Impaired Baroreflex Sensitivity Predicts Mortality in Chronic Kidney Disease

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Abstract

Autonomic nervous system dysfunction is common in patients with chronic kidney disease (CKD) and is associated with adverse cardiovascular (CV) outcomes and mortality in non-CKD populations, but has not previously been shown to predict all cause mortality in CKD.

134 patients were recruited to an observational study. CV structure, function and inflammatory status were quantified. Survival was assessed at 4 years.

There were 38 fatalities. Unadjusted Cox-regression analysis demonstrated lowest tertile baroreflex sensitivity (BRS) increased mortality risk by 2.43x. Stepwise multivariate analysis showed that this effect was independent of age, inflammation and vascular calcification.

Reduced BRS is common in CKD, however even within such a population lowest values were still independently associated with additional mortality.

1. Introduction

Cardiovascular (CV) mortality is grossly elevated in patients with chronic kidney disease (CKD), and is associated with a wide variety of structural and functional abnormalities. These issues have driven additional attempts to further characterise these abnormalities to elucidate the pathophysiology involved, assess individual risk and/or target and monitor therapies specifically directed at the CV system.

The impact of vascular calcification (VC), arterial stiffness and inflammation on CV risk and mortality are well documented. Autonomic nervous system dysfunction is common in CKD and is implicated in intradialytic haemodynamic instability [1, 2]. We have previously demonstrated impaired BRS in CKD stage 4 and haemodialysis (HD) patients, associated with increased arterial stiffness and VC [3]. Impaired BRS is associated with adverse CV outcomes and mortality in non-CKD populations [4, 21], but has not previously been shown to predict all cause mortality in CKD patients.

We aimed to investigate if BRS impairment also predicted poor outcome in CKD stage 4 and 5 patients, independent of other known risk factors.

2. Methods

We studied 134 subjects (46 CKD stage 4, 60 HD, 28 peritoneal dialysis (PD)) recruited from Derby City General Hospital. Exclusion criteria included previous transplantation, limb amputation, active sepsis or malignancy. All prevalent patients were approached (291 patients in May 2003, at the start of recruitment). CKD stage 4 patients were defined by a minimum of two creatinine clearance measurements of 15-30ml/min. Dialysis modality was subject to patient choice and no patient had altered modality. All dialysis patients had been established for at least 6 months.

PD patients were treated with bicarbonate/lactate buffered fluid (Physioneal®, Baxter, Newbury, UK). 9 patients used automated PD, 19 patients used continuous ambulatory PD (3-5 exchanges/day). HD patients received three sessions of at least 4 hours per week. Hospal Integra (Hospal, Mirandola, Italy) monitors and low-flux polysulphone dialysers (1.5-2.0 m^2, LOPS 15-20®, Braun Medical Ltd, Sheffield, UK) were used. All sessions used bicarbonate-based HD utilising dialysate containing 1.25mEq/l calcium and 134 mmol/l sodium.

Outcome data were collected until 4 years (January 2008). Appropriate ethical approval was granted by the South Derbyshire Local Research Ethics Committee and all patients provided written informed consent.

Age, gender, comorbiditity, medication, height, weight, tobacco and alcohol use were recorded for all patients. Biochemical parameters (haemoglobin, serum phosphate, corrected calcium and bicarbonate) were time-averaged over the previous 6 months. High sensitivity CRP was assayed by ELISA (DRG Diagnostics, Marburg, Germany). The most recent (less than one

month before visit) dialysis adequacy was recorded.

BRS was calculated using non-invasive fingertip plyethsysomography (Finometer®, FMS, Amsterdam, The Netherlands). This device has been extensively used to provide continuous recording of blood pressure from which central haemodynamic variables are calculated using validated inbuilt transfer functions [5]. The Finometer tracks percentage change for all parameters, except blood pressure, which is calibrated against the brachial blood pressure at the commencement of monitoring thus providing absolute values. Cross-correlation time-domain BRS analysis was performed offline using software analysing the relationship between beat-to-beat blood pressure and inter beat interval (PRVBRS.EXE, FMS) [6]. We have previously successfully utilised this technique in CKD patients [3, 16].

VC was assessed by computed tomography utilising a GE Medical Systems LightSpeed16® multi-slice spiral scanner. Non-contrast enhanced images were obtained from supine subjects. A standardised 5cm section of thigh was scanned, 20cm above the tibial plateau, in 2.5mm slices without overlap. Scoring was undertaken using GE Medical Systems Advantage Workstation® software, using the Agatston technique as previously described [7]. This method has been previously demonstrated as being highly sensitive and capable of tracking functionally significant prospective change [8].

