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Relation of Baseline Plasma Phospholipid Transfer Protein (PLTP) Activity to Left Ventricular Systolic Dysfunction in Patients Referred for Coronary Angiography

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Abstract

Phospholipid transfer protein (PLTP) is an important modulator of phospholipid transfer and exchange among lipoproteins and also plays a role in inflammation and oxidative stress. Accordingly, PLTP has been implicated in the development of atherosclerosis. Left ventricular (LV) systolic dysfunction is common in patients with atherosclerosis, and both inflammation and oxidative stress have also been implicated in its development and progression. The goal of the present study was to examine the relation between plasma levels of PLTP and LV systolic function. Baseline plasma PLTP activity was measured in 389 male patients referred for coronary angiography for a variety of indications. Detailed clinical, angiographic and laboratory characteristics were available for the patients. Compared to those patients with normal LV function (defined as an ejection fraction of $\geq 55\%$ on ventriculography), patients with any degree of LV dysfunction had elevated PLTP activity (median PLTP 17.8 pmol/ul/h versus 15.9 pmol/ul/h, $p=0.0038$). Using multivariate analysis, and adjusting for a variety of confounding variables known to affect both LV function and PLTP activity, PLTP activity was an independent predictor of the presence of any left ventricular systolic dysfunction in the entire population (OR 1.47, 95% CI 1.12–1.93, $p=0.0052$). Furthermore, PLTP activity was an independent predictor of the presence of LV dysfunction in both patients with and without myocardial infarction on presentation (OR 2.39, 95% CI 1.18–4.86, $p=0.0161$ and OR 1.41, 95% CI 1.05–1.89, $p=0.0206$, respectively). In conclusion, PLTP activity may represent a novel marker of LV systolic dysfunction in patients with known or suspected coronary artery disease.

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Keywords

phospholipid transfer protein; inflammation; left ventricular systolic dysfunction; atherosclerosis

Introduction

Phospholipid transfer protein (PLTP) is an important modulator of plasma HDL levels, HDL particle size, and HDL particle composition.¹ It is also involved in the metabolism of very low density lipoproteins (VLDL).² For these reasons, it has been suggested that PLTP plays an important role in the development of atherosclerosis.³ PLTP-deficient mice have been demonstrated to have smaller atherosclerotic lesions in the aorta,^{2,4} while PLTP transgenic mice have been shown to have larger atherosclerotic lesions.^{3,5} In humans, PLTP activity has been shown to be positively and independently related to CAD.⁶ In addition, PLTP activity has been shown to be increased in several different clinical settings that are closely related to dyslipidemia and atherosclerosis, such as aging,⁷ obesity,^{8,9} and both type 1 and type 2 diabetes mellitus.^{10–12} Furthermore, it has recently been reported that PLTP possesses proinflammatory properties which could also contribute to its pro-atherosclerotic potential.^{13–15} Finally, PLTP has been associated with oxidative stress.^{4,5}

Left ventricular systolic dysfunction is one of the most common causes of heart failure in the United States.¹⁶ Conditions that are often associated with its development and/or progression include atherosclerosis, hypertension, diabetes mellitus, and obesity.^{17–19} However, in addition both inflammation and oxidative stress play important roles in the pathophysiology of LV dysfunction and heart failure. Plasma levels of a variety of proinflammatory cytokines and their cognate receptors are elevated in relation to disease severity and predict adverse outcomes.^{20–23} Because of their known direct negative effects on cardiac myocytes and extracellular matrix, inflammatory cytokines have been implicated in ventricular remodeling and disease progression.²⁴ Markers of oxidative stress have also been associated with worsening clinical status and impaired survival in patients with chronic heart failure.^{25,26}

Despite the common associations of PLTP activity and LV dysfunction with disease states such as atherosclerosis as well as pathophysiologic processes such as inflammation and oxidative stress, there have been no animal or clinical studies that have examined the relation between PLTP activity and left ventricular systolic dysfunction. Given the strong associations between PLTP activity and the variables known to be related to LV systolic dysfunction, we hypothesized that PLTP would be an independent predictor of LV systolic dysfunction. Accordingly, we sought to examine the relation between PLTP activity and LV systolic function in a broad and unselected population referred for coronary angiography.

