

The recent effects of small dose of folic acid on lipoprotein-associated phospholipase A2 and systolic blood pressure variability in coronary heart disease patients with hyperhomocysteinemia

A single-center prospective cohort study

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Abstract

To investigate the recent effects of small dose of folic acid on lipoprotein-associated phospholipase A2 (LP-PLA2) and systolic blood pressure variability in coronary heart disease (CHD) patients with hyperhomocysteinemia.

In this prospective cohort study, a total of 167 CHD patients with hyperhomocysteinemia were consecutively enrolled, and they were divided into Group A (without folic acid intervention, n = 99), Group B (with 0.4 mg of folic acid intervention, n = 34), Group C (0.8 mg of folic acid intervention, n = 34). General information, fasting blood glucose, and blood lipid, folic acid, homocysteine, Lp-PLA2, and blood pressure variability were compared among 3 groups. The above indicators were reviewed after 3 months of treatment.

There were no statistically significant differences of age, gender, blood pressure, incidence of type 2 diabetes mellitus, fasting blood glucose, folic acid, homocysteine, Lp-PLA2, total cholesterol, 3 acyl glycerin, apolipoprotein B, lipoprotein (a), high density lipoprotein cholesterol, and low density lipoprotein cholesterol were found among 3 groups ($P > .05$); however, after being treated for 3 months, there was statistically significant difference in folic acid among 3 groups ($P < .05$), there was statistically significant difference in apolipoprotein A between Group A and Group B ($t = 0.505$, $P = .039$), and also between Group A and Group C ($t = 0.052$, $P = .017$). There were statistically significant differences in Lp-PLA2 ($t = 24.320$, $P = .016$) and systolic blood pressure variability ($t = 0.154$, $P = .018$) between Group A and Group C.

For CHD patients with hyperhomocysteinemia, the higher dose (0.8 mg) of folic acid supplement was beneficial for increasing the apolipoprotein A, reducing the Lp-PLA2, and improving the systolic blood pressure variation, which might help to improve the prognosis in these patients.

Abbreviations: ApoA = apolipoprotein A, ApoB = apolipoprotein B, BMI = body mass index, CHD = coronary heart disease, FBG = fasting blood glucose, Hcy = homocysteine, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, Lp (a) = lipoprotein (a), LP-PLA2 = lipoprotein-associated phospholipase A2, T2DM = type 2 diabetes, TC = total cholesterol, TG = 3 acyl glycerin.

Keywords: blood pressure variability, coronary heart disease, folic acid, heart rate variability, homocysteine, lipoprotein-associated phospholipase A2

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The datasets generated during and/or analyzed during the current study are publicly available.

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1. Introduction

Acute or chronic inflammatory reaction played an important role in the process of formation and progress of coronary heart disease (CHD).^[1–3] Scholars think that we could improve atherosclerosis by reducing inflammatory markers.^[4] They have confirmed that plasma homocysteine (Hcy) and serum lipoprotein-associated phospholipase A2 (LP-PLA2) belonged to specific indicators which could reflect the vascular inflammation and coronary artery atherosclerosis lesions, and be related to the coronary artery stenosis.^[5,6] The higher Hcy and LP-PLA2 levels were, the higher the adverse events in CHD patients would be.^[7,8] At the same time, abnormal blood pressure variability was associated with hypertension, cardiovascular events, mortality, and adverse events of CHD,^[9,10,11] in particular, abnormal systolic blood pressure variation in the general population caused higher all-cause mortality and increased risk of CHD.^[12] Our previous studies have confirmed that serum LP-PLA2 level was positively correlated with severity of coronary artery lesions and could reflect the severity of coronary artery lesions in CHD patients complicated reverse-dipper blood pressure.^[6] Previous studies have showed that low-dose folic acid could slow down the progress of chronic renal insufficiency,^[13] lower blood uric acid,^[14] reduce the incidence of cerebral infarction in hypertension patients with hyperhomocysteinemia,^[14,15] and decrease retinal atherosclerosis in the patients of hypertension combined with type 2 diabetes and hyperhomocysteinemia.^[16] Mohler ER 3rd, et al^[17] found Darapladib belonged LP-PLA2 inhibitors could decrease interleukin (IL)-6 and high-sensitivity C-reactive protein in CHD patients who were treated with statin. And Zhang J et al^[18] found Darapladib could reduce Rho kinase activity, whereas nitric oxide production was enhanced and cardiomyocyte apoptosis was also significantly reduced in atherosclerotic models performed in male Sprague-Dawley rats. Can small doses of folic acid reduce Hcy and LP-PLA2 level, improve blood pressure variation, and further improve the prognosis of CHD patients with hyperhomocysteinemia? Scholars studied the influence of folic acid supplementation on plasma Hcy, but we did not find the reports about the influence of folic acid supplementation on LP-PLA2 and blood pressure variation. Therefore, we designed a trial to clarify whether small doses of folic acid supplement can to reduce the LP-PLA2 level, improve the blood pressure variation, and further improve the prognosis of patients with CHD patients with hyperhomocysteinemia.

