Effect of Obesity on Cardiac Autonomic Nervous System of Continuous Ambulatory Peritoneal Dialysis Patients

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ABSTRACT

Both the obesity and end stage renal disease (ESRD) treated with continuous ambulatory peritoneal dialysis (CAPD) have been known that have the adverse effect on the cardiac autonomic nervous system. Therefore, the objective of this study is to investigate the reinforcement of the obesity in the CAPD patients to function of the cardiac autonomic nervous system. In this study, the non-invasive techniques were used to evaluate the cardiac autonomic nervous system. The results showed that the systolic blood pressure (SBP) and heart rate (HR) of both CAPD patients groups were significantly highest values with p = 0.000 for rest period. It was the result from the sympathetic hyperactivity. In the other hand, the comparison between the obese and non-obese groups of both healthy subjects and the CAPD patients showed that there were no any significant differences on the cardiac autonomic nervous system detected by resting blood pressure and heart rate. However, the obesity can induce the parasympathetic hypoactivity in the CAPD patients resulting from the decrease in heart rate responses to deep breathing (p = 0.048). For the orthostatic test, the CAPD patients had the higher difference of the systolic blood pressure (DSBP) between supine and standing positions than that in non-CAPD patients. The results indicated that the sympathetic hypoactivity has been found in the CAPD patients. The mechanism of this phenomenon may be due to the high uremic toxin concentration which gradually deteriorated the baroreceptor reflex activity. Interestingly, the obesity did not obviously augment the cardiac autonomic nervous system in the CAPD patients in this study.

Keywords: obesity; continuous ambulatory peritoneal dialysis; autonomic nervous system; heart rate

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1. INTRODUCTION

The obesity has been clearly considered as the excessive accumulation of the body fat leading to the abnormal overweight. The overeating and/or sedentary habits are considered as main causes of obesity [1][2]. At present, the obesity population has been rapidly growing up and seriously causes of hospitalization, morbidity and mortality rates. From the international obesity task force (IOTF), the population of normal weight, overweight, and obesity are determined when their body mass index (BMI) are 18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2, and over 29.9 kg/m^2, respectively [3]. The previous studies had been found that the obesity can induce the abnormality of cardiac autonomic nervous system function via the impaired sympathetic and parasympathetic systems [1][4][5]. However, these effects of obesity on autonomic nervous system remain different.

ESRD has been defined as the loss of the essential kidney functions, which are the homeostatic control of total body water and uremic waste products. Subsequently, ESRD patients have to receive one of the renal replacement therapy (RRT). Currently, there are three methods of RRT; kidney transplantation (KT), hemodialysis (HD), and continuous ambulatory peritoneal dialysis (CAPD). In Thailand, the national health security office (NHSO) has supported the expenditure of medical treatments for the CAPD patients. Therefore, the number of the CAPD patients may be the main population of ESRD patients. However, the high mortality rates of these CAPD patients have been the result from the dysfunction of cardiac autonomic nervous system [6]. The most common cause of death is the cardiac arrhythmia [7]. The previous studies have been found that the CAPD procedure leading to the obesity by increasing of the body fat percentage and body mass index. These two parameters of the obesity have directly related to the duration of treatment [8]-[10]. Manji et al. has proposed that the highly concentrated dextrose in dialysate solution fully diffuses into the blood circulation via peritoneal membrane [11]. This may be the reason why the CAPD patients were easily induced to the obesity. From the earlier mentions, not only the CAPD procedure can induce the obesity but also both the CAPD procedure and obesity have caused the cardiac autonomic nervous system dysfunction.

However, none of up-to-date literature has studied whether the obesity can reinforce to cause the cardiac autonomic nervous system dysfunction in the CAPD patients. Consequently, in this study aims to investigate the effect of obesity on the cardiac autonomic nervous system of the CAPD patients.

