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Effect of Increasing the Plasma Phospholipase A2 Mass on the Risk of Masked Hypertension in Humans

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Abstract

Background: Masked Hypertension (MHT) is associated with an increased risk for Cardiovascular Disease (CVD). The etiopathogenesis of MHT is thought to be affected by oxidative stress and vascular inflammation. This study aimed to analyze the relationships between Lipoprotein-Associated Phospholipase A2 (Lp-PLA2), a unique vascular inflammation marker, with blood pressure variation and traditional risk factors in patients with MHT, and to determine the clinical significance.

Methods: One hundred eighty-three patients without any prior therapeutic medications were included and divided into the following three groups: MHT (n=82); True Hypertension (THT) [n=52]); and normotensive (n=59). An Ambulatory Blood Pressure Monitor (ABPM) was used. Clinical biochemical parameters and the Lp-PLA2 mass in each group were measured, and the related clinical characteristics and risk factors for CVD were statistically analyzed.

Results: The level of Lp-PLA2 in MHT group was significantly higher than the normotensive (191.8 ± 62.58 vs.108.3 ± 44.74 ng/ml, $p<0.01$) and true hypertension groups (191.8 ± 62.58 vs. 169.3 ± 54.55 ng/ml, $p<0.05$). Furthermore, the incidence of MHT was correlated with the increase in Lp-PLA2, around 65% of MHT patients with a Lp-PLA2 level ≥ 225 μ mol/L. The Lp-PLA2 level had a positive correlation with ABPM measurements, office-measured systolic blood pressure, and serum Uric Acid (UA) and Low-Density Lipoprotein Cholesterol (LDL-C) levels, but a negative correlation with the High-Density Lipoprotein Cholesterol (HDL-C) level.

Conclusion: An increased LP-PLA2 level was closely associated with the metabolic stress and incidence of MHT, thus exhibit an important role in the pathophysiology and diagnostic assessment of MHT.

Keywords: Biomarker, Vascular inflammation, Oxidative stress, Endothelial dysfunction, Blood pressure variability.

Abbreviations: MHT-Masked Hypertension, CVD-Cardiovascular Disease, Lp-PLA2-Lipoprotein-associated phospholipase A2, AS-Atherosclerosis, THT-True Hypertension, IDACO-International Database of Ambulatory Blood Pressure and Cardiovascular Disease, SBP-Systolic Blood Pressure, DBP-Diastolic Blood Pressure, LDL-C-Low-Density Lipoprotein Cholesterol, BMI-Body Mass Index, eGFR-estimated Glomerular Filtration Rate, MDRD-Modification of Diet in Renal Disease, HbA1c-Glycosylated Hemoglobin, TOD-Target Organ Damage, Lyso-PC-Lyso-Phosphatidylocholine, CAD-Coronary Heart Disease, SMC-Smooth Muscle Cell.

Introduction

Masked Hypertension (MHT) is a special phenotype of abnormal blood pressure variation associated with increased Cardiovascular Disease (CVD) risk, and accounts for 30% of pre-hypertensive patients. In clinical practice, early screening and risk stratification of CVD for patients with MHT are challenging due to variability of dynamic blood pressure and unmarked early target organ damage in hypertension. So, it is necessary to find novel possible biomarkers to comb with ABPM for screening and diagnostic assessment of the masked hypertension. Lp-PLA2 is a unique biomarker for vascular inflammation and CVD risk function as a pro-inflammatory enzyme. Recent studies demonstrated that Lp-PLA2 play a key role in the proatherogenic effects and development of Atherosclerosis (AS), which have clinical application value to predict potential cardiovascular diseases. However, there is limited clinic evidence on The effect of Lp-PLA2 on Masked hypertension. The relationship between MHT-related inflammation and A2 (Lp-PLA2) has not been reported. The current study aimed to analyze the association between the plasma Lp-PLA2 mass with blood pressure variation and traditional risk factors in MHT patients and to determine the clinical significance of the association [1-6].