2. Subjects and methods

2.1. Study design and participants

This is a prospective, cohort study designed to evaluate the recent effects of small dose of folic acid on LP-PLA2 and systolic blood pressure variability in CHD patients with hyperhomocysteinemia. The CHD patients (Coronary artery stenosis greater than or equal to 50% cleared by coronary angiography or coronary computed tomography angiography) with hyperhomocysteinemia (>10 $\mu\text{mol/L}$) hospitalized in department of cardiovascular medicine, Yue Bei People's Hospital Affiliated to Shantou University from January 2017 to October 2019 were selected. This study was approved by Yue Bei People's Hospital ethics committee, and all subjects signed informed consent. Patients were excluded if they had taken folic acid or B vitamin drugs within nearly 3 months, if they had obvious abnormal liver and

kidney function, blood system diseases, and acute or chronic infection. Based on the doses of folic acid supplementation, the patients were divided into 3 groups: Group A: taking on folic acid tablets (100 cases), Group B: taking 0.4mg of folic acid (35 cases), Group C: taking 0.8mg of folic acid (35 cases). The patients were performed CHD standardized medication, including antiplatelet, beta blockers, angiotensin II receptor blockers, statins, and so on.

2.2. Data collection

Baseline clinical data were collected, including gender, age, blood pressure status (0 indicated normal blood pressure, 1 indicated high blood pressure level 1, 2 indicated high blood pressure level 2 and 3 indicated high blood pressure level 3), type 2 diabetes (1 represented not type 2 diabetes and 2 represented type 2 diabetes). After admission, the patient's height and weight were measured and body mass index (BMI, $\text{BMI} = \text{weight}/\text{height}^2$) was calculated. On the second day early in the morning, the blood of the patients was collected for detecting Folic acid, fasting blood glucose (FBG), total cholesterol (TC), 3 acyl glycerin (TG), and apolipoprotein A (ApoA), apolipoprotein B (ApoB), lipoprotein (a) (Lp (a)), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), 4mL blood taken from the patients were stored in 2 tubes with ethylenediamine tetraacetic acid anticoagulation and separated with a speed of 3500r/min centrifuge for 10minutes (centrifugal radius 10cm). One was used to return the plasma for detection of Hcy levels with circulating enzymatic according to the Kit instructions supplied by Wuhan Life Origin Biotech Joint Stock Co., Ltd (Wuhan City, China), and the other was used to return serum for detection for detection of LP-PLA2 levels with immune enhancement turbidimetry according to the Kit instructions supplied by Nanjing Norman Biological Technology Co., Ltd (Nanjing City, China). The above indexes were reviewed after 3 months. 24hours ambulatory blood pressure of patients were detected with the DMS Tim – ABP type dynamic blood pressure recorder which was programmed to obtain readings at intervals of no more than 30 minutes between 6 AM and 10 PM as daytime ambulatory blood pressure, and at intervals of no more than 60 minutes between 10 PM and 6 AM as nighttime ambulatory blood pressure. Efficient monitoring data required was more than 85%. The circadian blood pressure state was divided into the dipper type blood pressure, the non-dipper blood pressure, and the reverse dipper blood pressure. The dipper type blood pressure presented by 1 was from 10% to 20% of nocturnal blood pressure reducing rate, the non-dipper blood pressure presented by 2 was from 0% to 10% of nocturnal blood pressure reducing rate, and the reverse dipper blood pressure presented by 3 was below 0 of nocturnal blood pressure reducing rate. The 24 hours ambulatory blood pressure was reviewed after 3 months.