2. EXPERIMENTAL DESIGN

2.1 Subject

The healthy subjects and the CAPD patients were precisely invited to participate in this study. The study protocol was considered and approved by Nopparat Rajathanee Hospital human subject committee. All subjects were informed about the experimental study and were asked to write their willing consent forms. In addition, they can terminate their participation whenever they need. All participants were evaluated their medical histories and their daily habits. From Nopparat Rajathanee Hospital, both the sixty-nine healthy subjects (31 males and 38 females) who were intently selected from annual health check-up and the fifty-three CAPD patients (28 males and 25 females) who were invited to join in the investigation. The inclusion criteria for CAPD patients were as the follows: 1) Double bag system containing 1.25% dextrose for the removal of the excess volume or ultrafiltration (UF) and four cycles of 2-L dianeal solution (Baxter, USA) exchanges per day were used. 2) Kt/V, dialysis adequacy index, must be over 1.7 according to NKF-DOQI (National Kidney Foundation Dialysis Outcomes Quality Initiative) recommendation. 3) Neither sign of any inflammation nor infection such as peritonitis was found. For the CAPD patients, the exclusion criteria were 1) uncontrolled diabetes mellitus, severe hypertension, heart failure, cardiac arrhythmias, heart block and myocardial infarction. 2) continuous cigarette smoking and alcohol drinking. In addition, the clinical data such as age, race, gender, and total months on dialysis before enrollment of the CAPD patients were also documented.

In this study, body mass index was used to categorize all subjects into four groups. 1) The twenty-eight subjects (15 males and 13 females) were assigned as normal healthy group (N) who had normal BMI. 2) The forty-one subjects (16 males and 25 females) were assigned as normal obesity group (NO) who had BMI over 120 percent of normal healthy group. 3) The thirty-two CAPD patients (18 males and 14 females) were assigned as normal CAPD group (CN) who had normal BMI. 4) The twenty-one CAPD patients (10 males and 11 females) were assigned as the CAPD obesity group (CO) who had BMI over 120 percent of normal healthy group. Each volunteer of healthy subjects and the CAPD patients was recorded their vital signs, body temperatures, heart rates, respiratory rates, and blood pressures. Additionally, the twelve lead of standard electrocardiogram (ECG) was also monitored and diagnosed by cardiologists or nephrologists. The subjects who had the abnormal either vital sign or ECG were rejected from the study. The selected participants were subsequently measured their body weight (BW), body height (Ht), and waist circumference, respectively. For only CAPD patients, the blood was drawn in order to examine the parameters concerning the CAPD procedure and obesity. Unfortunately, both the CN and CO group in the current study has been limited by their routine medications which may affect the autonomic nervous system (ANS) functions. Therefore, the patients were requested to stop taking the ANS medications which were antihypertensive and/or cardiovascular drugs from 8.00 p.m. to 8.00 a.m. Because, if the cessation of drug was long-lasting, the adverse effect to the patients treatment may be occurred.

2.2 Electrocardiogram Recording

All four groups of the subjects had been recorded their ECGs on the morning of the convenient day. The subjects were invited to rest in the comfortable and quiet room with temperature of $25°c$ for 20 minutes. The vital signs were documented with the vital sign monitor (Nihon Kohden, Japan). After the electrodes were applied to their positions, the standard ECG of each subject was recorded by the ECG monitor (Fukuda 800, Japan). Then, the ECG was analyzed and the subjects who had abnormal ECG were excluded from the study.

2.3 The Measurement of Cardiac Autonomic Nervous System Responses

All four experimental tests of cardiac autonomic nervous system responses were done on the same day. Prior to the testing, the subjects were allowed to rest at least for ten minutes.

2.3.1 Orthostatic test

After fifteen-minute rest, blood pressures were measured with the sphygmomanometer at the proper arm in the supine position and then the immediately, the third minute, and the fifth minute blood pressures were recorded after standing up. These three values of the standing blood pressure were computed as mean standing blood pressure. The differences of systolic blood pressure (DSBP) between supine and mean standing position were calculated. Similarly, the differences of diastolic blood pressure between supine and mean standing (DDBP) position were calculated. The duplicate procedures of orthostatic test were done completely. The higher value of orthostatic test was considered as selected results. The orthostatic test is a method for sympathetic nervous system evaluation [1].

2.3.2 Valsava ratio method

The electrodes for lead II were applied on the right arm and the left leg while the right leg was set as electrical ground. Lead II was then recorded using the ECG monitor (Biopac AC system MP 36, USA). Prior to the testing, the procedure was trained to all subjects until they were familiar. Each subject blew via mouthpiece connected to the aneroid manometer at 40 mmHg for 10 seconds while the nose was clipped. After 30 minutes of the releasing pressure, the ratio of the longest to the shortest of the interval from R wave to R wave (R-R interval) was computed as valsava ratio. The valsava ratio was a method for parasympathetic nervous system evaluation [1].

2.3.3 Heart rate responses to deep breathing

After five-minute rest with sitting position, each subject was instructed and trained to respire deeply at the frequency of six breaths per minute. While the ECG was recoding with the speed of 50 mm per second, heart rate responses to deep breathing were calculated. The mean difference between maximum and minimum heart rate of each cycle in one minute. The heart rate responses to deep breathing were a method for parasympathetic nervous system evaluation [1].

