Original Article

The correlation of heart rate variability with parathyroid hormone in hemodialysis patients with secondary hyperparathyroidism

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Abstract

Introduction: Hyperparathyroidism (HPTH) which is often found in end stage of chronic renal disease patients replaced by hemodialysis (HD) may cause the cardiac autonomic neuropathy.

Method: Healthy subjects and HD patients categorized into two groups by parathyroid hormone (PTH) levels: high PTH group (H-PTH; PTH = 150 - 300 pg/mL) and ultra high PTH group (UH-PTH; PTH > 300 pg/mL) were investigated. Frequency and time domains of heart rate variability (HRV) were analyzed. The frequency domain parameters were then transformed by the fast Fourier transform and its normalized unit was calculated in terms of natural logarithms (ln). The correlations between PTH concentration and each parameter of HRV were analyzed by Pearson's correlation.

Result: The results of the current study showed that frequency and time domains of UH-PTH were at lowest values. The values of lnTP (total power), lnLF (low frequency), LF/HF ratio (low frequency and high frequency ratio), SDANN (standard deviation of the averages of N-N intervals in all 5-minute segments), SDNN (standard deviation of N-N intervals), TINN (triangular interpolation of N-N interval) and HRV index, were significantly lower in UH-PTH compared to H-PTH. Moreover, lnLF showed the highest negative correlation with lnPTH concentration. This correlation coefficient (r) was -0.633.

Discussion and Conclusion: The greatest reduction in LF and SDNN, and the highest negative correlation between lnLF and lnPTH indicated that the sympathetic nervous system was, at least in part, activated by hyperparathyroidism. It is suggested that PTH plays a role as an important uremic toxin which involves in the initiation of cardiac sympathetic hyperactivity.

Key words: Frequency domain, Hemodialysis, Heart rate variability, Parathyroid hormone, Time domain

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Introduction

End stage of chronic renal disease (ESRD) is the irreversible stage of kidney malfunctions. Due to the fact that hemodialysis (HD) is the most popular method of the renal replacement therapies, the ESRD patients treated with HD have been the biggest population of ESRD patients in Thailand. However, the high mortality rate of these patients is mainly due to sudden cardiac death (SCD)[1]. A predisposing cause of SCD in these patients has been known as dialysis inadequacy leading to the accumulation of the waste products in which it can be called uremic toxin. However, the PTH has been generally accepted as a very potent uremic toxin. The main function of PTH is the homeostasis control of calcium and phosphorus level. A number of studies have found that this hormone can damage multi-organ systems, particularly, the cardiovascular system[2]. The long term effect of PTH causes an irreversible change of the myocardial function and vascular calcification[2]. Generally, the heart has auto-regulatory function which is manipulated by the sympathetic and parasympathetic nervous system. The imbalance of the autonomic nervous system (ANS) has been insisted as an etiology of SCD[3]. It has been reported in healthy dogs that PTH intravenous injection causes the abolition of nerve conduction velocity (NCV) and an electroencephalogram (EEG) and these disturbances were attenuated after parathyroidectomy[3]. Thus, it might be that the normal cardiac function regulated by the ANS is, at least in part, maintained by appropriate level of PTH. There are few studies related to the effect of PTH on HRV parameters in HD patients. Therefore, this study aimed to examine the effect of PTH on the cardiac ANS and their correlations in HD patients using the HRV method, a non-invasive technique for the evaluation of cardiac ANS functions.

