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Serum endocan and circadian heart rate variability in non-dialysis stage 5 chronic kidney disease patients

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Abstract

Background Chronic kidney disease (CKD) is very common now and is associated with high overall and cardiovascular mortality. Numerous studies have reported that elevated heart rate (HR) is a risk factor for cardiovascular mortality. We investigated the link between serum endocan and circadian heart rate variability in non-dialysis stage 5 CKD patients.

Methods In a cross-sectional study, we enrolled 54 prevalent *n* non-dialysis stage 5 CKD patients (32 males, aged 48.2 ± 14.92 years). HR was measured with an automatic system. Serum endocan level was analyzed by ELISA.

Results Night/day HR ratio was independently predicted by serum endocan level ($P < 0.01$) and hypertension history ($P < 0.05$). Adjusted R^2 of the model was 0.222.

Conclusion Increased serum endocan is significantly associated with circadian heart rate variability in non-dialysis stage 5 CKD patients. Further investigation is needed to explore the potential benefits of serum endocan lowering therapy in this patient group.

Keywords Endocan · Heart rate · CVD

Introduction

Chronic kidney disease (CKD) has been a major problem in the world. A national epidemiological survey found that CKD affects 10.8% of the Chinese general population and imposes substantial morbidity and cost [1]. CKD associated with high overall and cardiovascular (CV) mortality [2, 3]. It is reported that up to 45% of pre-dialysis CKD patients may die before reaching end-stage renal disease (ESRD), which makes cardiovascular disease (CVD) the leading cause of death in CKD [4]. The reasons for this high cardiovascular mortality are not fully understood, but increased heart rate (HR) might be an important risk factor based on the association of elevated HR with increased CV morbidity and mortality in the general [5], in patients with ischemic heart disease [6], and CKD [7] populations.

HR is one of the simplest measures of hemodynamics in humans, and could be a marker of general health [8], but it is affected by a variety of conditions such as anemia or physical activity. Higher resting HR might reflect increased sympathetic and/or reduced parasympathetic activity. Early study also suggests that high resting HR, even within the normal range (< 100 beats/min), is a predictor of mortality in the general population [8]. Woodward et al., who analyzed a pooling data of 112,680 subjects in 12 cohort studies with 7.4-year follow-up, also showed that resting HR has positive associations with total mortality and a range of major cardiovascular events [9]. It is also found that HR non-dipping status, resting HR does not exhibit the typical nocturnal decline, was significantly associated with increased risk of CVD [10]. And it is also found that a greater increase in night/day HR ratio, i.e., a lesser decrease in nocturnal HR, was associated to increased arterial stiffness [11].

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Endocan, previously called endothelial cell-specific molecule-1 (ESM-1), is a soluble proteoglycan (50 kDa), secreted by human vascular endothelial cells, which can be detected in the circulation and is an indicator of angiogenesis and endothelial cell activation [12]. Endocan increases in the presence of decreasing eGFR and influences all-cause mortality and CV events in patients with CKD independent of traditional and non-traditional risk factors [13].

In the present study, we aimed to investigate the link between circadian heart rate variability and endocan in non-dialysis stage 5 CKD patients.

Methods

Study population and biochemical measurements

All prevalent non-dialysis stage 5 CKD patients at the Division of Nephrology of the First Affiliated Hospital of Kunming Medical University were enrolled in a cross-sectional study. The exclusion criteria were (1) clinical or laboratory evidence of heart failure, coronary artery disease, and/or cerebrovascular disease; (2) less than 18 years old; (3) unwillingness to participate in the study. The ethics committee of Kunming Medical University approved this study protocol. Patients' smoking status was recorded as non-smoking or smoking. Patients' use of beta-blocker was recorded as using or non-using.

Glomerular filtration rate estimation

Glomerular filtration rate (GFR) was estimated according to the simplified version of the Modification of Diet in Renal Disease formula [14]:

$\mathrm{GFR}\left(\mathrm{ml/min/1.73\,m^2}\right) = 186 \times \mathrm{Pcr}^{-1.154} \times \mathrm{age}^{-0.203} \times 0.742$(if female).

Pcr stands for plasma creatinine (mg/dL).

