EFFECTS OF OBESITY ON HEART RATE VARIABILITY IN CONTINUOUS AMBULATORY PERITONEAL DIALYSIS PATIENTS

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ABSTRACT

Not only obesity but also chronic kidney disease (CKD) replaced with continuous ambulatory peritoneal dialysis (CAPD) have been known as the cause of cardiac autonomic nervous system dysfunction (CAD) but there has been no study on these both conditions affecting the CAD. Thus, this aims to study the effects of obesity in CAPD patients on CAD which was evaluated by the heart rate variability (HRV) method. There are 77 subjects aged between 30-60 years old, categorized from their body mass index (BMI) as; normal health (NH) group, CAPD normal (CN) group, and CAPD obese (CO) group. From the results, when compared between CO and CN groups, it was found that the parasympathetic nervous system (PNS) function of CO group has been decreased. This was confirmed by the decline of the percentage of adjacent NN intervals with a difference more than 50 millisecond (pNN50). In addition, the higher increase of sympathetic nervous system (SNS) of CO group has been shown by the elevation of systolic blood pressure (SBP) and heart rate (HR) compared to the CN group. Thus, the CAPD patients with obesity have been apparently shown that they have more CAD than CAPD patients with normal body weight. When the data were analyzed for correlation, the results showed that natural logarithm of high frequency (lnHF) is inversely related to triglyceride (TG) level with $r = -0.335$, $p = 0.009$, whereas, natural logarithm of low frequency (lnLF) is directly related to TG level with $r = 0.314$, $p = 0.014$. Consequently, it can be proposed that TG level may be an indicator for CAD in CAPD obese patients.

Keywords: obesity, continuous ambulatory peritoneal dialysis, heart rate variability, cardiac autonomic nervous system dysfunction

1. INTRODUCTION

Obesity is a condition from which the body has an excess accumulation of fat, which may cause from current daily routines and activities such as overeating and/or lacking of exercise [1]. According to the International Association for the Study of Obesity (IASO), the International Obesity Task Force (IOTF) and the World Health Organization (WHO) proposed BMI cut-points 23.0 to 24.9 kg/m^2 for being overweight and above 25.0 kg/m^2 for obesity in adult Asians [2].

CKD is a condition from which the kidney has been damaged and is not able to perform its functions completely. Subsequently, the retention of both body waste products such as blood urea nitrogen and creatinine, and excess water has been occurred [3]. The CKD patients can be treated by one of the renal replacement therapy (RRT) methods. One of the most popular methods from Thailand renal replacement therapy registry report is CAPD [4] and it is one technique of the dialysis which performs at blood vessels of peritoneal wall. Peritoneal dialysis (PD) solution has been used as the media for the waste product exchanges from the blood circulation. The important gradient of the PD solution is the glucose consisting of various concentrations which are 1.25, 1.5, 2.50, and 4.25%. However, the glucose has been absorbed through capillary vessels at the peritoneal wall, particularly, during dialysis procedure which may lead to the phenomenon of hyperglycemia. The abundant glucose in the blood circulation of the patients with sedentary habit will be transformed to the fat and accumulated at body tissues and organs. Comparing to hemodialysis (HD) patients, this mechanism induces the high opportunity to the obesity and dyslipidemia of CAPD patients [5]. Additionally, according to the study of W. Litwin, et al [6]., the patients initiated replacement with CAPD had a higher risk of death than those with HD. The main prevalence cause of its mortality rate occurs from cardiovascular abnormality.

Cardiac autonomic nervous system (CANS) is the normal neural control of cardiac functions. However, CAD caused from CKD may be documented from the study of M. Cignarelli, and O. Lamacchia [7]. It has been found that the activations of SNS in CKD patients are

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increased due to the effects from the over secretion and excitation of renin hormone. Subsequently, the CAD is an important cause of death in CKD patients.

HRV measurement is a method used to evaluate the function of CANS. The study of W. Khrisanapant, et al. has recommended that HRV analysis is a popular, convenient, non-invasive, and effective method [8]. It can be analyzed in form of both time domain (TD) and frequency domain (FD). From the study of S.L. Birch, et al [9]., the HRV value between healthy and obese children was investigated. The data were indicated that HRV value was abnormally found by the elevation of SNS in obese children comparing to healthy children. The result was able to conclude that the obesity has higher risk for CAD. Likewise, for the CAPD patients, the study of B. Dursun, et al., has reported that HRV value of the CAPD patients was abnormal and significantly different from the healthy person [10]. From a number of the previous studies, the CAD can be particularly occurred not only in CAPD patients but also in the obese person and may lead to the high risk for the mortality. As above mentioned, the patients with CAPD apparently tend to grow up their body weight and become to the obesity. Consequently, the obesity may be able to augment the CAD in CAPD patients. However, no study of CAD evaluated by HRV method in CAPD patients with obesity has been investigated. Therefore, the CANS of the CAPD patients with obesity would be evaluated by a HRV method.