2.3. Statistical analysis

Data were expressed as the means \pm standard deviation or a median (interquartile range) for continuous variables and as a frequency for categorical variables. The continuous variables were checked for the normal distribution assumption using Kolmogorov–Smirnov statistics and tested via the Kruskal–Wallis *H*-test or 1-way analysis of variance followed by least significant difference multiple *t*-tests to determine significant differences among the experimental groups where appropriate.

Table 1**Comparison of general information among 3 groups.**

| Variable | A group | B group | C group | F (χ^2) value | P value |
|---------------------------------|-------------|------------|------------|----------------------|---------|
| N | 99 | 34 | 34 | | |
| Age, yrs | 62.46±9.98 | 59.91±9.38 | 60.50±9.79 | 1.096 | .337 |
| Gender (male/female) | 82/17 | 28/6 | 25/9 | 1.476 | .478 |
| Blood pressure status (0/1/2/3) | 33/16/15/35 | 11/6/8/9 | 12/3/5/14 | 3.415 | .755 |
| The condition of T2DM (0/1) | 71/28 | 21/13 | 23/11 | 1.199 | .549 |

Blood pressure status (0 indicated normal blood pressure, 1 indicated high blood pressure level 1, 2 indicated high blood pressure level 2 and 3 indicated high blood pressure level 3), type 2 diabetes (1 represented not T2DM and 2 represented T2DM).

The categorical variables were tested via Pearson χ^2 test. For all analyses, a *P*-value < .05 was considered statistically significant. All statistical analyses were performed with the use of SPSS software, version 22.0 (IBM Corp, Chicago, IL).

3. Results

Three patients (1 in each group) did not participate in the review after 3 months. Thus, 167 patients were included in the final analysis. There were no statistically significant differences in the baseline clinical characteristics including gender, age, blood pressure points, the condition of type 2 diabetes among 3 groups (*P* > .05, see Table 1). Before the treatment, there were no statistically significant differences in TC, TG, LP(a), ApoA, ApoB, HDL-C, LDL-C, FBG, Hcy, LP-PLA2, BMI (*P* > .05). After the treatment for 3 months, there were no statistically significant differences in TC, TG, LP(a), ApoB, HDL-C, LDL-C, FBG, Hcy, and BMI (*P* > .05), the ApoA of Group B was higher

than Group A with statistically significant differences (*t*=0.505, *P*=.039), and also between Group A and Group C (*t*=0.052, *P*=.017). The LP-PLA2 was lower than before and there was statistically significant differences among 3 groups (*t*=24.320, *P*=.016) (see Table 2 and Fig. 1). Before the treatment, there was no statistically significant difference in blood pressure variability (*P* > .05). After the treatment, the systolic blood pressure variability has been improved, and there was statistically significant difference in the circadian systolic blood pressure state (*t*=0.154, *P*=.018) (see Table 3 and Fig. 2).

4. Discussion

In order to clarify the effects of the small doses of folic acid supplement on LP-PLA2 level, and the blood pressure variation in patients with CHD, we divided CHD patients complicated with hyperhomocysteinemia (the Hcy level >10 umol/L) and gave them standardized treatment of CHD into 3 groups. Group A

Table 2**Comparison of FBG, Hcy, LP-PLA2, folic acid, blood lipid, and BMI among 3 groups.**

