Reduced Paraoxonase 1 Activity as a Marker for Severe Coronary Artery Disease

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Paraoxonase-1 (PON1), a high-density-lipoprotein- (HDL-) associated enzyme, has the potential to protect against atherogenesis. We examined the relationships between plasma PON1 activity and the progression of atherosclerosis as well as coronary artery disease (CAD). Fasting blood samples were collected from female apolipoprotein E-deficient (apoE−/−) mice and 149 patients undergoing coronary angiography for the biochemical parameters measurement. The severity of CAD was defined using angiographic Gensini score (GSS). Compared to 3-month-old apoE−/− mice, aged mice had significantly lower PON1 activity, which is negatively correlated with the size of atherosclerotic lesion and plasma interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) levels. In study patients, PON1 activity was correlated with age, sex, and HDL-cholesterol, apolipoprotein AI, and high-sensitivity C-reactive protein (hs-CRP) levels and was significantly lower in CAD group than that in non-CAD control group. Interestingly, PON1 activity in severe CAD group (GSS > 40) was further significantly reduced compared to those in mild and moderate subgroups (GSS ≤ 40) (P < 0.01). There is a significant correlation between PON1 activity and the severity of CAD as assessed by GSS (r = −0.393, P < 0.001). PON1 activity may be a potential biomarker for the severity of CAD.

1. Introduction

Atherosclerosis is characterized by accumulation of lipids and inflammatory cells in the artery wall and is the cause of coronary artery disease (CAD). Although the mechanisms are still not entirely resolved, previous studies have indicated that dyslipidemia, enhanced oxidative stress, and inflammation result in the development of atherosclerosis and its complications, CAD [1, 2].

There is increasing evidence that oxidized low-density lipoprotein (LDL) has a key role in the initiation and progression of atherosclerosis; high-density lipoprotein (HDL) has an antiatherogenic role in part by its antioxidantive and anti-inflammatory properties through preventing LDL oxidation [3]. The HDL-associated enzyme paraoxonase-1 (PON1), a calcium-dependent esterase, is largely responsible for the antioxidant and anti-inflammatory actions of HDL due to its ability to hydrolyze oxidized phospholipids [4, 5]. Many experiments have shown that knockout of PON1 gene is proinflammatory and pro-atherogenic by increasing oxidized LDL and cell adhesive molecules, while transgene or overexpression of PON1 is antiatherogenic by decreasing LDL oxidation and inflammatory status [6–9]. Recent meta-analyses of clinical studies suggested that lower plasma PON1 activity is associated with increased CAD risk [10, 11] and that decreased PON1 activity might be a factor responsible for the acceleration of CAD in type 2 diabetes mellitus [12]. It has been shown that PON1 activity is affected by both genetic
polymorphisms and environmental factors including age, gender, lifestyle, and pharmaceutical interventions [13, 14]. Despite the current knowledge, the function and mechanism of PON1 in the initiation and progression of atherosclerosis warrant further investigation.

In this study, we first used apolipoprotein E-deficient (apoE\(^{−/−}\)) mice to investigate the change of plasma PON1 activity during the progression of atherosclerosis. ApoE\(^{−/−}\) mice have been widely used in atherosclerosis studies because they develop severe hypercholesterolemia and spontaneous atherosclerotic lesions with age. Next, we extended our study by examining the relationship between plasma PON1 activity and the severity of coronary artery stenosis in Chinese CAD patients confirmed by coronary angiography.

2. Materials and Methods

2.1. Experimental Subjects. ApoE\(^{−/−}\) mice (on C57BL/6 background) were obtained from Jackson Laboratories and housed in microisolator cages on a rodent chow diet. Animal care and experimental procedures were performed under the regulations of the Animal Care Center of Wuhan University, in accordance with the guidelines laid down by the National Institutes of Health of the United States. Only female mice with different age were used for this study.