The ambulatory heart rate

Non-invasive HR was performed on a weekday with an automatic system (CB-2302-A, Bio Instrument, China), which recorded HR every 30 min from 8 am to 10 pm; and 60 min from 10 pm to 8 am next day. Resting and day time were defined on the basis of patients' diaries recorded during ambulatory blood pressure monitoring (ABPM), and night/day HR ratio was calculated accordingly.

Serum endocan measurements

All blood samples were obtained from patients in the morning after 12 h of fasting. Blood samples were collected in plain tubes to measure serum endocan levels. Serum was separated from the blood after centrifugation for 10 min. The serum samples were stored at − 80 °C until analysis. The concentration of human endothelial cell-specific molecule-1 was analyzed by ELISA using commercial kits (Abnova Bioscience, Taoyuan, TWN), in accordance with the manufacturers' instructions. Measurements were carried out using enzyme-linked immunosorbent assay plate reader Multiskan Go 1510-02669C spectrometer (Thermo Fisher Scientific Oy, Ratastie 2. FI-01620 Vantaa, Finland). Patients were divided into high serum endocan level (this cut-off value was set according to the mean of serum endocan value of the study population) and low serum endocan level groups according to serum endocan values.

Statistical analysis

Continuous variables were expressed as mean ± SD (normal distribution). Differences between groups were tested using independent-sample *t* test for normally distributed variables. Pearson's correlation was performed when the relationship between parameters was explored. Multiple regression analysis was performed to identify the relative dependence of observed correlations of night/day HR ratio (stepwise method). All tests were two-sided. A value of $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Baseline data were given in Table 1. Briefly, there were 54 non-dialysis stage 5 CKD patients (32 M/22 F) included in the present study. Patients' age was 48.2 ± 14.92 years with GFR 8.0 ± 3.50 ml/min/1.73^2. No patient was on maintenance dialysis or had been transplanted.

Table 1 Demographic data of the 54 non-dialysis stage 5 chronic kidney disease patients

Parameters	Values
Age (years)	48.2 ± 14.92
Gender (M/F)	32/22
Smoking (Y/N)	23/31
GFR (ml/min/1.73^2)	8.0 ± 3.50
Hypertension history (Y/N)	40/14
Diabetic history (Y/N)	11/43

GFR glomerular filtration rate

Table 2 Clinical parameters compared between low and high groups, which grouped by serum endocan level, in 54 non-dialysis stage 5 CKD patients

	High ($n=23$)	Low ($n=31$)
Age (years)	48.9 ± 15.60	47.7 ± 14.64
Gender (M/F)	14/9	18/13
Smoking (Y/N)	10/13	13/18
Hypertension history (Y/N)	17/6	23/8
Diabetic history (Y/N)	6/17	5/26
Beta-blocker (Y/N)	10/13	8/23
Height (cm)	164.2 ± 6.68	163.1 ± 8.11
Weight (kg)	61.1 ± 9.45	61.0 ± 14.49
BMI (kg/m^2)	22.6 ± 2.91	22.7 ± 4.10
GFR (ml/min)	7.1 ± 3.24	8.7 ± 3.58***
Hemoglobin (g/l)	81.1 ± 20.53	84.8 ± 21.23
Endocan (pg/ml)	1013.1 ± 340.10	326.6 ± 147.23**
Resting HR (bpm)	80.1 ± 11.81	73.4 ± 11.14*
Awake HR (bpm)	82.9 ± 10.22	81.2 ± 11.63
Night/day HR ratio	1.0 ± 0.07	0.9 ± 0.07*

BMI body mass index, *GFR* glomerular filtration rate, *HR* heart rate
*$P<0.05$, **$P<0.01$, and ***$P=0.092$ between low and high group

Different clinical variables of serum endocan groups

Clinical parameters of 54 non-dialysis stage 5 CKD patients based on serum endocan level were listed in Table 2. Patients' resting HR in low endocan group was significantly lower than that of high endocan group ($P<0.05$). Night/day HR ratio in high endocan group was significantly higher than that of low group ($P<0.05$). Patients in low endocan group had lower serum endocan value than that of high endocan group ($P<0.01$). There were no significant difference between the two groups in patients' age, gender, smoking status, hypertension history, diabetic history, use of beta-blocker, height, weight, BMI, hemoglobin, and awake HR.