Methods

Eighty-two patients with MHT (67 males and 15 females, 47.15 ± 14.5 years of age), 52 patients with True Hypertension [THT] (40 males and 12 females, 43.76 ± 13.8 years of age), and 59 normotensive patients (48 males and 11 females, 47.38 ± 13.8 years of age) were selected for the present cross-sectional study. None of the patients were treated pharmacologically. The THT and normotensive patients were age-matched with the MHT patients. The

patients underwent medical evaluation from April 2018 to December 2019 in the Department of Cardiology of Shenzhen Shekou People's Hospital, and defined as MHT, THT, and normotensive groups. All of the patients signed informed consent. This study was approved by the Shenzhen Shekou People's Hospital. The methods were carried out in accordance with the Declaration of Helsinki guidelines, including any relevant details [7].

Ambulatory Blood Pressure Measurements (ABPM)

All participants underwent 24-h ABPM with an automatic blood pressure monitor (Welch Allyn ABPM 6100 device; Welch Allyn Poland and Baltic States, Poznan, Poland), in accordance with the International Database of Ambulatory Blood Pressure and Cardiovascular Disease (IDACO). Daytime was defined as 10 am to 8 pm and nighttime was defined as 12 am (midnight) to 6 am. The device was programmed to obtain Blood Pressure (BP) readings at 20-min intervals. The recording was then calculated to obtain a 24h average Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP). When the readings exceeded at least 70% of the total readings programmed for the testing period, the recording was considered valid and satisfactory [8].

Measurement of Lp-PLA2

Blood samples were collected following a 12-h overnight fast and were used for Lp-PLA2 analysis. Blood samples (3 milliliter) were obtained from peripheral veins and collected into tubes with EDTA anticoagulants. The tubes were centrifuged immediately at 3000 r/min for 3 min. The separated upper plasma was stored at -80^{o} C. Lp-PLA2 analysis was performed every 7 days. The plasma Lp-PLA2 mass was determined using an ELISA kit (Lp-PLA2 Test Kit; Kangerke Technologies, Inc., Tianjin, China) according to the manufacturer's instructions. Measurement of biochemical parameters: Blood samples were collected following a 12-h overnight fast and were assayed for blood. Samples (5 milliliter) were drawn from peripheral veins and collected into tubes. The tubes were centrifuged immediately at 3000 r/min for 10 min. The separated serum samples were used for biochemical indices analysis using commercially available kits and an Architect C16000 (Abbott, Lake Forest, Ill, USA), and included a Fasting Blood Glucose (FBG), lipids, Blood Urea Nitrogen (BUN), Creatinine (Cr), and Uric Acid (UA). Low-Density Lipoprotein Cholesterol (LDL-C) was calculated using the Friedewald formula when the Triglycerides (TG) level was ≤ 5.0 m mol/l. No patient had a TG level ≥ 5.0 m mol/l [9].

Other Measurements

Body Mass Index (BMI) was obtained by dividing the body weight by the square of the height in meters. The estimated Glomerular Filtration Rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) study equation, as follows: eGFR (mL/min/1.73m^2)=30849 × [Scr (u mol)]$^{-1.154}$ × (age)$^{-0.203}$ × 0.742 (if female).

Diagnostic and Inclusion Criteria

According to the 2018 ESC/ESH guidelines for the management of arterial hypertension, normotension is defined clinically by an Office Blood Pressure (OBP) <140/90 mmHg and based on the following ABPM average daytime SBP<135 mmHg and/or DBP<85 mmHg average nighttime SBP<120 mmHg and/or DBP<70 mmHg and average 24h SBP<130 mmHg and/or DB <80 mmHg. The diagnostic threshold for THT is defined clinically by an OBP>140/90 mmHg and based on the following ABPM: average daytime SBP>135 mmHg and/or DBP>85 mmHg: average nighttime SBP>120 mmHg and/or DBP>70 mmHg and average 24-h SBP>130 mmHg and/or DBP>80 mmHg. According to the 2013 European Society guidelines for the management of ABPM, MHT is clinically defined as an OBP <140/90 mmHg, and masked daytime, masked nighttime, or masked 24-h hypertension from ABPM are categorized as MHT. Based on the average of all measurements between 10 am and 8 pm, daytime hypertension was defined as a SBP ≥ 135 mmHg and/or DBP ≥ 85 mmHg. Based on the mean of all measurements between 12 am and 6 pm, nighttime hypertension was defined as a SBP ≥ 120 mmHg and/or DBP ≥ 70 mmHg. Using the average of all available measurements from ABPM, 24h hypertension was defined as a SBP ≥ 130 mmHg and/or DBP ≥ 80 mmHg [10,11].