Arterial stiffness was measured by both pulse wave analysis and pulse wave velocity assessment using applanation tonometry (SphygmoCor®, AtCor Medical, Sydney, Australia). Augmentation index (AIx) was calculated as both augmentation pressure/pulse pressure (AP/PP) and second/first peak pulse pressure (P2/P1). Pulse wave velocity was assessed carotid to radial arteries (cr) and carotid to dorsalis pedis (cd).

All data were tested for normality. Group data are presented as mean ± SD unless otherwise stated. BRS, VC and hsCRP data were non-parametric, thus are presented as median ± IQR. Analysis was performed using SPSS v12.0.1 (SPSS Inc, Chicago, IL). Categorical data was compared using Chi-square test, continuous data using unpaired Students t-test or Mann-Whitney U test as appropriate.

3. Results

Average age at recruitment, gender, smoking, CV disease and diabetes prevalence were similar in all three modalities (Table 1). Baseline eGFR (4-variable MDRD) in CKD 4 group was 16 ± 6 ml/min.

Mean follow-up was 1495 ± 121 days with 38 fatalities (annual mortality rate 9.3%). The majority were CV related.

Baseline median BRS was 3.72 ± 3.57 ms/mmHg. Baseline median BRS was not significantly lower in those who died (2.72 ± 3.52; 3.92 ± 3.34 ms/mmHg; p=0.08).

Unadjusted Cox-regression modelling demonstrated that the lowest tertile of BRS increased mortality risk by a factor of 2.43 (Table 2). Height, weight, smoking, diabetes, medication and arterial stiffness did not significantly predict outcome.

Table 2. Univariate predictors of mortality.

	Hazard Ratio	**Sig.**
Age	1.055 (1.024-1.087)	<0.001
Male gender	3.471 (1.450-8.306)	0.002
Diabetes	2.009 (1.047-3.854)	0.042
CV disease	2.903 (1.529-5.512)	0.002
Calcification score	1.001 (1.001-1.001)	<0.001
hsCRP	1.025 (1.012-1.037)	0.002
Lowest tertile BRS	2.430 (1.150-5.113)	0.021

Table 1. Cohort demographics.

	CKD	**PD**	**HD**	**Sig.**
Age (yrs)	60.5 ± 14.3	60.5 ± 13.5	60.0 ± 15.2	ns
Gender (M:F)	26:20	17:11	43:17	ns
Diabetes (%)	22	36	28	ns
Smoking (%)	13	14	12	ns
CV disease (%)	24	43	18	ns
Dialysis Vintage (mths)	-	33 ± 23	35 ± 24	ns
BRS (ms/mmHg)	4.32 ± 2.81	3.54 ± 4.78	3.20 ± 2.75	P=0.045 CKD vs HD
AIx (AP/PP) (%)	66 ± 22	62 ± 17	72 ± 26	ns
AIx (P2/P1) (%)	142 ± 18	130 ± 24	140 ± 26	p=0.013 CKD vs PD
PWVcr (m/s)	8.9 ± 1.6	9.3 ± 1.5	9.1 ± 1.7	ns
PWVcd (m/s)	9.4 ± 3.1	10.8 ± 2.4	10.6 ± 3.7	ns
VC (units)	2 ± 198	26 ± 487	121 ± 623	P=0.005 CKD vs HD
hsCRP (mmol)	2.3 ± 4.1	3.4 ± 11.5	6.8 ± 11.1	P=0.009 CKD vs HD

Stepwise multivariate analysis demonstrated that age, gender, impaired BRS (lowest tertile), hsCRP and VC score but not diabetes or CV disease were independently predictive of mortality (overall model -2LL=171.357, p<0.0001, Table 3, Figure 1).

Table 3. Multivariate predictors of mortality.

