRD patients (Hayano et al., 1999; Fukuta et al., 2003a,b), with values less than 8.7 ms<sup>2</sup>, predictive of sudden cardiac death (Hayano et al., 1999). Time-domain estimates of HRV are also predictive of cardiac mortality, with SDNN estimates less than 50 ms reflective of a greater risk of sudden cardiac death (Hathaway et al., 1998; Hayano et al., 1999).

**Table 1 | Heart rate variability parameters in end-stage renal disease patients.**

Reference	Patient cohort	HRV parameters in ESRD patients	Comments
Celik et al. (2011)	31 ESRD patients on HD therapy 31 Healthy controls	Reduced SDNN Reduced SDANN Reduced RMSSD	Comparisons made with controls only following dialysis therapy Showed that HRV parameters improved following HD therapy
Yang et al. (2010)	14 ESRD patients on HD therapy 14 Healthy controls	Reduced total power Reduced LF power Reduced HF power	Showed that all HRV parameters had improved by 6 months following renal transplantation
Giordano et al. (2001)	20 ESRD patients (9 diabetic) on HD therapy 10 Healthy controls	Reduced total power Increased LF (nu) Reduced HF (nu)	Results shown here only include non-diabetic ESRD patients Total power and HF power lower in diabetic ESRD patients LF power higher in diabetic ESRD patients
Kurata et al. (2004)	13 ESRD patients on HD patients 10 Healthy controls	Reduced SDNN Reduced rMSSD Reduced LF power Reduced HF power	Renal transplantation had no effect on HRV parameters measured
Yang et al. (2010)	14 ESRD patients on HD that received renal transplants 14 Healthy controls	Reduced total power Reduced LF power Reduced HF power	Renal transplant normalized reduction in total power Renal transplant increased but did not normalize, LF and HF power
Fukuta et al. (2003a)	120 ESRD patients on HD therapy 62 Healthy controls	Reduced SDNN Reduced total power Reduced ULF Reduced VLF Reduced LF power Reduced HF power	Reduced VLF and ULF were predictive of cardiac death
Rubinger et al. (2009)	52 ESRD patients on chronic HD therapy 44 ESRD patients with renal transplants 41 Healthy controls	Reduced LF power Reduced HF power	LF power corrected 1 year following renal transplant HF power not altered 1 year following renal transplant
Furuland et al. (2008)	16 Stage 4 CKD patients 16 Healthy controls	Reduced SDNN Reduced SDANN No change in rMSSD No change in pNN50 Reduced total power Reduced LF power No change in HF power	Hemoglobin normalization corrected reduction in LF and total power Hemoglobin normalization did not affect time domain estimates of HRV
Studinger et al. (2006)	14 Juvenile ESRD patients on HD 14 Juvenile renal transplant recipients 14 Healthy controls	Reduced RMSSD Reduced LF power No change in HF power	Renal transplant recipients showed no difference in RMSSD or HF power
Steinberg et al. (1998)	66 ESRD patients (26 diabetic) on HD 33 Healthy controls	Reduced LF power Reduced HF power	Diabetes was a major determinant for reduced LF power Age was a borderline significant determinant for reduced HF power
Yamanaka et al. (2005)	27 ESRD patients (13 diabetic) on HD 46 Healthy controls	Reduced LF power Reduced HF power	LF and HF power was reduced further in diabetic ESRD patients

## BAROREFLEX SENSITIVITY AND EFFECTIVENESS

In comparisons to the numerous studies examining HRV in CKD/ESRD patients, relatively little is known regarding baroreceptor reflex control of HR. This may reflect the methodology required to investigate baroreceptor function, which requires a blood pressure recording as opposed to the simple acquisition of an ECG signal. It is not an indication, however, that assessing

baroreceptor reflex function is not a useful marker of cardiac risk. On the contrary, reduced baroreceptor reflex control of HR has been established as a strong predictor of cardiac mortality following myocardial infarction (La Rovere et al., 1998), and in heart failure patients (Mortara and Tavazzi, 1996).