The Exclusion Criteria Were As Follows

Secondary hypertension; acute cardio-cerebrovascular disease; heart failure; neoplasm; autoimmune and rheumatic diseases; pregnancy; acute and chronic infections; severe liver and kidney dysfunction; thyroid dysfunction; and recent surgical trauma. Statistical analyses were performed using the SPSS 19.0 (SPSS, Inc., Chicago, IL, USA). All variables were tested for normal distribution of the data. Data are presented as the mean ± Standard Deviation (SD) or the count number and proportion. Differences between the studied groups were examined using the Student's unpaired t-test for parametric data. The categorical data were examined with a chi-square test. Influencing factors of Lp-PLA2 were found by Spearman linear regression analysis. All comparisons were 2-sided at the 5% significance level. A P value <0.05 was considered to be statistically significant.

Results

Comparison of clinical characteristics, demographics, and biochemical indices are presented in **Table 1**. There were no statistically significant differences in age, gender, FBG, TG, LDL-C, Total Cholesterol (TC), Cr, and eGFR among the three groups (P>0.05).The proportion of patients with smoking history, BMI, Lp-PLA2 level, and serum UA level in the MHT group were significantly higher than the normotensive group (p<0.05). The level of HDL-C was significantly lower than the normotensive group (p<0.01). Comparison of OBP and ABPM are presented in **Table 2**. The mean OBP in the MHT group was significantly lower than the THT group (p<0.01), and significantly higher than the normotensive group (p<0.01). The average SBP, average DBP during the daytime, nighttime, and 24-h average in the MHT group were all significantly higher the normotensive group (p<0.01). The average diurnal BP difference and the rate of nighttime BP decrease in the MHT group was lower than the other groups, but there were no statistically significant difference among the three groups (p>0.05).

Comparison of the incidence of normotensive, THT, and MHT based on the Lp-PLA2 interquartile range are presented in **Figure 1**. The incidence of MHT was associated with an increase in the plasma Lp-PLA2 mass. Among the quartiles, the Lp-PLA2 level had the greatest impact on the occurrence of MTH. Moreover, the occurrence of MHT was up to 65% in patients with an Lp-PLA2 ≥ 225 μ mol/L (Figure 1). Spearman linear regression analysis of Lp-PLA2 with BP measurements and chemical indices were shown in **Table 3**.

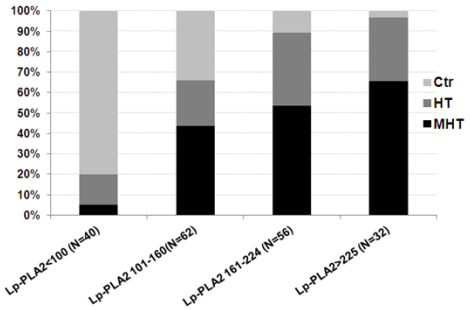

Figure 1 : The incidence of Nomotension, True Hypertension (THT) and Masked Hypertension (MHT) according to the Lp - PLA2 level classification.