The clinical study was performed in the Cardiology Division of Wuhan University Zhongnan Hospital in Hubei province, China. Patients (105 males and 44 females; mean age 61.1 ± 9.0 yrs) were recruited for this study when they visited the hospital for coronary angiography from September 2011 to May 2012. The percent stenosis of the coronary artery was determined by the hand-held caliper measurement. Patients with angiographic CAD (\(n = 118\)) were defined as the presence of stenosis ≥50% of the luminal diameter in at least one coronary artery. The severity of CAD was assessed using angiographic Gensini score (GSS) [15]. The GSS was calculated for each coronary stenosis based on the degree of luminal narrowing and its localization. Mild atherosclerosis was classified as a GSS ≤ 10, moderate atherosclerosis as a GSS > 10 and ≤ 40, and severe atherosclerosis as a GSS > 40 [16]. Those taking lipid-lowering drugs and antioxidants or having suspected infectious conditions, autoimmune-related disease, peripheral artery disease, or renal and hepatic diseases were excluded. Written informed consent was obtained from all participants before collecting blood samples and general information regarding health, medical history, and lifestyle habits. The study was approved by the Medical Ethics Committee of Wuhan University Zhongnan Hospital, confirmed with the Declaration of Helsinki of the World Medical Association.

Blood samples with or without heparin were collected after fasting overnight. Mouse blood was collected by retroorbital venous plexus puncture under the anaesthetization with 3% isoflurane. Human blood samples were obtained before coronary angiography. The plasma or serum was immediately separated by centrifugation of 4000 \(\times\) g 10 min at 4°C, and then serum was immediately aliquoted and stored at −80°C.

2.2. Biochemical Analyses. PON1 activity was measured spectrophotometrically using paraoxon (O,O-diethyl-O-(4-nitrophenyl) phosphate, Sigma Chemical Co., MO, USA) as substrate. Five microliters of serum or plasma without heparin mixed with 95 \(\mu\)L assay buffer (2.0 mol/L NaCl, 100 mmol/L Tris-HCl, 2.0 mmol/L CaCl\(_2\), pH 8.5) was placed in a 96-well plate, and then 100 \(\mu\)L paraoxon solution (2.4 mmol/L in assay buffer) was added into each well. The rate of generation of product p-nitrophenol was monitored by measuring the increase of absorbance at 405 nm at 25°C within 4 min. PON1 activity was calculated from the molar extinction coefficient (17,000 M\(^{−1} \cdot\)cm\(^{−1}\)). One unit of PON1 activity was defined as 1 nmol of p-nitrophenol formed per minute under the previous conditions and expressed as U/mL serum.

Plasma total cholesterol (TC) and triglycerides levels were measured by enzymatic colorimetric assays (Prodia diagnostics, Boetzingen, Germany). HDL-cholesterol (HDL-C) was determined after precipitation of the apolipoprotein B-containing lipoproteins, and LDL-cholesterol (LDL-C) was calculated using Friedewald formula (Sekisui, Tokyo, JP). Lipoprotein (a), apolipoprotein AI (apoAI), and apolipoprotein B100 (apoB100) were detected by immunoturbidimetric assays (Prodia diagnostics, Boetzingen, Germany). All the assays were performed blindly. Serum tumor necrosis factor alpha (TNF-\(\alpha\)) and interleukin-6 (IL-6) levels of mice were determined using an enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer’s instructions (Ebioscience, San Diego, USA). Each sample was assayed in triplicate, and the intra-assay coefficient of variation was less than 10%. The concentration of high-sensitivity C-reactive protein (hs-CRP) in human plasma was determined on an Olympus analyzer by a high sensitivity latex-enhanced immunoturbidimetry assay using Nanopia CRP kit (Sekisui, Tokyo, JP) with standards and controls supplied by the manufacturer.

2.3. Quantification of Atherosclerotic Lesions in Mice. The proximal aortas were collected from 3-, 6-, 12-, or 18-month old apoE\(^{−/−}\) mice fed a regular chow diet after the mice were sacrificed by an overdose of isoflurane. The extent of atherosclerosis was examined both in oil-red O-stained cross-sections of the proximal aorta (15 alternate 10 \(\mu\)m cryosections) and by en face analysis using the KS300 imaging system as described previously [17].