2.3.4 30/15 ratio method

Each subject was asked to rest with supine position for fifteen minutes while the ECG had been continuously recorded. After standing, the ratio of the R-R interval at 30^{th} beat to R-R interval at 15^{th} beat was calculated and recorded in term of 30/15 ratio. The highest ratio of double tests was the obtained result. The 30/15 ratio was a method for parasympathetic nervous system evaluation [1].

2.3.5 Statistical analysis

The data were analyzed statistically by the computer program. All data were presented as mean±standard deviation (SD), because they weren't normal distribution. The mean values between four groups were analyzed using analysis of variance (ANOVA) with Turkey's method and Mann Whitney U test was used when compared between two groups. The correlations between each parameter of cardiac autonomic nervous system and the parameters of either obesity or the CAPD procedure were considered with Pearson's correlation test. The p-value<0.05 was accepted as statistical significance.

3. RESULTS

The table 1 presents the demographics and clinical parameters of each studied group. The parameters of the obese population were body weight, waist circumference, body mass index, triglyceride, cholesterol, high density lipoprotein (HDL), and low density lipoprotein (LDL) while the parameters of the CAPD procedure were hematocrit (Hct), hemoglobin (Hb), albumin concentration, Kt/V (Dialysis adequacy), and nPNA (normalized protein nitrogen appearance). In the obese groups, waist circumference and body mass index of both NO and CO groups were higher than those of N and CN groups, respectively. These data were the follows: body weight (kg) (N; 57.60 ± 7.05 vs NO; 77.32 ± 10.85, p = 0.000), (CN; 57.44 ± 11.41 vs CO; 72.93 ± 10.57, p = 0.000), waist

Table 1: Demographics and clinical parameters of the studied group

Parameters	N(n = 28)	NO(n = 41)	CN(n = 32)	CO(n = 21)
Age (years)	46.71 ± 9.75	47.04 ± 11.10	49.68 ± 12.09	52.76 ± 10.35
Gender (M/F)	15/13	16/25	18/14	10/11
Body Weight (kg)	57.60 ± 7.05	77.32 ± 10.85***	57.44 ± 11.41###	72.93 ± 10.57***ttt
Height cm)	162.55 ± 7.32	162.01 ± 8.12	162.09 ± 19.68	159.82 ± 9.75
Waist Circumference (inch)	32.14 ± 3.39	39.94 ± 4.22***	33.98 ± 4.11###	40.29 ± 3.24***ttt
Body Mass Index (kg/m^2)	21.87 ± 2.24	33.37 ± 4.07***	21.56 ± 2.75###	35.47 ± 4.60***ttt
SBP (mmHg)	120.28 ± 18.44	129.80 ± 1153	150.31 ± 25.42***	155.76 ± 21.63***ttt
DBP (mmHg)	78.10 ± 11.12	82.53 ± 12.46	76.31 ± 13.53	79.19 ± 11.65
Heart rate (beats/min)	99.19 ± 14.01	106.17 ± 13.49	113.31 ± 15.25**	117.47 ± 13.39***ttt
Kt/V	NA	NA	2.10 ± 0.62	2.30 ± 0.17
nPNA	NA	NA	1.11 ± 0.38	1.02 ± 0.05
Triglyceride (mg/dl)	NA	NA	138.28 ± 67.28	178.19 ± 111.66t
Cholesterol (mg/dl)	NA	NA	176.06 ± 50.56	176.90 ± 53.44
HDL (mg/dl)	NA	NA	48.38 ± 14.80	41.86 ± 13.75t
LDL (mg/dl)	NA	NA	115.88 ± 42.91	108.62 ± 36.36
Hct (%)	NA	NA	34.35 ± 7.96	30.90 ± 6.74
Hb (g/dl)	NA	NA	12.06 ± 5.24	10.20 ± 2.19
Albumin (g/dl)	NA	NA	3.48 ± 0.62	3.56 ± 0.63

The values were shown as mean ± SD
NA = not access
p-value compared with N were $^*p< 0.05$, $^{**}p< 0.01$ and $^{***}p< 0.001$
p-value compared with NO were $^{\#}$ p< 0.05, $^{\#\#}$ p< 0.01 and $^{\#\#\#}$ p< 0.001
p-value compared with CN were ^{t} p< 0.05

circumference (inch) (N; 32.14 ± 3.39 vs NO; 39.94 ± 4.22, p = 0.000), (CN; 33.98 ± 4.11 vs CO; 40.29 ± 3.24, p = 0.000), and body mass index (kg/m^2) (N; 21.87 ± 2.24 vs NO; 33.37 ± 4.07, p = 0.000), (CN; 21.56 ± 2.75 vs CO; 35.47 ± 4.60, p = 0.000).