Methods

Study Design

The present analysis was derived from a database which had originally been created for the purpose of examining the prognostic significance of various plasma biomarkers in patients

with known or suspected coronary artery disease. The study population and design have been previously described in detail elsewhere.²⁷ Briefly, 389 male patients undergoing coronary angiography for a variety of indications (including acute myocardial infarction) constituted the study population. Detailed clinical and demographic information were obtained using interview and review of the computerized medical records. Fasting blood samples were obtained from all patients at the time of angiography for subsequent analysis.

Measurement of PLTP Activity

PLTP activity was measured with an assay kit (Cardiovascular Targets, Inc., New York, N.Y., USA). The kit includes both donor and acceptor particles. Incubation of donor and acceptor particles with 3 μ L of human plasma results in PLTP-mediated transfer of fluorescent phospholipid, which is present in a self-quenched state when associated with the donor. The transfer is determined by the increase in fluorescence intensity as the fluorescent lipid is removed from the donor and transferred to the acceptor. The interassay coefficient of variation of the PLTP activity was $3.3 \pm 0.5\%$. The linear range of PLTP activity in this assay was between 1 and 7 μ L of plasma. Three freeze-thaw cycles of plasma did not influence the assay. To validate the novel PLTP activity assay, we compared the results with those obtained by the classic radiolabeled method.^{28,29} There was a high degree of correlation between the 2 methods ($r=0.90$, $P<0.01$; $n=30$). Laboratory personnel were unaware of the study individual assignment.

Angiographic Data

The angiographic scoring system used for the present analysis has been described previously.^{30,31} All patients and their angiograms were graded for the number of diseased coronary arteries, taking into account the left main, left anterior descending, left circumflex, and right coronary arteries (minimum = 0, maximum = 4). A coronary artery was considered diseased and given a score of 1 if there was an obstructive lesion $\geq 50\%$ in that artery or one (≥ 2.5 mm) of its major branches. Stenosis severity was determined using visual estimation in 2 or more orthogonal views. All angiograms were read by 2 experienced angiographers working independently, and any differences in interpretation were subsequently reconciled by a third reviewer. Left ventricular systolic function was assessed using contrast ventriculography and categorized as normal (ejection fraction [EF] $\geq 55\%$, or mildly (EF 45% to 54%), moderately (EF 31% to 44%), or severely reduced (EF $\leq 30\%$). These 4 categories of LV function were scored as 0, 1, 2, and 3, respectively.

Operators reading the angiograms and left ventriculograms were blinded to the results of laboratory analyses.

Statistical Methods

The study population was divided into two groups based on LV function assessed using ventriculography as (1) normal, and (2) any degree of LV dysfunction (mild, moderate or severe). Summary statistics for continuous variables were presented as mean $\pm$ SD and median (interquartile range), and comparisons between groups were performed using nonparametric Wilcoxon's rank-sum test. The Kolmogorov Smirnov test was used to determine whether or not data were normally distributed. Log transformation was applied to

all biomarkers to decrease skewness and kurtosis of data. Categorical data were summarized as frequencies and percentages, and comparisons between groups were performed using Pearson's chi-square test or Fisher's exact test if the number of observations per cells was less than 5.