2. MATERAILS AND METHODS

Study subject: The considered subjects aged between 30-60 years old, are evaluated by questionnaire and physical examination. All procedures were considered from the Nopparat Rajathanee hospital ethics committee in human research. The clinical assessments and measurements require the consent of the subjects by signing consent form as the document. The subject groups are classified by BMI into 3 groups as: 1) 28 subjects of normal health (NH: 15 males, 13 females) with BMI between 18.5-24.9 kg/m^2, 2) 30 subjects of CAPD without obesity (CN: 16 males, 14 females) with BMI between 18.5-24.9 kg/m^2, and 3) 19 subjects of CAPD with obesity (CO: 10 males, 9 females) with BMI above 25.0 kg/m^2.

Experiments: The subjects were interviewed following the questionnaire about their general information, for example, gender, age, alcohol drinking and smoking habit. In addition, the stimulant drugs and agents were recorded. The body weight (BW, kilogram) and height (meter) using standard weight and height scales of each subject were recorded and calculated in term of BMI and waist circumference (WC). The clinical assessments were then performed as; heart rate, systolic blood pressure and diastolic blood pressure (DBP). Moreover, the electrocardiogram (ECG) using BIOPAC system (BIOPAC, USA) of the subjects will be analyzed by cardiologist. The subjects with ECG abnormalities will be excluded from the experiment. For the CAPD patients with and without obesity, the drawn blood from each subject was analyzed for cholesterol, very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), high-density lipoprotein (HDL), TG, hemoglobin A1c (HbA1c), fasting blood sugar (FBS), albumin, blood urea nitrogen (BUN), creatinine (Cr), normalized protein nitrogen appearance (nPNA), and Kt/V (dialysis adequacy) were also determined. After blood testing, the subjects were asked to lie with the supine position in a comfortable quiet room. Then, ECG signal was recorded and analyzed by BIOPAC system. The three electrodes for ECG lead II signals were attached on left and right arms meanwhile the right leg was used for electrical ground. The subjects were advised to be calm while their signals were collected for 40 minutes. Each collected signal was scanned and checked. The interference or noise signal will be gotten rid from the normal ECG signal. Then, 15 minutes of ECG signals were analyzed by BIOPAC BSL Pro 3.7.3 software and demonstrated the HRV parameters in form of both time and frequency domains.

Statistical analysis: The data were presented as mean and standard deviation (mean ± SD) and the normal distribution was analyzed by computer program. The one-way analysis of variances (one-way ANOVA) was used to investigate the significantly difference between the groups at $p<0.05$. The Pearson's correlation method was used to analyze the relationship between each HRV and obesity parameters.

3. RESULTS

Table 1: Demographics and clinical characteristics of each subject group

Variables	Normal subject	CAPD subject	
	NH group	CN group	CO group
Sex	28 (M15, F13)	30 (M16, F14)	19 (M10, F9)
Age (year)	43.71±9.73	48.57±11.64	49.68±7.80
BW (kg)	58.39±5.84	58.23±9.34	73.67±9.62$^{*\#}$
Height (cm)	162.61±6.94	162.43±8.98	160.04±10.13
BMI (kg/m^2)	22.09±1.84	21.74±2.07	29.07±4.40$^{*\#}$
WC (inch)	32.15±3.40	33.63±3.88	40.35±3.38$^{*\#}$
DD (year)	NA	1.89±0.68	1.79±0.67
Kt/V	NA	2.13±0.62	2.14±0.78
nPNA	NA	1.11±0.38	1.02±0.22
SBP (mmHg)	120.29±18.45	144.57±17.63*	156.21±18.15$^{*\#}$
DBP (mmHg)	78.11±11.13	75.57±12.15	97.74±11.38
HR (bpm)	99.20±14.01	110.07±11.24*	117.97±11.29$^{*\#}$

The values were shown as mean ±SD, NA = not assessment
**, # means the significant difference with NH and CN groups at $p<0.05$, respectively.*

The demographics and clinical characteristics of the subjects were presented in table 1. For the sex, age and height, they were shown insignificant differences among three groups. Similarly, the duration of dialysis (DD), Kt/V, and nPNA, they were not shown any significant differences between CO and CN groups. The CO group

showed the highest BW, BMI and WC while these parameters did not have any significant differences between NH and CN groups. Additionally, the SBP and HR of CO group showed the highest value meanwhile the CN group has higher of these values than the NH group