Additionally, the higher value of vital sign was significantly found in both groups of CAPD (CN and CO) when they were compared to both of non-CAPD groups (N and NO). The details of vital sign parameters were: systolic blood pressure (SBP: mmHg) (N; 120.28 ± 18.44 vs CN; 150.31 ± 25.42, p = 0.000) (NO; 129.80 ± 11.53 vs CO; 155.76 ± 21.63, p = 0.000) and heart rate (HR: beats per minute) (N; 99.19 ± 14.01 vs CN; 113.31 ± 15.25, p = 0.001), (NO; 106.17 ± 13.49 vs CO; 117.47 ± 13.39, p = 0.017). Comparing between the CN and CO groups, the results showed that age, Kt/V, nPNA, cholesterol (mg/dl), low density lipoprotein (mg/dl), hematocrit (%), and albumin (g/dl) were not significant differences. In contrary, the blood triglyceride of the CO group was higher than that of the CN groups (178.19 ± 111.66 vs 138.28 ± 67.28, p = 0.039) whereas, the blood HDL of the CO group was lower than that of the CN group (41.86 ± 13.75 vs 48.38 ± 14.80, p = 0.047).

The four parameters of cardiac autonomic nervous system responses were shown in table 2. The highest orthostatic test DSBP (difference of systolic blood pressure between supine and standing position: mmHg) was found in the CO group and the lowest orthostatic test DSBP was found in the N group.

Table 2:: Cardiac autonomic nervous system responses of each studied group

Test	N(n = 28)	NO(n = 41)	CN(n = 32)	CO(n = 21)
Orthostatic test DSBP (mmHg)	2.83 ± 2.56	4.49 + 2.65	8.92 ± 4.93$^{***\#\#}$	10.60 ± 5.87$^{**\#\#\#}$
Orthostatic test DDBP (mmHg)	4.22 ± 2.82	8.34 ± 5.15**	6.41 ± 4.39	9.19 ± 5.79**
Valsava ratio	1.44 ± 0.54	1.33 ± 0.40	1.22 ± 0.37	1.19 ± 0.28
HR responses to deep breathing	13.13 ± 3.16	12.72 ± 9.18	8.95 ± 7.86	6.26 ± 5.74$^{**\#\#t}$
30/15 ratio	1.01 ± 0.15	0.98 ± 0.14	1.22 ± 0.11	1.19 ± 0.13

DSBP = Difference of systolic blood pressure between supine and standing position
DDBP = Difference of diastolic blood pressure between supine and standing position
The values were shown as mean ± SD
NA = not access
p-value compared with N were $^{*}p< 0.05$, $^{**}p< 0.01$ and $^{***}p< 0.001$
p-value compared with NO were $^{\#}$ $p< 0.05$, $^{\#\#}$ $p< 0.01$ and $^{\#\#\#}$ $p< 0.001$
p-value compared with CN were ^{t} $p< 0.05$

This parameter of the CN group was higher than that of the N group (CN; 8.92 ± 4.93 vs N; 2.83 ± 2.56, p = 0.000) meanwhile the CO group was higher than that of the NO group (CO; 10.60 ± 5.87 vs NO; 4.49 ± 2.65, p = 0.000). Similarly, orthostatic test DDBP (Difference of diastolic blood pressure between supine and standing position: mmHg) of the CO group showed the highest value whereas this parameter of the N group showed the lowest value. Comparing between obese and non-obese groups, the orthostatic DDBP of the N group has lower value than that in the NO group (N; 4.22 ± 2.82 vs 8.34 ± NO; 5.15, p = 0.004) whereas there was no significant difference between the CN and CO groups. In addition, the lowest value of heart rate responses to deep breathing was found in the CO group. Furthermore, these values of the CO group were significantly lower than that not only NO group (CO; 6.26 ± 5.74 vs NO; 12.72 ± 9.18, p = 0.007) but also in the N group (CO; 6.26 ± 5.74 vs N; 13.13 ± 3.16, p = 0.007). Finally, the CO group has significantly lower value of heart rate responses to deep breathing than that in the CN group (CO; 6.26 ± 5.74 vs CN; 8.95 ± 7.86, p = 0.048). However, neither valsava ratio nor 30/15 ratio has been shown any significant difference among all four groups.