| Variable | | A group | B group | C group | F value | P value |
|--------------------------|----------------------|---------------|-------------------------|---------------------------|---------|---------|
| N | | 99 | 34 | 34 | | |
| FBG (mmol/L) | Before the treatment | 6.52±2.86 | 6.40±3.25 | 5.96±1.38 | 0.495 | .61 |
| | After the treatment | 6.40±2.23 | 6.49±1.57 | 6.73±2.37 | 0.294 | .746 |
| Hcy(umol/L) | Before the treatment | 15.72±5.45 | 17.98±15.45 | 17.44±7.52 | 1.087 | .34 |
| | After the treatment | 15.41±9.05 | 14.82±10.05 | 13.64±3.81 | 0.555 | .575 |
| LP-PLA2 (umol/L) | Before the treatment | 269.31±121.91 | 290.88±150.42 | 273.50±200.58 | 0.304 | 2.916 |
| | After the treatment | 213.84±120.31 | 201.85±123.36 | 155.35±98.95 ^a | 0.738 | .057 |
| Folic Acid (ng/mL) | Before the treatment | 10.27±4.22 | 10.49±4.21 | 8.98±5.08 | 1.021 | .364 |
| | After the treatment | 13.44±6.07 | 21.44±6.40 ^c | 21.39±8.74 ^{ab} | 22.686 | <.001 |
| TC (mmol/L) | Before the treatment | 4.44±1.15 | 4.73±0.75 | 4.22±1.05 | 1.837 | .163 |
| | After the treatment | 3.08±0.94 | 3.94±0.76 | 3.85±0.92 | 0.301 | .741 |
| TG (mmol/L) | Before the treatment | 1.61±0.87 | 1.52±0.84 | 1.49±1.04 | 0.285 | .753 |
| | After the treatment | 1.51±0.87 | 1.90±1.27 | 1.64±1.10 | 1.787 | .171 |
| Lp (a) (mmol/L) | Before the treatment | 17.50 (31.90) | 13.60 (28.67) | 16.90 (22.60) | – | .764 |
| | After the treatment | 16.95 (40.57) | 11.31 (30.47) | 13.15 (34.04) | – | .236 |
| ApoA (g/L) | Before the treatment | 1.30±0.27 | 1.37±0.34 | 1.30±0.27 | 0.774 | .463 |
| | After the treatment | 1.33±0.20 | 1.43±0.32 ^c | 1.45±0.29 ^a | 4.029 | .02 |
| ApoB (g/L) | Before the treatment | 0.84±0.24 | 0.93±0.18 | 0.82±0.22 | 2.234 | .11 |
| | After the treatment | 0.70±0.18 | 0.74±0.23 | 0.75±0.26 | 0.935 | .395 |
| HDL-C (mmol/L) | Before the treatment | 1.07±0.25 | 1.16±0.24 | 1.09±0.23 | 1.67 | .192 |
| | After the treatment | 1.17±0.29 | 1.24±0.30 | 1.19±0.31 | 0.675 | .511 |
| LDL-C (mmol/L) | Before the treatment | 2.81±0.98 | 3.08±0.67 | 2.64±0.96 | 1.922 | .15 |
| | After the treatment | 2.26±0.85 | 2.25±0.58 | 2.26±0.92 | 0.003 | .997 |
| BMI (kg/m ²) | Before the treatment | 24.86±3.74 | 24.05±3.49 | 24.72±3.69 | 0.522 | .595 |
| | After the treatment | 24.83±3.73 | 24.05±3.49 | 24.72±3.69 | 0.522 | .595 |

Compared with group C and A, a *P* < .05, compared with group C and B, b *P* < .05, compared with group A and B, c *P* < .05 after the treatment.

ApoA = apolipoprotein A, ApoB = apolipoprotein B, BMI = body mass index, FBG = fasting blood glucose, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, Lp (a) = lipoprotein (a), LP-PLA2 = lipoprotein-associated phospholipase A2, TG = 3 acyl glycerin.