LV function was categorized and scored as 0 (normal), 1 (mildly reduced), 2 (moderately reduced) and 3 (severely reduced). Univariate and multivariate analyses were performed using logistic regression to predict the presence of any LV dysfunction (i.e., LV score 0 versus 1, 2, or 3). Results were presented as odds ratios (ORs) and 95% confidence intervals (CIs). For inflammatory markers, ORs indicated an increment of 1 SD in the respective log-transformed variable. For all the logistic regression models, the following baseline variables were studied by univariate analysis: age, family history of premature CAD, diabetes mellitus, hypertension, active tobacco use, any history of tobacco use, myocardial infarction of presentation, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, triglycerides, serum creatinine, body mass index, aspirin use, beta-blocker use, angiotensin-converting enzyme inhibitor use, statin use, angiotensin receptor blocker use, previous coronary artery bypass graft surgery, number of diseased coronary arteries, hs-CRP, white blood cell count, fibrinogen, and PLTP activity. Only univariate predictors with $p < 0.05$ were subsequently entered into multivariate models.

All analyses used 2-sided tests with an overall significance level of $\alpha = 0.05$. All statistical analyses were performed using SAS Statistical Software, version 8.2 (SAS Inc., Cary, North Carolina).

Results

Baseline characteristics

In total, 389 men were enrolled in the study. Data for LV systolic function obtained using ventriculography were available for 366 patients. Baseline clinical, angiographic and laboratory characteristics of the study population stratified by LV systolic function as either normal (LV score 0) versus any impairment (LV score 1, 2, or 3) are listed in Table 1.

LV dysfunction was seen in association with angiotensin-converting enzyme inhibitor use, number of diseased coronary arteries on angiography, MI on presentation, hs-CRP, fibrinogen, and PLTP activity (Table 1). Specifically, with respect to PLTP activity, median baseline plasma PLTP activity in the group of patients with normal LV function was 15.9 compared with 17.8 in the group with any LV function impairment ($p = 0.0038$).

Association of PLTP with any LV dysfunction in the entire cohort

To determine the ability of baseline variables to predict the presence of any LV systolic dysfunction using ventriculography, LV function was categorized as 0 (normal LV function) versus 1, 2, or 3 (mild, moderate or severe dysfunction, respectively). Using univariate logistic regression analysis, baseline variables associated with the presence of any LV systolic dysfunction were angiotensin-converting enzyme inhibitor use, number of diseased coronary arteries on angiography, MI on presentation, hs-CRP, fibrinogen and PLTP activity. Using multivariate logistic regression analysis, variables independently associated

with the presence of moderate to severe LV dysfunction were angiotensin-converting enzyme inhibitor use, number of diseased coronary arteries on angiography, hs-CRP, and PLTP activity (Table 2).

Association of PLTP with LV dysfunction in the MI and non-MI subpopulations

Because of the known effects of MI on LV function and lipoprotein levels, additional analyses were performed in the MI (n = 107) and non-MI (n = 282) subpopulations using the same covariates as for the entire cohort. In both the MI and non-MI subpopulations, PLTP activity was still independently associated with LV dysfunction using multivariate logistic regression (Tables 3 and 4). In the MI subpopulation, the HR for the presence of any LV dysfunction was 2.39 (95% CI, 1.18 to 4.86, p=0.0161). In the non-MI subpopulation, the HR for the presence of any LV dysfunction was 1.41 (95% CI, 1.05 to 1.89, p=0.0206).

Discussion

The most significant finding of our study was that PLTP activity was independently associated with the presence of LV systolic dysfunction. To our knowledge, this is the first report of such an association. Importantly, the relation between PLTP activity and LV function persisted even after adjustment for covariates associated with LV dysfunction, such as the extent of CAD or the use of angiotensin-converting enzyme inhibitors. In addition, when analyses were restricted to patients with and without myocardial infarction on presentation, PLTP activity remained a strong and independent predictor of LV function in each of these subgroups. We believe the persistence of this association is a testimony to the validity of the findings.