2.4. Statistical Analysis. Statistical analysis was performed using the SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± SD (standard deviation) or median with 25th and 75th percentiles. The Student’s unpaired \(t\)-test for parametric variables or the Mann-Whitney \(U\) test for nonparametric variables was used to assess difference between two groups. Difference among multiple groups was analyzed by one-way analysis of variance (ANOVA) followed by pairwise comparison with the method of Fisher’s LSD. Univariate correlations of PON1 activity with risk factors were assessed by Pearson or Spearman correlation.
correlation. All tests were two tailed, and \( P \) values of < 0.05 were considered statistically significant.

3. Results

ApoE\(^{-/-}\) mouse is a widely used animal model for atherosclerosis study. Aged apoE\(^{-/-}\) mice develop advanced atherosclerotic lesions similar to those in human arteries. In this study, progressive atherosclerotic lesions were observed in apoE\(^{-/-}\) mice with increased age on a regular chow diet (Figure 1). The first sign of lesions was present in the aortic root and aortic arch at 3 months of age, and then the lesions of various stages widely appeared and were gradually accelerated throughout the arterial tree of elder mice. With the progressive atherosclerosis, hypercholesterolemia was also significantly aggravated in elder mice, whereas triglycerides levels were not significantly changed (Table 1). It is notable that serum PON1 activity in apoE\(^{-/-}\) mouse gradually decreased while atherosclerosis progressed. The lower activity of PON1 correlated with more severe lesions, and decrease in PON1 activity was accompanied with the increase of other known inflammatory factors, such as TNF-\(\alpha\) and IL-6.

We next examined the correlation of PON1 activity with the development of CAD in Chinese Han population. A total of 118 CAD patients (aged 61.6 ± 9.2 yrs, 29.7% women) and 31 non-CAD patients (aged 59.3 ± 8.3 yrs, 29.0% women) documented by the angiographic reports were included in the analysis. According to Gensini score (GSS), among the 118 CAD patients, 27 of them (22.9%) were mild (GSS ≤ 10), 43 (36.4%) were moderate (GSS >10 and ≤ 40), and 48 (40.7%) were severe CAD patients. The clinical and biochemical parameters of the study patients were shown in
Table 1: Plasma PON1 activity and biochemical index in apoE\(^{-/-}\) mice with different ages.

| Parameters        | 3 months (n = 8) | 6 months (n = 8) | 12 months (n = 7) | 18 months (n = 6) |
|-------------------|-----------------|-----------------|------------------|-----------------|
| TC (mmol/L)       | 13.34 ± 1.24    | 13.73 ± 1.03    | 14.74 ± 0.90\(^{*}\) | 15.64 ± 0.79\(^{**}\) |
| Triglycerides (mmol/L) | 1.91 ± 0.38   | 1.95 ± 0.41     | 1.63 ± 0.18      | 1.72 ± 0.20     |
| TNF-\(\alpha\) (pg/mL) | 74.1 ± 21.4    | 124.4 ± 24.8\(^{**}\) | 150.9 ± 23.9\(^{**}\) | 177.3 ± 10.0\(^{***}\) |
| IL-6 (pg/mL)      | 92.3 ± 11.8     | 114.0 ± 14.7\(^{*}\) | 111.0 ± 22.8     | 154.9 ± 17.9\(^{***}\) |
| PON1 activity (U/mL) | 121.9 ± 8.1    | 108.6 ± 8.2\(^{*}\) | 96.6 ± 13.2\(^{**}\) | 80.6 ± 6.7\(^{**}\) |

Data are given as mean ± SD. \(^{*}\)P < 0.05, \(^{**}\)P < 0.01, compared with 3 m group; \(^{***}\)P < 0.05, \(^{***}\)P < 0.01, compared with 6 m group; \(^{*}\)P < 0.05, \(^{**}\)P < 0.01, compared with 12 m group.

Table 2: Clinical and laboratory characteristics of the participants in the study.