Method

Subjects

All subjects who participated in this study were volunteers. The study protocol was approved by the Nopparat Rajathanee human subject committee (IRB/IEC reference 19-2555). Prior to writing consent forms, the experimental details were informed to the subjects. A total of twenty healthy subjects (10 males and 10 females) were randomly selected from those undergoing annual health check-up and invited to join the study. For HD patients, the subjects were recruited from the dialysis unit of Nopparat Rajathanee hospital and the HD centers in Bangkok. All patients were screened from their medical histories and selected to participate in the study by the following criteria: 1) receiving HD sessions thrice per week with Kt/V (dialysis adequacy index) being over 1.2 according to NKF-DOQI (National Kidney Foundation Dialysis Outcomes Quality Initiative) recommendation and the URR (urea reduction ratio) and nPCR (normalized protein catabolic rate) being adequate ranges, 2) having no sign of inflammation or infection, 3) having hypotensive resistance and body weight gain less than one liter per day during each HD session. The patients who had diabetes mellitus, cardiac arrhythmia and other cardiac diseases as well as those who took drugs that influence ANS for instance β-blocker and digitalis glycoside were excluded from the study. The demographic and clinical data such as age, race, gender, total months on dialysis, and causes of ESRD before enrollment were also documented. Each patient was conventionally treated by volumetric ultrafiltration control of the HD machine (Fresenius Kabi AG, Germany or Nikkiso Co., Ltd., Japan) and the concentration of bicarbonate-based dialysis fluid was kept constant. The concentration of sodium, potassium, chloride, bicarbonate and calcium were 138, 2, 109.5, 32 and 2.5 mEq/L, respectively. The membrane type of hollow fiber dialyzers was polysulphone. Aluminum hydroxide, calcium carbonate, calcium citrate, and lanthanum carbonate were prescribed for all patients as phosphate binder. Angiotensin-converting enzyme inhibitor and calcium channel blocker were used as antihypertensive drugs.

Protocol

The vital signs; body temperature, heart rate (HR), respiratory rate, blood pressure (BP), and the standard 12-lead electrocardiogram (ECG) were recorded and analyzed by cardiologist or nephrologist for all of the subjects. The abnormalities of vital signs, ECG and the history of tobacco smoking and alcohol drinking of the subjects

were neglected from this study. Blood was drawn from the subject's vein to examine serum PTH concentrations (using electrochemiluminescence immunoassay from Roche Diagnostics, Switzerland) and hematological parameters. The healthy subjects who had the abnormality in clinical or laboratory data were also excluded whereas the abnormalities of serum urea, creatinine, etc were found more often in the patients. Depending on the PTH concentration, the patients who had PTH concentration of 150 - 300 pg/mL were determined as high PTH group (H-PTH) whilst the ultra high PTH group (UH-PTH) was assigned in patients who had PTH of greater than 300 pg/mL. The appropriate dose of active-formed vitamin D, 1-α $(OH)_2D_3$, was prescribed by nephrologist to the patients who were in UH-PTH.

In this study, the subjects were divided into three groups. The first group was twenty healthy age-matched controls (HS) consisting of ten males and ten females. The second group was fifteen subjects (eight males and seven females) of H-PTH. The final group was twenty subjects (twelve males and eight females) of UH-PTH. Each patient was asked to stop taking their routine medications in particular antihypertensive drugs for twelve hours (8.00 p.m. to 8.00 a.m.) before the beginning of the study in order to avoid any effects on HR. Unfortunately, the longer duration of drug cessation could not be processed because the adverse treatment to the patients might be occurred. This should be considered and addressed as the limitation of the study.

Heart rate variability

The HRV measurement was performed on the morning of the day after dialysis while the HRV measurement of HS was conducted on the available morning day. After resting in the quietly comfortable room with adjusted temperature of approximately 25 °C for 20 minutes, the vital sign monitor (Nihon Kohden Co., Ltd., Tokyo, Japan) was used to monitor their vital signs. Prior to HRV recording, the relaxation of their body and emotion during the whole recording period were informed to each subject in order to diminish signal interference. Then, thirty minutes of raw signals from lead II ECG were recorded and stored in frequency range of approximately 0.5 - 35 Hz. The interfered signals of all subjects were manually monitored beat by beat and deleted when it was necessary. The stored signals were subsequently analyzed by the Biopac system MP 36 (Biopac system inc., Goleta, California, USA). The HRV consisting of time and frequency domain parameters were automatically calculated from R-R interval by using the Biopac Student lab pro software version 3.7.3. In the frequency domain, the raw signals of ECG were calculated by the fast Fourier transform method. The frequency domain parameters were LF (low frequency = 0.04 - 0.15 Hz), HF (high frequency = 0.15 - 0.4 Hz), and TP (total power ≤ 0.4 Hz). The LF/HF ratio was also computed. In order to get rid of the effects from the total power alteration, the absolute values had to be modified to normalized values (nu) which were calculated by using the following formula: LF or HF (nu) = LF or HF (100)/ (TP - VLF; very low frequency = 0.003 - 0.04 Hz) when TP = VLF + LF + HF. The natural logarithm was necessary for LF and HF transformation in order to avoid the skewness distribution. In this study, the measurement of HRV was in a short term since this short duration did not disturb the patient's daily life and all subjects were under similar controlled conditions.