Univariate correlations

Univariate correlations between night/day HR ratio with selected clinical and biochemical markers in non-dialysis stage 5 CKD patients were given in Table 3. Briefly, night/day HR ratio was positively correlated with age, serum endocan level, and resting HR. The relationship of night/day HR ratio and serum endocan level is shown in Fig. 1.

Regression models

The output from multivariate regression analysis of predictors for night/day HR ratio is shown in Table 4. Briefly,

Table 3 Univariate correlation coefficients for night/day HR ratio with selected clinical and biochemical markers in 54 non-dialysis stage 5 CKD patients

Variable	Night/day HR ratio
Age (years)	0.342*
Height (cm)	−0.079
Weight (kg)	0.129
BMI (kg/m^2)	0.217
GFR (ml/min)	−0.224***
Hemoglobin (g/l)	−0.154
Endocan (pg/ml)	0.433**
Awake HR (bpm)	−0.006
Resting HR (bpm)	0.516**

BMI body mass index, *GFR* glomerular filtration rate, *HR* heart rate
*$P<0.05$, **$P<0.01$, and ***$P=0.104$

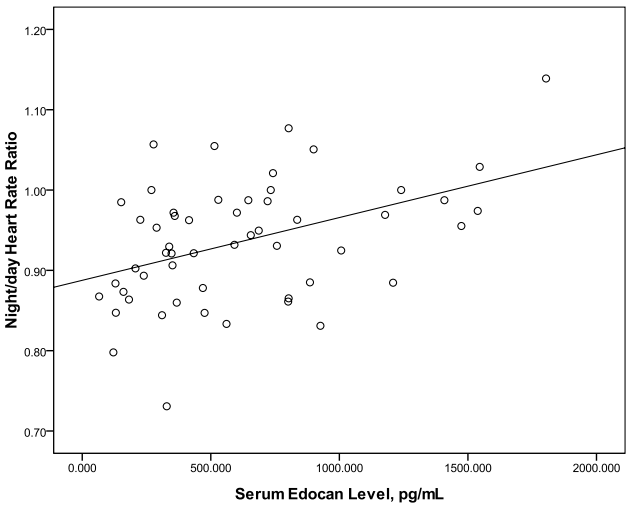

Fig. 1 Correlation between serum endocan level and night/day HR ratio in the 54 non-dialysis stage 5 CKD patients

Table 4 A multivariate regression model showing predictors of night/day HR ratio in 54 non-dialysis stage 5 CKD patients

	Beta	*P* value
Constant		<0.01
Endocan (pg/ml)	0.421	<0.01
Hypertension history (Y/N)	0.252	<0.05

Adjusted R^2 0.222

The initial model includes gender, smoking, use of beta-blocker, hypertension history, diabetic history, and serum endocan level, and GFR

HR heart rate, *GFR* glomerular filtration rate

night/day HR ratio was independently predicted by serum endocan level ($P < 0.01$) and hypertension history ($P < 0.05$). Adjusted R^2 of the model was 0.222.

Predictive performance of serum endocan for low and high night/day HR ratio

The ROC curve of serum endocan for the prediction of the low and high HR ratio is shown in Fig. 2. The area under the ROC curve of serum endocan for the prediction of the low and high night/day HR ratio was 0.702 (95% CI, 0.562–0.841) and the cut-off value was 495.0 pg/ml, with sensitivity of 66.7%, specificity of 70.4%.

Discussion

In the present study, we found a significant association between elevated night/day HR ratio and increased serum endocan value in non-dialysis stage 5 CKD patients. This association was still present even after adjustment for confounders, such as gender, smoking, use of beta-blocker, renal function, and diabetic history. Thus, despite the high prevalence of anemia in the present study, serum endocan still appeared to be an important predictor of high night/day HR ratio, a lesser decrease in nocturnal heart rate (circadian heart rate variability), in non-dialysis stage 5 CKD patients.