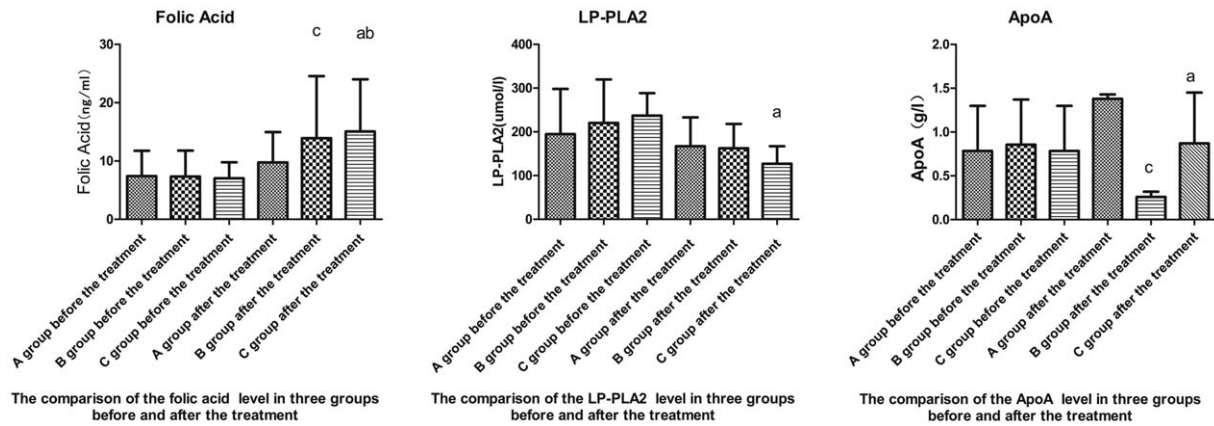


Figure 1. Comparison of Folic Acid, LP-PLA2, and ApoA among 3 groups. Compared with Group C and Group A, a $P < .05$, compared with Group C and Group B, b $P < .05$, compared with Group A and Group B, c $P < .05$ after the treatment. ApoA = apolipoprotein A, LP-PLA2 = lipoprotein-associated phospholipase A2.

was given only standardized treatment, Group B was provided 0.4 mg of folic acid and Group C was provided 0.8 mg of folic acid. Three groups of patients had no statistical significance in general information and the baseline indicators ($P > .05$). There was statistical significance in folic acid level and ApoA level ($t = 1.457$, $P = .000$, respectively, and $t = 0.505$, $P = .039$), and the rest of the indicators had no significant difference between Group A and Group B after the treatment of 3 months. The mechanism might be that folic acid involved in fat metabolism and intervened Hcy metabolism,^[19] thus raising the ApoA level. Comparing Group A with Group C, except the ApoA levels ($t = 0.052$, $P = .017$), folic acid further reduced the level of PLA2 ($t = 24.320$, $P = .016$), therefore, decreasing chronic inflammatory reaction, and could improve systolic blood pressure variation state ($t = 0.154$, $P = .018$). The lowering of LP-PLA2 and the improvement of systolic blood pressure variation not simply relied on the changes of blood Hcy levels ($t = 1.700$, $P = .287$), it was possible that the certain concentration of folic acid could promote the ratio of S-Adenosylmethionine and S-adenosyl Hcy, increase the mRNA and protein expression of vascular endothelial cells, thus improve endothelial cell function.^[20] At the same time, we speculated that Enalapril folate tablets outweighed pure enalapril tablets reducing starting stroke, not dependent on the step-down level,^[14] which might be associated with improvement of the above indicators by folic acid. There was no significant difference between Group A and Group C ($t = 2.076$, $P = .571$) in Hcy level decrease after treatment for 3 months with folic acid supplement. It might be associated with small sample sizes, or the above-

mentioned indicators improved by folic acid not only depended on the change of blood Hcy,^[20] but also on the differences of folic acid metabolism related genes polymorphisms.^[21,22]

This study suggests a small dose of folic acid treatment can improve the level of ApoA which protective against atherogenic dyslipidemia,^[23] and the level of ApoA was the variable strongly associated with HF in patients of CHD,^[24] therefore ApoA levels can suggest the prognosis of patients with CHD. This study suggests 0.8 mg of folic acid supplement could decrease LP-PLA2 level, our previous studies have confirmed that serum LP-PLA2 level was positively correlated with severity of coronary artery lesions and could reflect the severity of coronary artery lesions in CHD patients complicated reverse-dipper blood pressure,^[4] and Mohler ER 3rd, et al found Darapladib belonged LP - PLA2 inhibitors could decrease IL-6 and high-sensitivity C-reactive protein in CHD patients,^[16] therefore we speculate that 0.8 mg of folic acid supplements may improve the prognosis of CHD patients by intervening the LP-PLA2 level. At last, this study suggests 0.8 mg of folic acid supplement could improve systolic blood pressure variation, and Elvira OG, et al found higher systolic blood pressure variability in individuals with and without hypertension was associated with increased risks of all-cause mortality and incidence of CHD.^[25]

5. Strengths and limitations

We report for the first time 0.8 mg of folic acid supplements can raise ApoA level, reduce LP-PLA2 level, and improve systolic

Table 3
Comparison of blood pressure variability among 3 groups.