Statistical analysis

The data were presented as mean ± standard deviation (SD). The data were analyzed statistically by the computer program. The mean values were analyzed using analysis of variance (ANOVA). The correlations between PTH concentration and the parameters of HRV were calculated with Pearson's correlation test. The p-value of < 0.05 was considered statistically significant.

Results

Table 1 presented the demographic and clinical characteristics of each studied group. There were no significant differences among all studied groups in ages. Among three groups, only the systolic blood pressure (SBP) of HS was significant lowest level. In ESRD patients, none of the demographic and clinical characteristic results showed the significant difference, particularly duration of dialysis, dialyzer clearance of urea (Kt/V), normalized

protein catabolic rate (nPCR), urea reduction ratio (URR), and glomerular filtration rate (GFR) when compared between H-PTH and UH-PTH. The causes of ESRD of both patient groups were also shown in table 1. As shown in table 2, no significant differences were found in fasting blood sugar (FBS) and serum K in all groups. Among three groups, the levels of blood urea nitrogen (BUN), creatinine (Cr), and PTH concentrations of HS were the lowest whereas the concentrations of sodium (Na), chlorine (Cl), carbondioxide (CO_2), hematocrit (Hct), hemoglobin (Hb), and albumin were the highest values. In addition, the serum levels of PTH of UH-PTH were significantly higher than those of H-PTH whereas the other laboratory results did not differ between both groups.

The HRV parameters of time and frequency domains were shown in figures 1 and 2, respectively. The

Table 1 Demographic and clinical characteristics of each studied group

Parameter	HS (n = 20)	H-PTH (n = 15)	UH-PTH (n = 20)
Age (years)	50.3 ± 12.75	52.60 ± 11.75	53.70 ± 13.65
Gender (M/F)	(10/10)	(8/7)	(12/8)
Duration of dialysis (months)	NA	46.13 ± 17.32	46.45 ± 17.11
SBP (mmHg)	112.5 ± 10.05	138.27 ± 14.62***	142.90 ± 17.08***
DBP (mmHg)	78.6 ± 6.96	80.80 ± 12.82	79.90 ± 8.84
HR (beats/min)	72.0 ± 8.40	80.27 ± 12.94	77.65 ± 11.08
Kt/V	NA	1.52 ± 0.18	1.60 ± 0.19
nPCR	NA	1.08 ± 0.39	1.15 ± 0.51
URR (%)	NA	86.40 ± 3.66	84.70 ± 4.39
GFR (mL/min/1.73 m^2)	NA	7.35 ± 2.31	8.16 ± 3.48
Etiology			
Chronic glomerulonephritis	-	5	8
Chronic pyelonephritis	-	2	4
Polycystic kidney	-	3	2
Disease			
Nephrosclerosis	-	1	1
Hypertensive	-	2	3
Neuropathy			
Obstructive uropathy	-	0	1
Unknown	-	2	1

SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, Kt/V: dialysis adequacy index, nPCR: normalized protein catabolic rate, URR: urea reduction ratio, GFR: glomerular filtration rate. The values were shown as mean ± SD. The *p*-value compared with HS group was ***$p < 0.001$. NA = not assessed