There is growing evidence that the biological role(s) of PLTP extend far beyond phospholipid transfer and exchange among lipoproteins. In mice, PLTP deficiency has been associated with a reduction in systemic inflammation.^{13–15} Furthermore, in mouse models, PLTP deficiency has been associated with increased antioxidation potential,⁴ while the opposite has been observed in PLTP overexpression.⁵ In addition, PLTP is also involved in ABCA1-dependent cholesterol efflux, a process which is critical for reverse cholesterol transport.³² Finally, PLTP activity is closely related to obesity, diabetes mellitus, and insulin resistance.^{8–12} Although the mechanism of these associations remain poorly defined, it is likely related to the putative role of PLTP in the development of atherosclerosis, a common underlying factor in each of these disease states. Concordant with these observations is the present report of a strong and independent association of PLTP with left ventricular systolic dysfunction, which is itself a common correlate of clinical atherosclerosis.

Despite the strong experimental evidence in favor of a role for PLTP in the development of atherosclerosis, the clinical studies in this regard have been somewhat conflicting. We have previously reported that serum PLTP activity is increased in CAD patients in a cross-sectional design.⁶ In another study, de Vries et al. demonstrated that plasma PLTP activity was a positive determinant of carotid artery intima-media thickness in type 3 diabetes mellitus, suggesting that high PLTP activity is involved in accelerated atherosclerosis in this disease.³³ In contrast, Yatsuya et al. found PLTP mass decreased in Japanese patients with CAD.³⁴ However, PLTP activity (which correlates poorly with PLTP mass) was not

measured in that study. In another study, Schgoer et al. found that low PLTP activity was a risk factor for peripheral atherosclerosis.³⁵ Although the reasons for these conflicting findings are unknown, it is likely that differences in both design and study population may have accounted for these discrepant results. However, we believe that both the basic science literature and the current report of a strong association between PLTP activity and left ventricular dysfunction are consistent with our earlier work of an association between increased PLTP activity and clinical atherosclerosis. It is also worth emphasizing that these two clinical studies were performed in two different patient populations (one European and the other North American) but with similar clinical characteristics.

Whether increased PLTP activity merely represents a marker of LV dysfunction or is intimately involved in its pathogenesis is unknown. There are no reports in the literature of PLTP production by either the normal or failing myocyte. Given the strong association of atherosclerosis with both PLTP activity and LV dysfunction, it is conceivable that the relation between PLTP activity and LV dysfunction may simply represent a surrogate of atherosclerosis in these patients. However, it is important to point out that all our analyses adjusted for the extent of angiographic CAD and that the association between PLTP activity and LV dysfunction persisted even after adjustment for this potentially confounding variable. It is also conceivable that the relation between PLTP activity and LV dysfunction may simply represent the association of both these variables with inflammation. However, once again, our analyses adjusted for markers of inflammation (specifically, hs-CRP and fibrinogen) and the relation between PLTP activity and LV dysfunction was independent of these well-established markers of inflammation. Furthermore, at least in our patient population, there was no significant association between PLTP activity and either fibrinogen or hs-CRP (while, as expected, there was a very strong and significant association between hs-CRP and fibrinogen).

This study has a number of limitations. First, it was conducted exclusively in men, and as such, the results cannot be extrapolated to women. Second, the independent relation of PLTP activity with LV systolic dysfunction should be studied in the context of more established biomarkers of LV systolic dysfunction, such as BNP. Future studies are underway to examine the relative significance of these markers in the identification of LV systolic dysfunction, as well as their comparative utility in prognostication. Third, given the relatively small number of patients with normal or non-obstructive CAD in our study population, we were unable to perform meaningful subgroup analyses of the relation between PLTP activity and LV systolic dysfunction in patients free of atherosclerosis. By virtue of its association with both PLTP and LV systolic dysfunction, atherosclerosis remains a potential confounder despite adjustments for this variable in our multivariate analyses. Fourth, the population was a very heterogeneous one representing a broad spectrum of both risk and LV systolic function. Therefore, it is unknown PLTP activity would be similarly predictive of LV dysfunction in a more uniform cohort (either high or low risk) in which the range of LV systolic function would be expected to be much narrower. Along the same lines, larger studies in healthy populations are needed to determine the reference range of PLTP activity and the factors that influence its levels in the absence of atherosclerotic disease. Finally, the size of the population was relatively small and the study was not designed with a priori calculations with respect to sample size or

statistical power. As such, the findings need to be confirmed in larger and prospectively designed studies.