Baroreceptor reflex control of HR can be assessed by examining the sensitivity of the reflex (BRS), i.e., the ability of the

baroreceptor reflex to produce reflex bradycardia or tachycardia. Alternatively, although not as utilized, the effectiveness of the baroreceptor reflex (BEI), i.e., how often the baroreceptor reflex produces a change in HR in response to a perturbation in blood pressure, can be examined (Di Rienzo et al., 2001). High BRS and BEI scores are reflective of healthy baroreceptor reflex control of HR.

Baroreceptor reflex control of HR, as examined by BRS (Pickering et al., 1972; Lazarus et al., 1973; Agarwal et al., 1991; Gerhardt et al., 1999; Gao et al., 2005; Studinger et al., 2006) and BEI (Johansson et al., 2005, 2007), is impaired in renal disease patients and may worsen as the disease severity increases. To date, only two studies (Bavanandan et al., 2005; Lacy et al., 2006) have examined BRS in moderate to severe non-diabetic CKD patients. Both studies showed that BRS was positively correlated to GFR, implying that BRS reduced as renal disease severity increases (i.e., GFR decreased). Furthermore, Lacy et al. (2006) demonstrated that BRS was lower in stage 4 CKD patients compared with stage 3 CKD patients. However, neither study included a control group. Therefore, it is still unknown at which point in the disease process baroreceptor reflex control of HR alters. In addition to the impact of worsening renal function, additional co-morbidities may have additive negative effects on baroreceptor reflex function, with greater reductions in BRS and BEI noted in diabetic versus non-diabetic ESRD patients (Johansson et al., 2005).

The decline in BRS and BEI in ESRD can be reversed as conversion from chronic to nocturnal hemodialysis increases BRS and BEI (Chan et al., 2005, 2008). This is hypothesized to result from an increase in arterial compliance as the improvement in BRS that follows conversion to nocturnal hemodialysis is positively correlated with an increase in stroke volume to pulse pressure ratio (Chan et al., 2005). Furthermore, following renal transplantation, BRS and BEI is increased to control levels (Studinger et al., 2006; Rubinger et al., 2009).

The exact cause(s) of impaired baroreceptor reflex function in ESRD is unknown, but may relate, in part, to an inability for the

baroreceptors to sense changes in blood pressure. This could arise from vascular stiffness in the aortic arch and carotid sinus, the origin of baroreceptor afferents, as BRS is negatively correlated with increased carotid artery stiffness (Studinger et al., 2006) and an increase in vascular calcification, albeit in the superficial femoral artery, in dialysis patients (Chesterton et al., 2005). Alternatively, it could be due to abnormal central processing of the baroreceptor reflex or an inability for the cardiac vagal or sympathetic efferents to produce effective changes in HR.

Despite the limited number of studies examining BRS and BEI in ESRD patients, a reduction in these parameters confers an increased risk of mortality. Reduced BEI is an independent predictor of all-cause mortality, while reduced BRS, an independent predictor of sudden cardiac death (Johansson et al., 2007). The impact of reduced BRS in ESRD is not limited to a potential predisposition to life threatening arrhythmias. A reduction in BRS may also contribute to hemodialysis related hypotension, a significant cause of mortality in hemodialysis patients, due to an inability to counteract dialysis induced volume depletion (Heber et al., 1989; Chesterton et al., 2010). Further studies are required, however, to verify and strengthen the use of BRS as a predictive marker of an increased risk of cardiac mortality in CKD/ESRD.

## CONCLUSION

Heart rate variability, BRS, and BEI are reduced in ESRD patients. These three parameters convey different information regarding cardiovascular health and may provide independent indications of a greater risk of cardiovascular mortality. Although individual HRV parameters are inconsistently reported as reduced in CKD/ESRD patients, a simple estimation of overall HRV (SDNN) can easily identify CKD/ESRD patients at risk of sudden cardiac death. Comparatively little is known regarding baroreceptor reflex function in CKD. Nevertheless, BRS and BEI have been shown to predict sudden cardiac death and all-cause mortality in ESRD patients respectively.

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