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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 proteins. It 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 PLTP activity 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 ≥55% on ventriculography), patients with any degree of LV dysfunction had elevated PLTP activity (median PLTP 17.8 pmol/μl/h versus 15.9 pmol/μl/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.

1. 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 proatherosclerotic 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]. In addition, however, 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].

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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 activity 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.

2. Methods

2.1. 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 was 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.

2.2. Measurement of PLTP activity

PLTP activity was measured with an assay kit (Cardiovascular Targets Inc., New York, NY, USA). The kit includes both donor and acceptor particles. Incubation of donor and acceptor particles with 3 μl 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 ± 0.5%. The linear range of PLTP activity in this assay was between 1 and 7 μl 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 assignation.

2.3. 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 ≥50% in that artery or in one of its major branches (≥2.5 mm). 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] ≥55%, or mildly (EF 45–54%), moderately (EF 31–44%), or severely reduced (EF ≤ 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.

2.4. 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 ± SD and median (interquartile range), and comparisons between groups were performed using nonparametric Wilcoxon's rank-sum test. The Kolmogorov Smirnoff 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 (past or present), 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, NC).

3. Results

3.1. 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 systolic 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 pmol/μl/h compared with 17.8 pmol/μl/h in the group with any LV function impairment ($p = 0.0038$).

3.2. 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