| Parameters            | Non-CAD patients (n = 31) | All CAD patients (n = 118) | p       | Mild CAD (Score ≤ 10, n = 27) | Moderate CAD (10 < score ≤ 40, n = 43) | Severe CAD (Score > 40, n = 48) |
|-----------------------|---------------------------|---------------------------|---------|-------------------------------|-----------------------------------------|----------------------------------|
| Gensini score         | 2.08 ± 1.72               | 37.03 ± 30.89             | <0.001**| 6.6.7 ± 2.03                  | 20.17 ± 7.03**                        | 69.20 ± 21.95**                   |
| Age (yrs)             | 59.3 ± 8.3                | 61.6 ± 9.2                | 0.205   | 61.4 ± 10.7                   | 61.7 ± 9.4                            | 61.6 ± 8.3                       |
| Sex (male/female)     | 22/9                      | 83/35                     | 0.946   | 15/12                         | 31/12                                  | 37/11                            |
| Smoking               | 12 (38.7%)                | 36 (30.5%)                | 0.597   | 7 (25.9%)                     | 10 (23.3%)                            | 19 (39.6%)                       |
| Diabetes (n (%))      | 3 (9.7%)                  | 42 (35.6%)                | 0.005** | 8 (29.6%)                     | 13 (30.2%)*                           | 21 (43.8%)**                     |
| Hypertension (n (%))  | 12 (38.7%)                | 79 (66.9%)                | 0.004** | 20 (74.1%)**                  | 25 (58.1%)                            | 34 (70.8%)**                     |
| Triglycerides (mmol/L)| 1.14 (0.95–1.61)          | 1.50 (1.14–2.35)          | 0.009** | 2.32 (1.23–3.85)**            | 1.46 (1.20–2.07)                      | 1.53 (1.04–2.23)                 |
| TC (mmol/L)           | 4.16 ± 0.80               | 4.42 ± 1.29               | 0.285   | 4.65 ± 1.36                   | 4.33 ± 1.35                           | 4.38 ± 1.22                      |
| LDL-C (mmol/L)        | 2.63 ± 0.70               | 2.70 ± 1.00               | 0.71    | 2.53 ± 0.94                   | 2.76 ± 1.11                           | 2.74 ± 0.94                      |
| HDL-C (mmol/L)        | 1.15 ± 0.28               | 0.95 ± 0.22               | <0.001**| 0.99 ± 0.25*                  | 0.92 ± 0.23**                         | 0.94 ± 0.18**                    |
| HDL-C/LDL-C           | 0.47 ± 0.18               | 0.39 ± 0.13               | 0.004** | 0.39 ± 0.11                   | 0.38 ± 0.13                           | 0.37 ± 0.13                      |
| ApoAI (g/L)           | 1.22 ± 0.20               | 1.09 ± 0.24               | 0.007** | 1.21 ± 0.30                   | 1.08 ± 0.25**                         | 1.03 ± 0.17**                    |
| ApoB100 (g/L)         | 0.87 ± 0.22               | 0.90 ± 0.27               | 0.597   | 0.86 ± 0.22                   | 0.91 ± 0.33                           | 0.91 ± 0.25                      |
| ApoAI/ApoB100         | 1.51 ± 0.41               | 1.27 ± 0.38               | 0.002** | 1.40 ± 0.37                   | 1.22 ± 0.34                           | 1.21 ± 0.37                      |
| Lipoprotein(a) (mg/dL)| 84.8 (40.9–176.4)         | 78.6 (39.5–173.1)         | 0.912   | 66.7 (21.9–118.7)             | 87.5 (39.7–167.0)                      | 94.9 (41.3–268.4)                |
| PON1 activity (U/mL)  | 506.4 ± 118.8             | 368.2 ± 120.0             | <0.001**| 404.3 ± 117.6**               | 403.8 ± 113.6**                       | 316.0 ± 109.5**                  |
| hs-CRP (mg/L)         | 1.60 (0.31–2.56)          | 2.40 (0.99–6.17)          | 0.003** | 1.58 (0.80–4.07)              | 1.53 (0.81–4.46)                      | 4.30 (2.00–9.02)**               |

Data for continuous variables as mean ± SD or median (25th and 75th percentiles); data presented as numbers (percentages) of participants.

\(^{*}\)P < 0.05, \(^{**}\)P < 0.01, compared with non-CAD group; \(^{**}\)P < 0.05, \(^{*}\)P < 0.01, compared with mild stenosis; \(^{***}\)P < 0.01, compared with moderate stenosis.