Table 2 Laboratory characteristics of each studied group

Parameter	HS (n = 20)	H-PTH (n = 15)	UH-PTH (n = 20)
BUN (mg/dL)	13.15 ± 3.05	69.33 ± 15.94***	67.50 ± 13.41***
Cr (mg/dL)	0.97 ± 0.23	8.83 ± 3.36***	9.23 ± 2.33***
FBS (mg/mL)	92.25 ± 8.68	94.43 ± 10.72	91.80 ± 11.07
Na (mEq/L)	144.65 ± 3.91	136.15 ± 3.47***	139.30 ± 3.70***
K (mEq/L)	4.75 ± 0.66	4.71 ± 0.47	4.87 ± 0.64
Cl (mEq/L)	102.90 ± 2.65	97.41 ± 3.46***	98.26 ± 5.13**
CO_2 (mEq/L)	26.70 ± 2.79	24.92 ± 2.56*	24.44 ± 3.21*
Ca (mg/dL)	NA	8.30 ± 2.14	8.89 ± 2.00
P (mg/dL)	NA	5.99 ± 2.67	5.79 ± 1.58
Ca-P product (mg^2/dL^2)	NA	46.78 ± 17.45	50.08 ± 14.86
Hct (%)	43.8 ± 3.19	35.03 ± 3.96***	33.08 ± 2.51***
Hb (g/dL)	13.63 ± 2.06	11.47 ± 1.37***	10.88 ± 0.90***
Albumin (g/dL)	4.59 ± 0.26	4.23 ± 0.38**	4.27 ± 0.37*
PTH (pg/mL)	28.9 ± 11.8	209.27 ± 41.04***	698.40 ± 203.95***###

BUN: blood urea nitrogen, Cr: creatinine, FBS: fasting blood sugar, Na: sodium, K: potassium, Cl: chloride, CO_2: carbondioxide, Ca: calcium, P: phosphorus, Ca-P product: calcium-phosphorus by product, Hct: hematocrit, Hb: hemoglobin, PTH: parathyroid hormone. The values were shown as mean ± SD. The *p*-value compared with HS were *$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$. The *p*-value between H-PTH and UH-PTH was ###$p < 0.001$. NA = not assessed

triangular interpolation of N-N interval (TINN) and natural logarithm of high frequency (lnHF) values of HS were highest among three subject groups. Although most of the HRV parameters including standard deviation of N-N intervals (SDNN), root mean square of the successive differences (RMSSD), natural logarithm of total power (lnTP) and, natural logarithm of low frequency (lnLF) were at highest levels in HS, their values did not reach statistically significant differences. Comparison to UH-PTH, the RMSSD value of HS was higher significantly. In addition, the highest value of lnLF/HF ratio was shown in H-PTH group. Compared between both hyperparathyriod groups, the values of standard deviation of the averages of N-N intervals (SDANN), SDNN, TINN, HRV index, lnTP, lnLF, and lnLF/HF ratio of UH-PTH were significantly lower than those of H-PTH group.

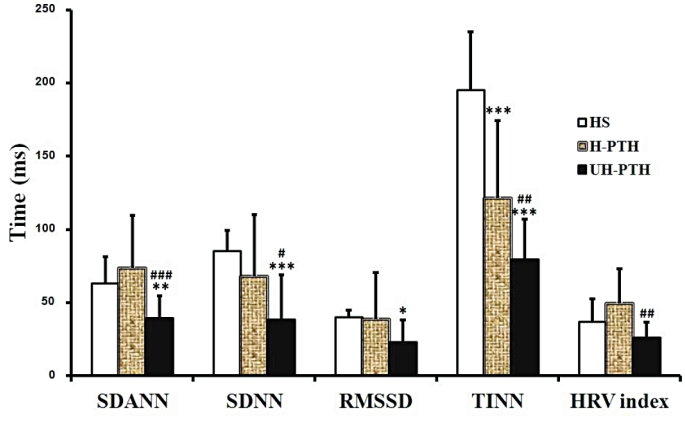

Figure 1 The time domain parameters of heart rate variability in hemodialysis patients with secondary hyperparathyroidism

Data were shown as mean ± SD. The *p < 0.05, **p < 0.01 and, ***p < 0.001 were significant when compared with HS group. The #p < 0.05, ##p < 0.01, and ###p < 0.001 were significant when compared between H-PTH and UH-PTH groups.

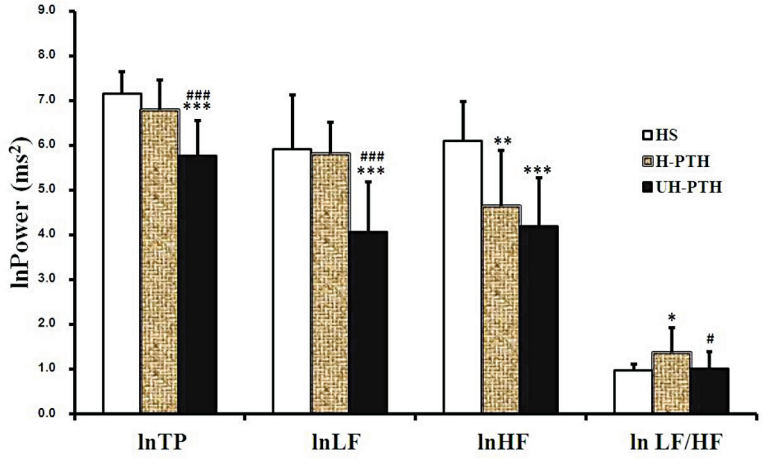

Figure 2 The power of frequency domain parameters of heart rate variability in hemodialysis patients with secondary hyperparathyroidism