Characteristics	MHT (n=82)			THT (n=52)		Normotension (n=59)
	Mean ± SD	P value (compared with normotension)	P value (compared with THT)	Mean ± SD	P value (compared with normotension)	Mean ± SD
Age (years)	47.25 ± 11.27	0.9143	0.1139	43.77 ± 9.63	0.0693	47.39 ± 14.06
Male, n (%)	66 (81)	0.14	0.18	42 (81)	0.16	40 (77)
Smoking, n (%)	30 (37)	0.01	0.08	14 (27)	0.03	7 (12)
BMI (kg/m^2)	25.58 ± 3.96	0.0032	0.3667	25.04 ± 2.96	0.0353	23.84 ± 2.88
Lp-PLA2 (ng/ml)	191.80 ± 62.58	<0.0001	0.0318	169.30 ± 54.55	<0.0001	108.30 ± 370.2
LDL-C（m mol/L)	3.20 ± 0.88	0.1599	0.8672	3.21 ± 0.78	0.2276	3.00 ± 0.98
HDL-C（m mol/L)	1.08 ± 0.22	0.0039	0.242	1.16 ± 0.46	0.137	1.31 ± 0.55
TG (m mol/L)	2.12 ± 1.41	0.2011	0.7256	2.05 ± 1.06	0.3291	1.83 ± 1.28
UA (u mol/L)	418.60 ± 89.24	0.0023	0.5721	407.70 ± 117.10	0.0674	370.20 ± 91.06
Cr（u mol/l）	78.75 ± 13.45	0.9234	0.4813	80.78 ± 17.51	0.4579	78.52 ± 13.68
$eGFR(ml.min^{-1}.(1.73\ m^2)^{-1}$	90.05 ± 16.81	0.4333	0.7848	91.61 ± 38.32	0.7244	94.18 ± 37.55
FBG（m mol/L)	5.93 ± 1.86	0.7867	0.112	6.19 ± 2.29	0.0656	5.56 ± 0.72

Table 1: Comparison of general clinical information among the Nomotension, True Hypertension (THT), and Masked Hypertension (MHT) group.

Index	MTH (n=85)			THT (n=52)		Normotension (n=59)
	Mean ± SD	P value (compared with normotension)	P value (compared with THT)	Mean ± SD	P value (compared with normotension group)	Mean ± SD
Office						
SBP (mmHg)	131.70 ± 5.72	<0.0001	<0.0001	151.90 ± 13.90	<0.0001	122.40 ± 11.44
DBP (mmHg)	82.39 ± 7.70	0.0001	<0.0001	96.90 ± 11.37	<0.0001	75.36 ± 10.91
Day time						
SBP (mmHg)	131.30 ± 9.72	<0.0001	0.0001	140.80 ± 12.69	<0.0001	117.70 ± 7.71
DBP (mmHg)	80.86 ± 8.65	<0.0001	<0.0001	90.57 ± 8.68	<0.0001	71.97 ± 7.30
Night time						
SBP (mmHg)	124.50 ± 9.32	<0.0001	0.0037	131.30 ± 13.02	<0.0001	109.20 ± 8.34
DBP (mmHg)	75.23 ± 6.97	<0.0001	<0.0000	82.71 ± 9.06	<0.0001	65.09 ± 5.73
24 h						
SBP (mmHg)	130.50 ± 9.27	<0.0001	0.0001	139.80 ± 12.47	<0.0001	116.50 ± 7.33
DBP (mmHg)	80.41 ± 7.76	<0.0001	<0.0001	89.62 ± 8.56	<0.0001	70.91 ± 6.98
Diurnal SBP difference (mmHg)	6.90 ± 7.55	0.2165	0.2477	8.91 ± 9.88	0.5912	10.67 ± 17.30
Diurnal DBP difference (mmHg)	5.83 ± 6.20	0.5933	0.105	7.94 ± 7.16	0.2988	6.45 ± 5.45
The nighttime SBP decrease rate (%)	3.24 ± 5.51	0.8775	0.1894	1.96 ± 4.76	0.2315	3.42 ± 5.42
The nighttime DBP decrease rate (%)	3.96 ± 7.43	0.7451	0.4168	2.87 ± 6.76	0.3696	4.52 ± 8.59

Table 2: Comparison of office BP level and ambulatory blood pressure measurement among the Nomotension, True Hypertension (THT), and Masked Hypertension (MHT) group.

The Lp-PLA2 level had a positive correlation with office SBP, ABPM, and serum UA and LDL-C levels, but a negative correlation with the HDL-C level.