Table 2. There were no significant differences in TC, LDL-C, apoB100, and lipoprotein(a) levels between non-CAD group and CAD group. Compared with non-CAD group, the incidences of related diseases (diabetes and hypertension) and triglycerides level were significantly higher (P < 0.01), whereas levels of HDL-C and apoAI, HDL-C/LDL-C ratio, and apoAI/apoB100 ratio were significantly lower (P < 0.01) in the CAD group. When the severity of CAD was evaluated by angiographic GSS, no statistically significant differences in classic risk factors, except for apoAI level, were observed between the groups with different extent of CAD. Meanwhile, we examined plasma hs-CRP as an inflammatory biomarker in all subjects, and our result showed that hs-CRP level in CAD patients was 2.40 (0.99–6.17) mg/L which was significantly higher than that of non-CAD group (P < 0.01). Highest hs-CRP level appeared in severe CAD group, but there was no significant difference in hs-CRP level between mild, moderate CAD, and non-CAD groups.

Interestingly, PON1 activity in different CAD groups was significantly lower than that of non-CAD patient group (P < 0.01), exhibiting a close relationship with the risk of CAD. The decreases of PON1 activity in severe CAD group were especially evident compared with those in mild or moderate CAD group (P < 0.01), while subjects with mild and moderate CAD had comparable PON1 activities. The linear regression analysis revealed a significant correlation between PON1 activity and the severity of CAD as assessed by GSS (r = -0.393, P < 0.001) (Figure 2).

The relationship between PON1 activity and clinical or biochemical parameters was also examined. The analysis by Pearson or Spearman correlation showed that PON1 activities in all subjects were positively associated with HDL-C (r =
Figure 2: Correlation between PON1 activity and the severity of atherosclerosis in patients. The linear regression analysis revealed a significant correlation between PON1 activity and the severity of atherosclerosis as assessed by the angiographic Gensini score (GSS) (Pearson correlation coefficient $r = -0.393$, associated $P < 0.001$).

More than 95% of PON1 is associated with HDL particles in the circulation. PON1 may contribute substantially to the antiatherogenic properties of HDL through its well-established anti-oxidant and anti-inflammatory role by hydrolyzing oxidized lipids [4, 18]. In addition, PON1, with its well-established anti-oxidant and anti-inflammatory role, partially to the antiatherogenic properties of HDL through its enzymatic activity exhaustion and downregulation of hepatic PON1 mRNA levels [22, 23]. There is increasing evidence linking lower PON1 activity in serum or plasma to an increased likelihood of CAD [10, 11]. The main finding of our study was that PON1 activity is reversely correlated with the severity of CAD.

4. Discussion

More than 95% of PON1 is associated with HDL particles in the circulation. PON1 may contribute substantially to the antiatherogenic properties of HDL through its well-established anti-oxidant and anti-inflammatory role by hydrolyzing oxidized lipids [4, 18]. In addition, PON1, as a lactonase, has the ability to detoxify homocysteine-(hcy-) thiolactone and to minimize protein damage by N-homocysteinylation, which is an independent risk factor of atherosclerosis [19]. There is increasing evidence linking lower PON1 activity in serum or plasma to an increased likelihood of CAD [10, 11]. The main finding of our study was that PON1 activity is reversely correlated with the severity of CAD.

ApoE−/− mice develop severe hypercholesterolemia and spontaneous atherosclerosis with age. The mice fed a chow diet exhibited increased plasma TC (5–8-fold) and triglycerides (1.7-fold) compared to C57BL6 mice, the complexity of the progressive lesions and is similar to that described in humans, therefore representing an important model to study the influence of genetic and environmental factors on the atherogenic process [20, 21]. In present study, using female apoE−/− mice of different ages fed a regular chow diet, we found that hypercholesterolemia was significantly aggravated in elder mice, and in these mice progressive atherosclerotic lesions were obviously observed in the aortic root and throughout the arterial tree compared to those of 3-month-old mice. It is striking that serum PON1 activity in apoE−/− mice gradually decreased with age and was reversely correlated with the severity and extent of atherosclerotic lesions. We also found that lower PON1 activity was accompanied with elevated levels of inflammatory cytokines, such as TNF-α and IL6, suggesting that the decrease in PON1 activity may occur as integral part of an inflammatory response. It has been reported that inflammatory conditions result in PON1 enzymatic activity exhaustion and downregulation of hepatic PON1 mRNA levels [22, 23].