When the correlation between the four parameters of cardiac autonomic nervous system responses and the either obese or CAPD parameters of the CO group were statistically evaluated, only DSBP and DDBP were significantly correlated with waist circumference (r = 0.320; p = 0.037 and r = 0.312; p = 0.039) and body mass index (r = 0.249; p = 0.047 and r = 0.300; p = 0.022). These results were shown in figure 1 and 2, respectively.

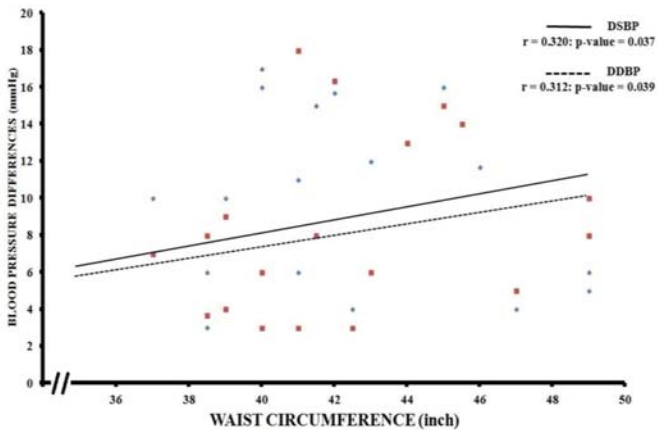

Fig.1:: The correlation between both DSBP and DDBP of orthostatic test and waist circumference of the CO group.

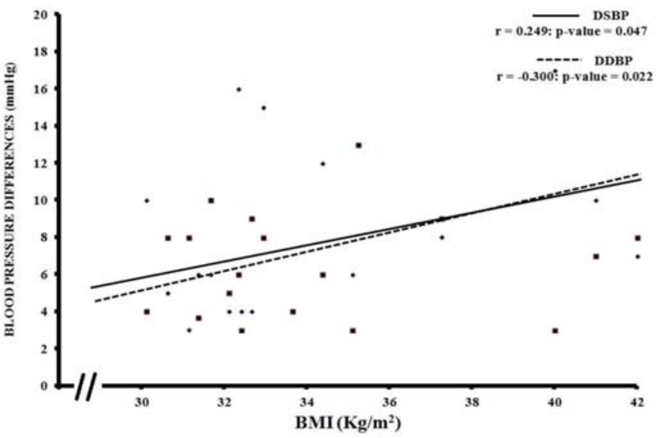

Fig.2:: The correlation between both DSBP and DDBP of orthostatic test and body mass index of the CO group.

4. DISCUSSION

The current study has indicated that the obese group obviously showed the higher of waist circumference and body mass index than those in the subjects with normal weight. When the obese patients treated with CAPD were considered, the higher of blood triglyceride and the lower of high density lipoprotein of the CO group were found when compared to the CN group. The obtained results have been supported by the study of Paschoal et al [12]. Unfortunately, there was no significant difference of cholesterol between these two groups. The consequence from the results demonstrated that the high concentration of blood lipid leads to increase in the body fat deposition, body weight, body mass index, and waist circumference, simultaneously [12]. Particularly, the high level of blood lipid leads to both atherosclerosis and arterial stiffness in the CAPD patients [12]. Interestingly, the incidences of arterial stiffness in the CAPD patients have been directly increase with mortality rate.

Gupta et al has proposed that these abnormalities of vascular are likely possible to induce the autonomic nervous system dysregulation via the impairments of baroreceptor reflex activity and cardiac autonomic nervous system function [13]. However, there was no effect of obesity on the resting blood pressure and heart rate. In the meantime, the obese and non-obese groups of ESRD patients who treated with CAPD have the higher resting SBP and HR than those in both groups of normal kidney subjects, respectively. The reason may be due to either the sympathetic hyperactivity or the overproduction of catecholamine stimulating the cardiac autonomic nervous system functions which increase cardiac contraction, heart rate, and vasoconstriction [14]. Moreover, the cardiac autonomic nervous system dysfunction has been known as the consequence from the accumulation of uremic toxin which can inhibit the synthesis of vasodilation enzymes. These are both endothelial and neuronal nitric oxide synthases [15][16]. Briefly, all these alterations caused by the effects of ESRD treated with the CAPD method.