In conclusion, we found that baseline plasma PLTP activity was elevated in patients with LV dysfunction. Furthermore, baseline plasma PLTP activity was an independent predictor of LV systolic dysfunction in a population of patients referred for coronary angiography. Importantly, this association was independent of factors known to affect both LV function and PLTP activity, such as the extent of atherosclerosis and the inflammatory status of the patient. PLTP activity may thus represent a novel marker of LV systolic dysfunction in patients with known or suspected coronary artery disease.

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Table 1

Baseline characteristics stratified by the presence or absence of any degree of left ventricular systolic dysfunction

Characteristics	EF $\geq$ 55% (N=135)	EF < 55% (N=231)	Total Population (N=389)	p-value for trend
Age (yrs)				0.8771
Mean (SD)	65.5 (8.8)	65.4 (10.4)	65.3 (10.0)	
Race				0.7542
Black (N)	40 (29.6%)	75 (32.5%)	122 (31.4%)	
Hispanic (N)	39 (28.9%)	69 (29.9%)	111 (28.5%)	
White (N)	56 (41.5%)	87 (36.6%)	156 (40.1%)	
Family history of premature CAD	37 (27.4%)	60 (21.7%)	96 (24.7%)	0.2115
Diabetes mellitus	53 (39.3%)	105 (45.5%)	169 (43.4%)	0.2483
Hypertension*	116 (85.9%)	187 (81.0%)	325 (83.6%)	0.2239
Any history of tobacco use	114 (84.4%)	180 (77.9%)	316 (81.2%)	0.1239
Active tobacco use	39 (28.9%)	68 (29.4%)	120 (30.9%)	0.9114
Myocardial infarction on presentation	25 (18.5%)	75 (32.5%)	107 (27.5%)	0.0039
Body mass index (kg/m²)				0.5705
Median	28.4	27.7	27.9	
25 th –75 th	25.1 – 31.5	24.5 – 31.5	24.7 – 31.5	
Prior coronary artery bypass graft surgery	5 (3.7%)	21 (9.1%)	35 (9.0%)	0.0590
Number of diseased coronary arteries**				<0.0001
0	33 (24.4%)	31 (13.4%)	72 (18.5%)	
1	29 (21.5%)	34 (14.7%)	63 (16.2%)	
2	42 (31.1%)	55 (23.8%)	99 (25.4%)	
3	26 (19.3%)	101 (43.7%)	136 (35.0%)	
4	5 (3.7%)	10 (4.3%)	19 (4.9%)	
Aspirin use	116 (85.9%)	194 (84.0%)	331 (85.1%)	0.6183
β-blocker use	90 (66.7%)	162 (70.1%)	267 (68.6%)	0.4900
Angiotensin converting enzyme inhibitor use	66 (48.9%)	157 (68.0%)	236 (60.7%)	0.0003
Angiotensin receptor blocker use	4 (3.0%)	16 (6.9%)	22 (5.7%)	0.1518
Statin use	67 (49.6%)	126 (54.6%)	205 (52.7%)	0.3634
Fibrate use	8 (6.0%)	8 (3.5%)	16 (4.1%)	0.2937