	Hazard Ratio	Sig.
Age	1.065 (1.025-1.106)	<0.001
Male gender	7.567 (1.552-36.898)	0.001
Diabetes	-	ns
CV disease	-	ns
Calcification score	1.001 (1.000-1.001)	0.017
hsCRP	1.025 (1.005-1.045)	0.019
Lowest tertile BRS	4.197 (1.762-9.998)	0.001

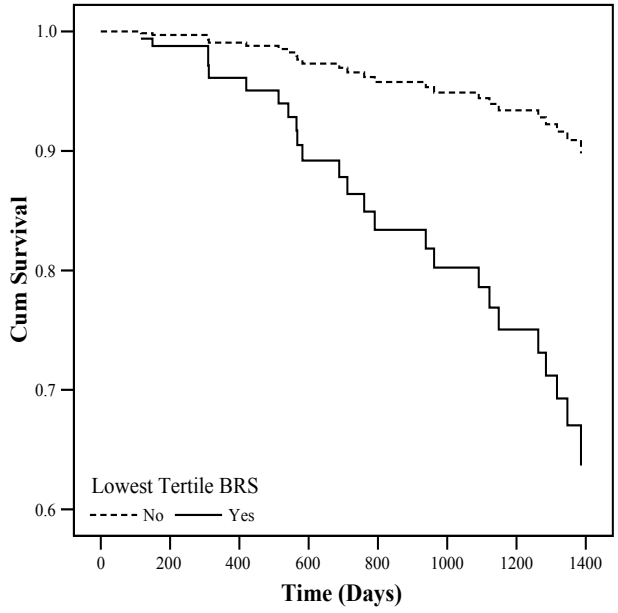

Figure 1. Adjusted Cox-regression model demonstrating the effect of lowest tertile BRS on mortality.

4. Discussion and conclusions

Autonomic dysfunction is common in patients receiving dialysis, and those with significant CKD. Short-term regulation of blood pressure is largely controlled by appropriate autonomic nervous activity through the baroreflex arc [9]. BRS is therefore well recognised as an integrated assessment of the autonomic nervous system [10]. Impairment of BRS is associated with an increased incidence of cardiac arrhythmias [11], falls propensity, intradialytic haemodynamic instability [1], cardiac damage, metabolic syndrome [12] as well as cardiovascular events and all cause mortality after myocardial infarction [4].

BRS as a marker of the fundamental control of blood pressure is also of great physiological significance in HD. Impaired BRS has been demonstrated in patients who are unstable on HD [13] and transfer from conventional thrice weekly to nocturnal HD increases BRS [14], although further work is required to evaluate outcomes.

Initial BRS measurement methodology was based on the assessment of the CV response to vasoactive drugs [15]. These were both invasive, and only provided a snapshot view of resting BRS. Contemporary techniques, as used here, however focus on spontaneous BRS assessment allowing assessment of spontaneous BRS both at rest [3] and during interventions such as HD [2] and PD [16].

BRS may be computed from such recordings via either frequency-domain or time-domain techniques. Frequency-domain techniques rely on spectral analysis, whilst time-domain quantifies BRS by regression analysis of the relationship between systolic blood pressure and pulse rate change. These different techniques have been shown to produce broadly consistent results [17], with reproducibility similar between techniques [18].

In this study, BRS has been assessed using time-domain analysis performed using software available from the manufacturer of the Finometer. Traditional time-domain analysis did not allow for a delay between blood pressure change and the compensatory modification of pulse rate. This software has been specifically developed to find BRS activity with these physiological delays, and thus performs a phase-shift to search for valid correlations across a range of possible values. The most significant correlation is then selected. We have utilised this technique previously [2, 3, 16]. PRVBRS.EXE is based on xBRS.EXE, which has been previously utilised [19, 20] and its satisfactory performance has been confirmed against the EUROBAVAR dataset [6].

The concept of BRS impairment predicting mortality is well described, but there is variability regarding the level at which risk significantly elevates. The level of BRS impairment that predicted increased risk in our population (2.94 ms/mmHg) is consistent with that reported by other groups in the cardiac literature. La Rovere et al [21] and De Ferrari et al [4] have demonstrated that a time-domain BRS less than 3 ms/mmHg was predictive of mortality post-MI, although there were differences in BRS assessment methodology.

Age, gender, inflammation and vascular calcification are known to predict mortality in CKD. Johansson et al [22] have recently reported that decreasing BRS is predictive of sudden death, but not all-cause mortality, in CKD. We have shown for the first time that impairment of baroreflex sensitivity predicts all-cause mortality risk,

and is additional to traditional risk-factors. We have demonstrated that a simple, non-invasive technique may be able to further quantify an individual's mortality risk, in a group that suffer an extremely high CV risk burden. This population are also characterised by significantly reduced BRS, yet even within this spectrum severe BRS impairment was still associated with additional mortality, independent of inflammatory status or VC.

These findings imply that whilst assessment of BRS may add prognostic information, a critical area for further investigation is to quantify the impact of modification (either indirectly by exercise, or directly by electrical stimulation) of BRS on the high mortality rate in CKD.

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