Table 2: The blood parameters of CAPD patients with and without obesity

Variables	CAPD subject	
	CN group	CO group
TG (mg/dL)	126.30±54.47	173.68±87.58 *
Cholesterols (mg/dL)	176.33±52.21	173.26±53.87
VLDL (mg/dL)	31.23±16.92	35.67±22.88
LDL (mg/dL)	117.50±43.57	108.16±38.09
HDL (mg/dL)	48.43±15.27	42.53±14.21
Albumin (mg/dL)	3.55±0.51	3.55±0.65
BUN (mg/dL)	41.57±13.86	48.11±12.54
Cr (mg/dL)	9.85±4.02	14.93±24.82
HbA1c (%)	5.94±1.43	7.62±3.22 *
FBS (mg/dL)	111.43±33.73	133.79±30.30 *

The values were shown as mean ±SD
** mean the significant difference at p<0.05.*

The laboratory parameters of blood analysis were presented in table 2. Considering the effect of obesity, when the comparing of the data between CN and CO groups were performed, the parameters consisting of TG (p=0.024), HbA1c (p=0.016), and FBS (p=0.023) have been shown statistically significant differences, respectively.

Table 3: Time and frequency domain parameters of each subject group

Variables	Normal subject	CAPD subject	
	NH group	CN group	CO group
SDANN (ms)	47.58±25.22	42.97±28.52	23.87±13.80 *#
SDNN (ms)	53.13±25.20	41.81±25.18	28.22±13.81 *
RMSSD (ms)	33.76±4.86	28.25±3.45 *	27.53±3.31 *
pNN50 (%)	49.32±52.94	45.82±27.58	11.20±12.29 *#
lnLF (ms^2)	4.25±0.31	4.30±0.17	4.37±0.12 *
lnHF (ms^2)	3.17±0.50	3.10±0.33	2.95±0.44
lnLF/HF ratio	1.08±0.80	1.25±0.44	1.42±0.55 *

The values were shown as mean ±SD
**, # means the significant difference with NH and CN groups at p<0.05, respectively.*
SDANN; the standard deviation of the average NN intervals,
SDNN; the standard deviation of NN intervals,
RMSSD; the root mean square of the successive differences,
lnTTP; natural logarithm of the total power,
lnVLF; natural logarithm of the very low frequency,
lnLF/HF ratio; natural logarithm of LF/HF ratio

The parameters of time and frequency domain from the HRV analysis were presented in table 3. Considering the effect of the CKD replaced with CAPD method, the RMSSD values showed the significant lower in CN group when compared to NH group (p=0.000). In the group of CAPD patients with obesity, the almost parameters of time domain including SDANN, SDNN, RMSSD and pNN50 present the lower values when were compared with NH group. Additionally, the effect of obesity on CAPD patients was able to induce the less values of time domain confirmed by the comparisons between CO and CN groups. These parameters were shown as follows: SDANN (p=0.030), and pNN50 (p=0.006). For the frequency domain, considering the effect of obesity accompany with the CAPD, the CO group has greater value of lnLF (p=0.043), and lnLF/HF ratio (p=0.047) than NH group.

The graphic correlations between TG level and each parameter of time and frequency domains in CO group were presented in figure 1. With TG level, the lnHF value presented the highest inverse correlation with r = -0.335; p = 0.009 whereas, the lnLF, and lnLF/HF ratio value presented direct correlation with r = 0.314; p = 0.014 and r = 0.274; p = 0.028, in figure 1A and 1B, respectively.

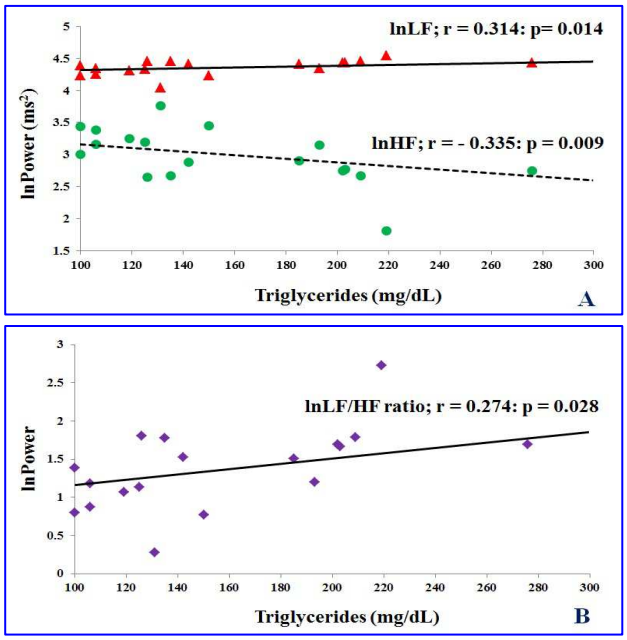

Fig 1: The correlation coefficients between TG and FD of CO group (A) lnLF and lnHF, (B) lnLF/HF ratio.