Data were shown as mean ± SD. The *p < 0.05, **p < 0.01, and ***p < 0.001 were significant when compared with HS group. #p < 0.05, ##p < 0.01, and ###p < 0.001 were significant when compared between H-PTH and UH-PTH groups.

In figures 3 and 4, the significant negative correlations between PTH levels and each time domain parameter of HRV were demonstrated as follows: TINN (r = -0.564; p-value < 0.001), SDANN (r = -0.410; p-value < 0.01), and HRV index (r = -0.229; p-value < 0.05), respectively. For the frequency domain parameters, the statistically inverse correlations with lnPTH were also found for lnTP (r = -0.462; p-value < 0.01), lnLF (r = -0.633; p-value < 0.01), and lnLF/HF (r = -0.394; p-value < 0.05). Obviously, the lnLF showed the highest negative correlation with lnPTH.

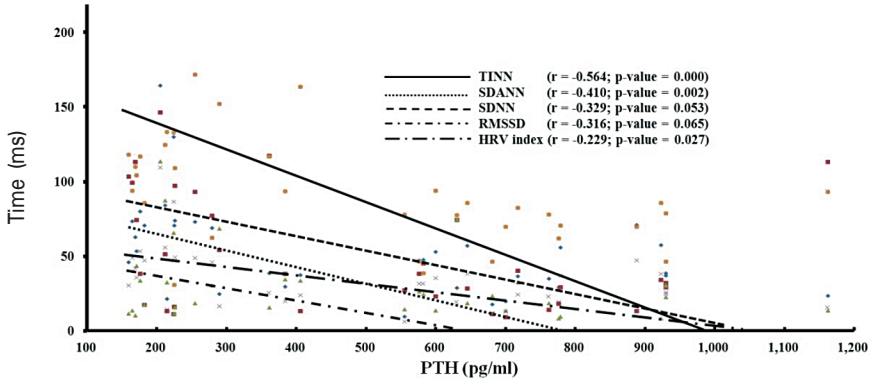

Figure 3 The correlation between serum PTH concentration and time domain parameters of HRV

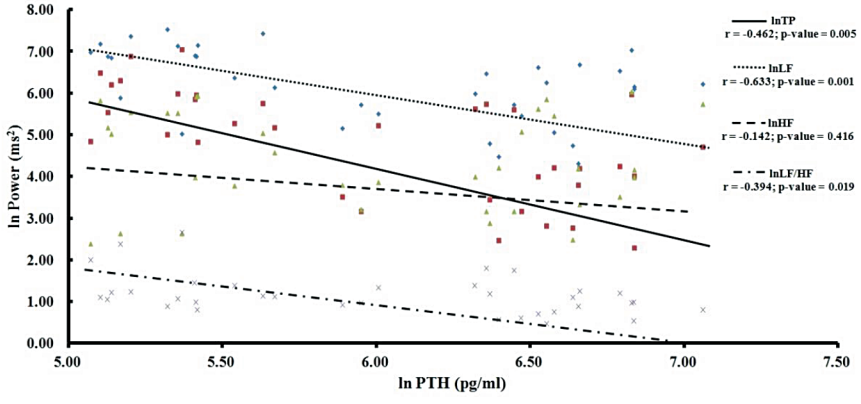

Figure 4 The correlation between serum lnPTH concentration and frequency domain parameters of HRV

Discussion and Conclusion

All subjects who participated in this study had no complication for HRV interference. In addition, there were no differences in age, gender, and dialysis duration which may affect HRV. For HD patients, SBP was significantly higher than that of control group (HS). It was believed that the increased BP may be due to the elevation of serum PTH level[5, 6]. The proposed mechanism was probably due to the elevation of intracellular calcium promoting arteriolar smooth muscle contraction resulting in hypertension from the increased total arteriolar peripheral resistance[5]. Another mechanisms of HPTH-induced hypertension are suggested to be the sympathetic hyperactivity[7] and the increased cardiovascular reactivity to noradrenaline[8]. To confirm that HPTH is the cause of hypertension, the study of Heyliger *et al*. indicated that parathyroidectomy attenuated the elevation of SBP and DBP in hypertensive patients with primary hyperparathyroidsm[6].