Discussion

Previous studies had indicated that MHT was affected by oxidative stress and vascular inflammation. However, the etiopathogenesis of which remains completely uncertain. Findings from the current study suggest that that the proportion of patients with smoking, obesity, and high UA level in the Masked Hypertension (MHT) group was significantly higher than the normotensive group ($p<0.05$), rather than Total Cholesterol (TC), LDL-C and fasting glucose. This is consistent with The Jackson Heart Study, which suggested that better diet, not smoking and lower clinic BP were each associated with a lower prevalence of masked daytime hypertension.

More and more clinic evidences demonstrated that high levels of SUA were an independent risk factor associated with risk of hypertension beyond traditional risk factors, although the intrinsic mechanism needs further elucidation. Studies had reported that MHT was independently associated with increased serum Glycosylated Hemoglobin (HbA1c) and CRP levels, and Type 2 diabetic patients with MHT had higher risk of Target Organ Damage (TOD).

However, in our present study, glycol metabolism assessment was only performed on the fasting blood glucose. Future trials to measure HbA1c and 2 Hours 'Postprandial Blood is warranted to investigate the association between glycol metabolism and the prevalence of MHT [12-18].

Additionally, the data from current study also showed that TC and LDL-C levels had no significantly difference among three groups. Recent studies by Tsimikas et al had demonstrated that Lp(a)-linked Oxidized Phospholipids (OxPLs) play a key role in the proatherogenic effects of Lp(a). In a study by Bergmark et al unlike LDL, Lp(a) had the physiological function of preferentially binding to OxPL in circulation.

Moreover, Lp(a) could be preferentially aggregated to the vascular lesion site, causing the formation of OxPL and resulting in marked increase of Lp-PLA2 enzyme activity so as to significant enhancing the atherogenesis. Lp-PLA2 is another important factor in LP (a) function, which had been proved to be a special biomarker related to endothelial dysfunction and vascular inflammation via hydrolysis of OxPL leading to the release of inflammation mediators [lyso-phos phatidylocholine (lyso-PC) and Oxidized Fatty Acids (ox-FA) [19,20].

Index	LP-PLA2 (ng/ml)	
	Pearson correlation (r)	P (two sides)
Office Systolic blood pressure (mmHg)	0.261	0.0002
24h Systolic blood pressure (mmHg)	0.35	<0.0001
24h Diastolic blood pressure (mmHg)	0.356	<0.0001
Daytime Systolic blood pressure (mmHg)	0.352	<0.0001
Daytime Diastolic blood pressure (mmHg)	0.358	<0.0001
Nighttime Systolic blood pressure (mmHg)	0.345	<0.0001
Nighttime Diastolic blood pressure (mmHg)	0.361	<0.0001
Diurnal DBP different (mmHg)	0.143	0.0497
The nighttime SBP decrease rate (%)	0.228	0.0015
The nighttime DBP decrease rate (%)	0.169	0.0199
LDL-C (m mol/L)	0.251	0.0005
HDL-C (m mol/L)	-0.212	0.0033
UA (u mol/L)	0.179	0.0136
Estimated glomerular filtration rate (ml/min per 1.73 m^2)	0.151	0.0578

Table 3: Spearman linear regression analysis in Lp-PLA2 level with blood pressure and biochemical indexes.

Previous clinical and epidemiologic studies had demonstrated that Lp-PLA2 activity is an independent predictor of Coronary Heart Disease (CAD) and stroke beyond traditional risk factors in the general population. However, there is limited knowledge on the effect of Lp-PLA2 on early inflammatory cardiovascular damage. Our current study investigated the relationships between the plasma Lp-PLA2 mass and BP variation in pre-hypertensive patients without pharmacological treatment.

The results showed that plasma Lp-PLA2 mass in both MHT and THT group were significantly higher than nomotensive individuals matched for age and sex. It is worth noting that the incidence of MHT reached 65% among patients with an Lp-PLA2 $\geq$ 225 μ mol/L. In agreement with this result, recent studies had reported that MHT was associated with vascular inflammation-induced endothelial dysfunction and early arterial damage also provided a clinic evidence of prehypertension-associated elevations in plasma Lp-PLA2 activity, OxPL, and lysoPCs [5,6,21-23].