4. DISCUSSION

In CN group, the higher of the SBP and HR compared to NH group were shown. These results are partly due to the activation of renin-angiotensin system which is the elevations of vasoconstriction, cardiac muscle contraction and heart rate [11]. According to the study of P.E. Brovo, the nitric oxide production induced by renal ischemia has been proposed as its mechanism [12]. Moreover, the highest of the SBP and HR were found in CO group as well. These results demonstrated that the obesity reinforced the sympathetic effect on cardiovascular system in CAPD patients. Although the mechanism has been fully unclear, the studies of W. Triprom [13], and K.A. Sikaris [14], have mentioned that it may be the consequence from the leptin hormone secreted by adipose cells. Both increase of sympathetic neurotransmitter,

norepinephrine, secretion and the activation of adrenergic receptor sensitivity at the arterial smooth muscle and myocardial were influenced by the leptin hormone. The predisposing factor for the obesity in CAPD patients may be due to the diffusion of high glucose concentration from the PD solution into the blood circulation. This can be confirmed by the significant elevation of HbA1c, and FBS of the CO group compared to CN group. The corresponding results have been found by the studies of F.H. Zayr, et al [15].

They indicated that the obese people have higher of these two parameters of diabetes mellitus than normal healthy. The similar result that the higher level of TG in CO group compared to CN group may be the result from the alteration of the excess blood sugar and blood lipid [13]. The study of M.A. Paschoal, et al., demonstrated that the obesity group significantly more increases in TG and VLDL whereas more decrease in HDL [16]. Unfortunately, the current data found that only the TG elevation of the CO group was found. The study of M. Cignarelli, et al [7]., and M.A. Paschoal, et al [16]., proposed that the atherosclerosis from hyperlipidemia causes the ischemic effects to the various organs such as kidney, heart, and cerebrum. Particularly, the renal ischemia is the common consequence for the hypertension by the activation and secretion of the renin hormone. In addition, the CAD may be occurred from either heart or cerebral ischemia [7]. The greater decrease of time domain including pNN50 of the CO group when compared to the CN group indicated that the obesity might augment the CAD in the CAPD patients with obesity. Although, it has been investigating, the proposed mechanism may be due to the effect of leptin hormone. A number of studies have been documented that a large amount of leptin hormone was found in the obese subjects [12, 17-18]. These studies suggested that leptin hormones may cause the abnormality of baroreceptor reflex [11] and eventually induces the CAD [8-9]. For the current study, the CAD of CAPD patients with obesity is occurred from the decrease of parasympathetic activity which was documented by the decrease of pNN50. According with the study of B. Dursun, et al., and J. Pei, et al., the obesity inhibits the parasympathetic activity demonstrated by the lower values of RMSSD, pNN50 and lnHF, but the increase of sympathetic activity is clarified by the elevation of lnLF [10, 19]. Unfortunately, the lower of only pNN50 in this current study has been found.

Particularly, the correlation analysis between the parameters of obesity and HRV in CO group indicated that the concentration of blood TG is directly related with lnLF and lnLF/HF ratio values whereas it is inversely related with lnHF. The high level of TG can induce the increasing of blood viscosity [20] especially cerebral thrombosis affecting to autonomic nervous system function [7, 17]. That is the main factor related to obesity and cardiovascular diseases. The study of M.A. Paschoal, et al [16]., and J. Hirsh, et al [21]., has suggested that the abnormality of SNS is the consequence from high level of TG. From the result, the benefits are the using of the TG concentration as an indirect index to preliminary evaluation for the CAD and the nephrologists should be aware of prescribing the medication involving the autonomic nervous system in CAPD patients with obesity.

5. CONCLUSION

In summary, the elevation of TG level in CAPD patients with obesity is a factor that has the influence on the HRV as increasing of lnLF, and decreasing of lnHF. These show the increased functioning of SNS. Also, the renin secretion is the stimulation of SNS documented by the increasing of HR and SBP in CAPD patients. Moreover, the obesity categorized by BMI value promotes the deterioration effect to CANS in CAPD patients via abnormality on the baroreceptor reflex. Consequently, the CAPD patients with obesity have more sensitive to CAD leading to the increasing of mortality rate.

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