Sodium retention is one of the most important causative factors for the hypertension in HD patients[9]. The obtained results showed that the serum sodium concentration of HD patients was significantly lower than that of HS. No matter how, their values were in normal ranges. As a consequence, the sodium retention was not the main factor for hypertension in HD patients in this study. The lower serum sodium concentration in HD patients might be due to the sufficient sodium ion removal from their blood to dialysate fluid during HD procedure and the properly restricted low dietary sodium of these patients. Additionally, the metabolic acidosis is a normal complication of HD patients because of the inability of kidney to excrete excess hydrogen ion[10]. Therefore, the lower serum CO_2, metabolic

acidosis status, was found undoubtedly. However, their values were within normal limit. For HD patients, the Hct and Hb values were lower when compared to HS. This might result from the reduction of erythropoietin synthesis and bone marrow fibrosis induced by PTH[11].

Compared to the HS, a few HRV parameters were found at lower values in H-PTH whereas a large number of these parameters were observed in UH-PTH. Additionally, the significantly lower values of SDANN, SDNN, TINN, HRV index, TP, and LF were also observed in UH-PTH compared to H-PTH. These results suggested that the levels of serum PTH lead to gradual elevation in cardiac autonomic dysfunction. The related study by Polak *et al.* reported that the group with PTH ≥ 275 pg/mL had higher value of TP and lower values of LF than the group with PTH < 275 pg/mL but the difference in LF values did not reach statistical significance (*p*-value = 0.06). Insignificant differences in HF and LF/HF ratio between these groups were also shown in their studies[12]. Some different results found in the present study were not only TP and LF but also LF/HF ratio of UH-PTH which were significantly lower when compared to H-PTH. These discrepancies might be due to the classification of HD patients according to serum PTH concentration. Following NKF-DOQI, the target range of serum PTH concentration in mild HPTH is approximately 150 - 300 pg/mL and severe HPTH is over 300 pg/mL[13]. In addition to the study of Polak *et al.*, the time domain parameters were also investigated in this study and the results corresponded to the frequency domain parameters.

The parameters of total ANS activity (SDANN, HRV index, TINN, and TP) and the parameters of sympathetic nerve activity (SDNN and LF) were significantly lower in UH-PTH. In contrast, the parasympathetic nerve activity represented by RMSSD and HF did not show any significant difference. The results can be summarized that PTH exerts the unfavorable effects to cardiac ANS and its effect is rather on the sympathetic nerve activity than parasympathetic activity in HD patients. Some authors stated that the sympathetic nerve activity significantly negatively correlated not only to SDNN but also LF whilst the parasympathetic nerve activity was directly related to HF and RMSSD[14]. In this study, the significantly lower levels in LF and SDNN of UH-PTH when compared to H-PTH implied that the high serum PTH concentration influenced on the increased sympathetic nerve activity instead of the decreased parasympathetic nerve activity. When Pearson's correlation method was utilized, the negative correlation coefficients between serum PTH concentration and LF (r = -0.633; p-value = 0.001) and SDNN (r = -0.329; p-value = 0.053) can be again confirmed to this conclusion.

A number of studies have investigated the mechanism of HPTH to induce the cardiac sympathetic hyperactivity. Armemgol *et al.* demonstrated that HD patients with HPTH had elevated catecholamine release[15]. Barletta *et al.* revealed that chronic HPTH leads to hypercalcemia activation which is the permissive role of the stimulation of catecholamine release by PTH[16]. The study of Potthoff *et al.* postulated the signaling pathway of PTH induced the catecholamine release. The PTH mediated the activation of PTH receptors which were G-protein couple receptor and its secondary messenger was cAMP[17]. In this study, the greatest reduction in LF and SDNN were found in UH-PTH. Furthermore, the Pearson's correlation coefficient between serum PTH concentration and LF as well as SDNN strongly confirmed the effect of PTH on sympathetic hyperactivity in HD patients. Consequently, the potential benefit from this study of the antihypertensive drug should be carefully considered in HD patients who were HPTH. Angiotensin converting enzyme inhibitor (ACEI) and angiotensin converting enzyme (ACE) blocker which are not affected by PTH may be the drug of choice. In addition, the HRV method can be utilized as the prognostic predictor for cardiac autonomic neuropathy in HD patients with HPTH.