It is well known that patients with CKD have approximately 20 times the mortality risk of the general population, and they mainly die from CV-related deaths [15]. Endothelial dysfunction plays a central role in the atherosclerotic process [16] and is considered of central importance in cardiovascular disease in CKD patients [17]. Comorbidities including obesity [18], inflammation [19], metabolic syndrome [20], and other environmental risk factors trigger a complex events engendering arterial stiffness. HR is in fact determined by a complex interplay of sympathetic and parasympathetic components of the autonomic nervous system (ANS) on the cardiac electrical system, baroreceptors, vascular tone, endothelial function, and cardiac contractility in response to different stimuli in physiological and pathological conditions. The night/day HR ratio expresses a lesser decrease in nocturnal HR, and has been found to have a direct relationship with all the parameters evaluating arterial stiffness, including PWV [11]. Our previous study also shows that increased sleep heart rate is significantly associated with elevated arterial stiffness in CKD patients [21]. HR reduction by ivabradine can improve endothelial function in patients with coronary artery disease [22].

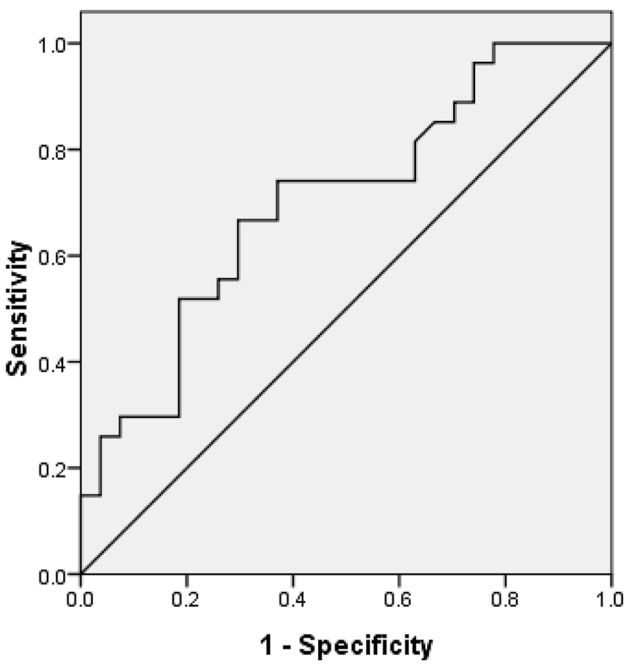

Fig. 2 ROC curve of serum endocan's discriminatory ability regarding night/day HR ratio (low vs. high)

Endocan is a soluble proteoglycan expressed by the vascular endothelium. It has reported that endocan is overexpressed in cancer [23] and is related to patients' outcome [24]. Endocan also plays roles in the vascular contribution to organ-specific inflammation and in endothelium-dependent pathological disorders which may represent a novel endothelial cell dysfunction marker [25–27]. Endocan has been proved to correlate with cardiovascular risk and/or activity of disease in psoriasis vulgaris [28], Behçet disease [29], and Obstructive Sleep Apnea [30]. Our study found that an elevated night/day HR ratio, which represents lesser decrease in nocturnal HR, significantly associated with increased serum endocan value in non-dialysis stage 5 CKD patients. Our finding shows that serum endocan may take part into the endothelial damage caused by circadian HR variability, and further studies are needed to prove that.

De Souza et al. found a positive correlation between the serum endocan concentration and systolic blood pressure in renal transplant patients [31]. As endothelial dysfunction is associated with the development of hypertension and other cardiovascular diseases in CKD patients, it is possible that the presence of this condition could, at least in part, reflect the processes that were involved in increasing the endocan levels in our study population.

The potential effect of control of hyperlipidemia and pleiotropic effects of statin use on endocan levels were not discussed. Because we routinely stopped statin use when our CKD patients reach stage 5, for the lack of clear clinical benefits in this group of patients [32].

The main limitation of our study is its cross-sectional design, and our study group is too small by which a cause-and-effect relationship cannot be discerned. Future prospectively designed studies are needed to determine whether the

serum endocan would predict night/day HR ratio in non-dialysis stage 5 CKD patients. Second, although a number of potential confounding factors have been evaluated, the existence of other unrecognized confounding variables should be considered.

In conclusion, increased serum endocan is significantly associated with elevated night/day HR ratio in non-dialysis stage 5 CKD patients. This suggests that serum endocan level maybe useful for predicting circadian heart rate variability in non-dialysis stage 5 CKD patients, and further investigation is needed to explore the potential benefits of serum endocan lowering therapy in this patient group.

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Compliance with ethical standards

Conflict of interest None of the authors declare any conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments of comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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