The non-invasive techniques were used to evaluate the cardiac autonomic nervous system responses in this study. They were consisted of valsava ratio, heart rate responses to deep breathing, and 30/15 ratio. These three methods represent the activity of parasympathetic nervous system. On the other hand, orthostatic test was considered as the method evaluating the sympathetic nervous system activity [1]. For heart rate responses to deep breathing, the obvious results of this study have corresponded with the study of Jassal et al [17]. Furthermore, this method has been proposed as a good index of cardiac autonomic nervous system function for the CAPD patients [17]. Due to the influence of only ESRD replaced by CAPD method, this value of the CO group was lower when compared to the NO group. Therefore, the parasympathetic hypoactivity can be found due to CAPD. Furthermore, the current results showed that heart rate response to deep breathing of the CO group was less than that in the CN groups. Therefore, the parasympathetic hypoactivity should be occurred, at least in part, the additional effect of the obesity. Not only the CAPD therapy can induce cardiac autonomic nervous system dysfunction via sympathetic hyperactivity and parasympathetic hypoactivity but also the obesity reinforces the parasympathetic hypoactivity. For the other gold standard method, the parasympathetic activity has been analyzed by heart rate variability including of HF (High frequency) power, RMSSD (root-mean square of differences between adjacent normal R-R intervals in a time interval), pNN50 (percentage of adjacent R-R intervals with a difference of duration greater than 50 ms). The previous studies have proposed that HF, RMSSD, and pNN50 decrease in both obese children and adults [4], [18]. Interestingly, this technique will be used in further investigation in order to confirm our current studies. However, the proposed mechanisms were that the high body fat causes the decrease of the receptor activity of parasympathetic system and/or increase both sympathetic outflow [19] and nor-epinephrine releases from sympathetic hyperactivity [20]. Consequently, the conclusion of this study was that the obesity likely augments with the CAPD procedure in term of the decrease of parasympathetic activity.

In this study, although the obesity may not be the main cause, it is able to reinforce in ESRD replaced with the CAPD method for cardiac autonomic nervous system dysfunction. Consequently, the advantage from the current study has been the medical prescription, particularly; the influencing drug to the cardiac autonomic nervous system should be carefully observed and monitored. Otherwise, the extreme abnormality of blood pressure and heart rate may be occurred in the obese-CAPD patients.

For orthostatic hypotension, the normal weight (CN) and the obesity (CO) of the CAPD patients had more DSBP than the healthy (N) and the healthy obesity (NO) subjects, respectively. These data indicated that the CAPD method induces the sympathetic hypoactivity during the changing from supine to standing position. Additionally, the obesity has also affected the increase in DDBP of the NO group when this group was compared to the N group. This result indicated that the phenomenon of sympathetic hypoactivity as a result of obesity can be occurred. Although the DSBP and DDBP of the CO groups were insignificantly higher than that in the CN group, its data may help to confirm that ESRD treated with CAPD may be partly augmented by obesity leading to orthostatic hypotension.

The orthostatic hypotension has been defined as a decrease in SBP and/or DBP when the alteration from supine to standing position. From the results in this study, the greater influence of CAPD than the obesity on orthostatic hypotension was likely observed as proposed suggestion. This statement can be insisted by the obvious results. The significant higher of DSBP of both CAPD groups were found compared to the both healthy groups whereas only the NO group has higher value of DDBP than the N group. However, this hypothesis can be supported by the correlation data. It was found that the parameters of orthostatic test (DSBP and DDBP) of the CO group significantly correlated with waist circumference and body mass index. Consequently, the obesity may partially involve in orthostatic hypotension in the CAPD patients. Subsequently, the advantage of the study was that the patients with obesity should be recommended for the awareness of orthostatic hypotension during excess fluid removal by the CAPD method. They must slowly turn their position from supine to sitting or standing position, in particular, during ultrafiltration (UF) process. There have been reported that ultrafiltration with high dextrose concentration of the CAPD patients induced hypotension by cardiac sympathetic hypoactivity [17]. They suggested that the alpha 1 agonist of cardiac adrenergic receptor have been inhibited during ultrafiltration

[21]. Therefore, the CAPD patients who were in ultrafiltration procedure, the orthostatic hypotension easily and seriously occurred when they alter their position.

5. CONCLUSION

The effect of the obesity in ESRD patients treated with CAPD is divided into two phases. Firstly, the parasympathetic hypoactivity controlling cardiac nervous system functions were mainly influenced during resting. Secondly, the sympathetic activity was partly inhibited at adrenergic receptor leading to orthostatic hypotension when the alteration from supine to standing position in the duration of ultrafiltration was conducted.

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