Conclusion

PTH, a severe uremic toxin, produced by parathyroid glands could partly induce cardiac autonomic dysfunction, in particular an increased sympathetic activity, as detected by the lowest values of time and frequency domains in UH-PTH using the HRV method and the highest inverse correlation between lnLF and lnPTH.

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บทคัดย่อ

ความสัมพันธ์ระหว่างความแปรปรวนของอัตราการเต้นของหัวใจกับพาราไทรอยด์ฮอร์โมนในผู้ป่วยที่ได้รับการฟอกเลือดด้วยเครื่องไตเทียม

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บทนำ: การมีระดับของพาราไทรอยด์ฮอร์โมน (parathyroid hormone; PTH) สูงซึ่งมักพบในผู้ป่วยไตวายเรื้อรังระยะสุดท้ายที่ได้รับการบำบัดด้วยการฟอกเลือดด้วยเครื่องไตเทียมอาจเป็นสาเหตุที่ทำให้เกิดพยาธิสภาพของระบบประสาทอัตโนมัติของหัวใจ (cardiac autonomic neuropathy)

วิธีการศึกษา: ทำการศึกษาเปรียบเทียบทั้งโดเมนความถี่ที่ถูกแปลงด้วยการแปลงฟูเรียร์แบบเร็ว (fast Fourier transform) แสดงผลในรูปของลอการิทึมธรรมชาติ (natural logarithm; ln) และโดเมนเวลาของความแปรปรวนของอัตราการเต้นของหัวใจ (heart rate variability; HRV) ระหว่างกลุ่มควบคุมที่มีสุขภาพสมบูรณ์ กลุ่มผู้ป่วยที่มีระดับของ PTH สูง (H-PTH = ๑๕๐ - ๓๐๐ พิโคกรัม/มิลลิลิตร) และกลุ่มผู้ป่วยที่มีระดับของ PTH สูงมาก (UH-PTH > ๓๐๐ พิโคกรัม/มิลลิลิตร) นอกจากนี้ยังได้วิเคราะห์ความสัมพันธ์ระหว่าง PTH กับแต่ละตัวแปรของ HRV ด้วยสหสัมพันธ์เพียร์สัน

ผลการศึกษา: จากการศึกษาพบว่าทั้งโดเมนความถี่และโดเมนเวลาของกลุ่ม UH-PTH มีค่าต่ำสุดในขณะที่ค่าของ natural logarithm of total power (lnTP), natural logarithm of low frequency (lnLF), low frequency to high frequency ratio (LF/HF), standard deviation of the averages of N-N intervals (SDANN), standard deviation of N-N intervals (SDNN), triangular interpolation of N-N interval (TINN) และ HRV index ของกลุ่ม UH-PTH มีค่าต่ำกว่ากลุ่ม H-PTH อย่างมีนัยสำคัญ นอกจากนี้ยังพบว่า lnLF มีความสัมพันธ์แบบผกผันมากที่สุดกับระดับของ PTH ที่ r = -0.633

วิจารณ์ และสรุปผลการศึกษา: การที่พบค่าต่ำสุดของ LF และ SDNN ในกลุ่ม UH-PTH และการที่ LF มีความสัมพันธ์มากที่สุดกับระดับของ PTH มีผลทำให้เกิดภาวะ cardiac autonomic neuropathy จากความเป็นพิษของ PTH โดยมีผลทำให้เกิดภาวะ cardiac sympathetic hyperactivity

คำสำคัญ: โดเมนความถี่, การฟอกเลือดด้วยเครื่องไตเทียม, ความแปรปรวนของอัตราการเต้นของหัวใจ, พาราไทรอยด์ฮอร์โมน, โดเมนเวลา