Characteristics	EF >=55% (N=135)	EF < 55% (N=231)	Total Population (N=389)	p-value for trend
Serum creatinine (mg/dl)				0.1763
Median	1.0	1.1	1.1	
25 th –75 th	0.9 – 1.2	0.9 – 1.3	0.9 – 1.2	
hs-CRP (mg/L)				0.0008
Median	8.1	11.4	9.2	
25 th –75 th	3.0 – 13.7	4.5 – 26	3.8 – 18.8	
Fibrinogen (mg/dl)				0.0099
Median	347	367	360	
25 th –75 th	292 – 403	314 – 446	300 – 427	
White blood cell count (x 10⁹/L)				0.0386
Median	6.9	7.3	7.2	
25 th –75 th	5.8 – 8.1	6.0 – 8.9	5.9 – 8.7	
PLTP activity (pmol/ul/h)				0.0038
Median	15.9	17.8	17.0	
25 th –75 th	13.2 – 21.0	14.7 – 22.7	14.1 – 22.1	
Low density lipoprotein (mg/dl)				0.1515
Median	109.5	101.2	105.6	
25 th –75 th	82.6 – 129.4	84.2 – 125.8	83.8 – 126.6	
High density lipoprotein (mg/dl)				0.5007
Median	37	38	38	
25 th –75 th	32.0 – 43.5	31 – 46	31.0 – 45.0	
Total Cholesterol (mg/dl)				0.1475
Median	176.0	168	171	
25 th –75 th	149 – 203	146 – 195	146 – 199	
Triglycerides (mg/dl)				0.4389
Median	120	118	116	
25 th –75 th	82 – 184	73 – 174	76 – 174	

Data are presented as frequencies (percentages) for categorical variables and as means +/- SD and medians (25th, 75th percentiles) for continuous variables.

* Patients were diagnosed as hypertensive if they were documented to have a blood pressure greater than 140/90 mmHg on more than 2 occasions or were already on antihypertensive therapy.

** Takes into account the left main, left anterior descending, left circumflex, and right coronary arteries.

Table 2

Multivariate logistic regression analysis of baseline characteristics and the presence of any left ventricular dysfunction – entire cohort

Baseline variable	OR (95% CI)	p Value
PLTP activity	1.47 (1.12, 1.93)	0.0052
hs-CRP	1.42 (1.10, 1.85)	0.0082
Angiotensin converting enzyme inhibitor use	1.90 (1.17, 3.10)	0.0098
Number of diseased coronary arteries	1.53 (1.24, 1.88)	<0.0001

Twenty-three clinical, laboratory and angiographic variables were initially studied by univariate analysis (See Methods and Table 1). Only those predictors with a p Value < 0.05 (angiotensin converting enzyme inhibitor use, the number of diseased coronary arteries, PLTP activity, MI on presentation, fibrinogen and hs-CRP) were subsequently entered into a multivariate model, the results of which are presented.

Table 3

Multivariate logistic regression analysis of baseline characteristics and the presence of any left ventricular dysfunction – myocardial infarction subpopulation

Baseline variable	OR (95% CI)	p Value
PLTP activity	2.39 (1.18, 4.86)	0.0161
hs-CRP	1.89 (1.05, 3.40)	0.0348
Number of diseased coronary arteries	2.02 (1.22, 3.33)	0.0062

Twenty-three clinical, laboratory and angiographic variables were initially studied by univariate analysis (See Methods and Table 1). Only those predictors with a p Value < 0.05 (the number of diseased coronary arteries, PLTP activity, and hs-CRP) were subsequently entered into a multivariate model, the results of which are presented.

Table 4

Multivariate logistic regression analysis of baseline characteristics and the presence of any left ventricular dysfunction – non myocardial infarction subpopulation

Baseline variable	OR (95% CI)	p Value
PLTP activity	1.41 (1.05, 1.89)	0.0206
Number of diseased coronary arteries	1.42 (1.13, 1.78)	0.0031
Angiotensin converting enzyme inhibitor use	2.09 (1.21, 3.61)	0.0084

Twenty-three clinical, laboratory and angiographic variables were initially studied by univariate analysis (See Methods and Table 1). Only those predictors with a p Value < 0.05 (the number of diseased coronary arteries, PLTP activity, and angiotensin converting enzyme inhibitor use) were subsequently entered into a multivariate model, the results of which are presented.