Previous animal experiments reported by Wang et al demonstrated that Lp-PLA2 participates in OxPL-induced progression of atherosclerosis in many ways, not only by up-regulating genes expression of lp-PLA2 and proinflammatory molecules through p38 MAPK pathway in monocytes, but also by trigging the migration of Smooth Muscle Cell (SMC) and endothelial cell death by production of lyso-PC, thereby activating the systemic and localized vascular inflammatory cascade response and contributing to the development of atherosclerotic lesions. In addition, the hemodynamic changes induced by blood pressure fluctuations can also cause the vascular endothelial injury along with inflammation response [24-29].

Interestingly, a novel finding from current study was that Lp-PLA2 mass in MHT was significantly higher than the true hypertension group, although there was no difference in the incidence of carotid plaque between the two groups. Previous clinic studies had reported MHT had a high degree of recurrence, and pro-inflammation triggered by Lp-PLA2 catalyzed Ox-PLs hydrolysis could prompt arterial stiffness and vascular compliance in pre-hypertensive patients. Studies by Watanabe et al and Mazzali et al reported that oxidative stress over activity induced by increased sUA levels had a detrimental effect on the vascular endothelium and contribute to pressure fluctuations via stimulating the renin-angiotensin system and promoting acute retention of water and sodium. Our present study further confirmed that the plasma Lp-PLA2 mass has a positive correlation with BP variability based on measurements of ABPM in patients with MHT. Thus it is conceivable that a higher degree of oxidative stress-dependent inflammatory vascular responses may be considered to play an important role in pathogenesis of MTH [30-33].

Indeed, this persistent inflammatory vascular responses and pressure fluctuation had been proved to induce the development of arteriolosclerosis, renal interstitial fibrosis and permanent sodium-sensitive hypertension, which were involved in the process of true hypertension. A study by Sánchez-Lozada LG et al. [34] reported that a constant mildly hyperuricemia rats could develop renin-dependent hypertension and interstitial renal disease. So these studies indicated that oxidative stress and inflammatory response may exert different degree effect on the while pathophysiology processes of primary hypertension. In clinic practice, focusing on the baseline and on-treatment level of inflammatory markers in patient with MHT will better prevent and target the prevalence and development of hypertension and arteriolosclerosis.

Spearman linear regression analysis in current study revealed that Lp-PLA2 had a positive correlation with traditional CVD risk factors (UA and LDL-C), but a negative correlation with HDL-C. Chae et al. [35] also reported a positive association between plasma ox-LDL and Lp-PLA2 activity in metabolic syndrome. Uric acid acts as a useful biochemical marker of oxidative stress and endothelial function had been shown to be a well-established driver of local and systemic inflammatory vascular responses due to production of ox-LDL and pro-inflammatory factors, thereby increasing Lp-PLA2 activity and concentration, although the intrinsic mechanism needs further elucidation [36,37].

Similar to the present study, Theilmeier et al. [38] and Britesa et al. [39] demonstrated by in vitro and in vivo models that HDL-C could play an anti-atherogenic action via prevents the accumulation of lipid hydroperoxides in LDL-C. Thus, the increased Lp-PLA2 level in MHT patients may also be associated with suppression of anti-oxidative activity due to a decrease in HDL-C.

Limited by our cross-sectional and observational study, the potential utility of LP-PLA2 in patients with MHT as a biomarker in cardiovascular risk prediction and as the therapeutic target still warrants a prospective study. Because the expression of Lp-PLA2 is regulated by the PLA2G7 gene, its activity or mass differ in predicting different diseases. More experimental evidence is needed to fully interpret the intrinsic functional role of Lp-PLA2 in different inflammatory cardiovascular diseases.

Conclusion

In conclusion, the present study demonstrated that an increased plasma LP-PLA2 mass is closely associated with metabolic stress and the incidence of MHT, and provided new evidence that LP-PLA2 may be involved in dynamic regulation of oxidative stress-dependent inflammatory vascular responses, thus exerting pathophysiological effect on the development of MHT. In clinical practice, focusing on the detection and follow-up of the plasma LP-PLA2 level could facilitate risk stratification and targeted therapy against atherosclerosis in MHT patients.

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