We further explored the relationship between PON1 activity and the extent of atherosclerosis in angiographically proven CAD patients. In clinic, invasive coronary angiography is the gold standard for diagnosis of obstructive CAD and also useful for evaluation of the severity of CAD according to the degree of luminal stenosis using the Gensini score (GSS) [15]. Similar to the previous findings [10, 11], our data showed that PON1 activity was significantly lower in CAD patients than non-CAD patients; furthermore, the regression analysis revealed a strong reverse correlation between PON1 activity and the severity of CAD reflected by GSS in Chinese subjects.

Interestingly, the present data indicate that the etiology of atherosclerosis in the mouse model is different from the etiology of CAD in the human study. Elevated TC level is strongly correlated with the severity of atherosclerosis in apoE−/− mice. In human study, we did not find significant difference in TC and LDL-C levels between non-CAD group and CAD group; however, HDL-C level and HDL-C/LDL-C ratio were significantly lower in the CAD group. In addition, plasma triglycerides level was significantly higher in the CAD group. According to the recent AHA scientific statement, increase in triglycerides level is a critical risk factor for development of cardiovascular disease [24], so it is likely that multiple risk factors are responsible for the development of CAD in this population, such as decrease in plasma HDL-C level and increase in triglycerides level and inflammatory status.

Table 3: Correlation between paraoxonase-1 activity and other factors.

| Variables          | $r$ | PON1 activity |
|--------------------|-----|---------------|
| Age                | −0.218 | 0.008** |
| Sex                | −0.186 | 0.023* |
| Smoking            | 0.066 | 0.422 |
| CAD                | −0.409 | <0.000** |
| Diabetes           | −0.267 | 0.001** |
| Hypertension       | −0.088 | 0.285 |
| Triglycerides      | 0.006 | 0.944 |
| TC                 | 0.057 | 0.492 |
| HDL-C              | 0.242 | 0.003** |
| LDL-C              | 0.042 | 0.610 |
| ApoAl              | 0.220 | 0.007** |
| ApoB100            | 0.082 | 0.317 |
| Lipoprotein(a)     | −0.027 | 0.744 |
| hs-CRP             | −0.216 | 0.008** |

* $P < 0.05$; ** $P < 0.01$.?
Although the mechanism of PON1 regulation is currently not well understood, there is considerable evidence that PON1 activity is influenced by genetic and environmental factors, such as age, gender, smoking, alcohol consumption, fat-rich diet, and drugs [13, 25]. For example, the PON1-R192Q polymorphism is found to correlate with PON1 activity, in which the R192 allele gives rise to a higher PON1 activity profile, when compared with control mice [6, 7]. Recently, Fuhrman et al. reported that PON1 deficiency in mice resulted in reduced macrophage SR-BI expression, decreased cellular HDL binding, and loss of HDL-mediated cytoprotection against apoptosis, providing new insights suggesting that reduced PON1 activity could promote HDL dysfunction and diminish cytoprotective capacity of HDL [35]. Besler et al. also showed that reduced PON1 activity in CAD patients may be responsible for loss of the anti-inflammatory and repair-stimulating effects of HDL on endothelium [36]. It is convincible that PON1 not only has a main role in inactivation of LDL oxidation during the initiation of atherosclerosis, but also promotes HDL-mediated cytoprotection during the development of atherosclerosis. Our study supports that PON1 activity is affected by a variety of factors, for example, inflammatory status, and that decrease of PON1 activity further aggravates HDL dysfunction during the progressive atherosclerosis, suggesting that PON1 activity may serve as a potential biomarker for the severity of atherosclerotic CAD.

In conclusion, PON1, as an antioxidative and anti-inflammatory component of HDL, plays an important role in halting atherogenesis. Our experimental and clinical evidence demonstrates that the decrease of PON1 activity is accompanied with the increase of inflammatory status and is closely correlated with the progression of atherosclerosis. Thus, the present findings suggest that the lower PON1 activity may be an important inflammatory indicator for the severity of atherosclerosis and CAD events. Enhancing PON1 activity could be a promising strategy for reducing CAD risk and preventing the progression of cardiovascular atherosclerosis.

Authors’ Contribution

Chiyan Zhou and Jia Cao contributed equally to this work.

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