| Variable | A group | B group | C group | F value | P value |
|--|-------------|-------------|--------------------------|---------|---------|
| N | 99 | 34 | 34 | | |
| The circadian systolic blood pressure state | | | | | |
| Before the treatment | 2.07 ± 0.68 | 2.09 ± 0.73 | 2.23 ± 0.68 | 0.531 | .589 |
| After the treatment | 2.13 ± 0.72 | 2.07 ± 0.70 | 1.77 ± 0.77 ^a | 2.861 | .06 |
| the circadian diastolic blood pressure state | | | | | |
| Before the treatment | 1.96 ± 0.69 | 2.06 ± 0.84 | 2.23 ± 0.82 | 1.284 | .28 |
| After the treatment | 1.76 ± 0.78 | 1.90 ± 0.78 | 1.70 ± 0.79 | 0.525 | .593 |

Compared with group C and A, a $P < .05$ after the treatment. The circadian blood pressure state was divided into the dipper type blood pressure (presented by 1), the non-dipper blood pressure (presented by 2) and the reverse dipper blood pressure (presented by 3).

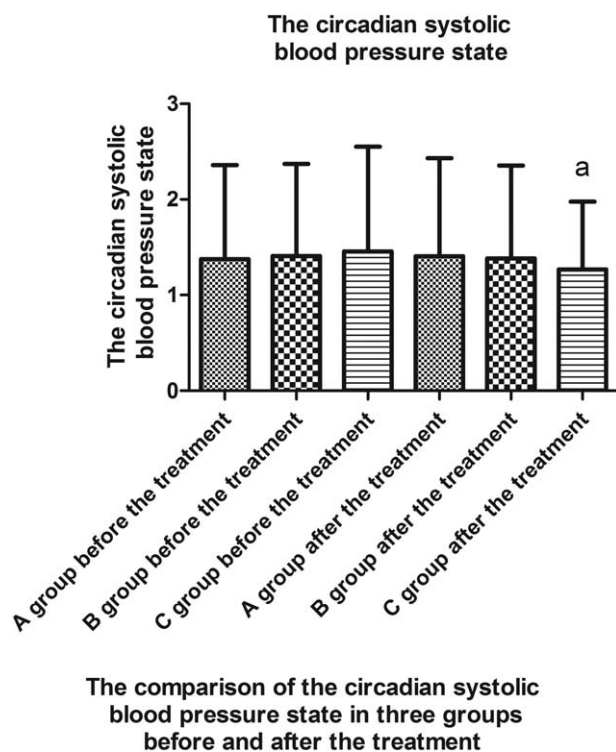


Figure 2. Comparison of the systolic blood pressure variability among 3 groups. Compared with Group C and Group A, a $P < .05$ after the treatment.

blood pressure variation in CHD patients with hyperhomocysteinemia. Combined our previous work^[6] and studies of other scholars,^[17,25] we speculate that 0.8 mg of folic acid supplements may improve the prognosis by the change of above factors in CHD patients with hyperhomocysteinemia. Some limitations to our study should be acknowledged. This is a single-center, cohort study selected consecutive patients with possible selection bias, and the overall sample size is small. Therefore, the results should be confirmed in future studies with a larger sample. We do not have additional information regarding the duration of diagnosis and medication of CAD, which may affect blood pressure variation. At the same time, we have observed there was no difference in blood pressure variation among 3 groups before treatment, however, we have not observed the difference among 3 groups in resting blood pressure. No difference in blood pressure variation does not mean no difference in resting blood pressure, while high-normal resting blood pressure has a harmful influence on populations.^[26] In addition, we have not observed the differences of folic acid metabolism related genes polymorphisms, therefore we have not ruled out possible impact of folic acid metabolism related genes polymorphisms on observation among 3 groups. We intend to test the folic acid metabolic gene polymorphisms in patients with CHD and to observe whether low-dose folic acid supplements might have the same effect in patients with CHD without hyperhomocysteinemia, so as to further clarify the role of folic acid in the treatment of in CHD patients. At last, we only observe the changes of indexes after 3 months, which have low predictive value in long-term prognosis in CHD patients.

6. Conclusions

Our study has demonstrated that low-dose (0.4 mg) folic acid supplement could increase ApoA level in CHD patients with hyperhomocysteinemia, and the higher dose (0.8 mg) of folic acid supplement was beneficial for increasing the ApoA, reducing the Lp-PLA2, and improving the systolic blood pressure variation, which might help to improve the prognosis in these patients.

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