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32) 建部俊介、福本義弘、杉村宏一郎、佐藤公雄、三浦　裕、後岡広太郎、青木竜男、山本沙織、下川宏明：左心系心疾患による肺高血圧症の臨床的特徴と予後.

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34) **佐藤公雄**、福本義弘、杉村宏一郎、三浦裕、青木竜男、後岡広太郎、建部俊介、山本沙織、清水　亨、下川宏明：酸化ストレス分泌蛋白 Cyclophylin A による肺高血圧促進機構　—Rho-kinase 系の関与—

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第 16 回日本心不全学会学術集会（11 月 30 日～12 月 2 日、2012 年、仙台）（主催）
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第 42 回日本心脈管作動物質学会学術集会（2 月 8 日～9 日、2013 年、奈良）
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＜一般演題＞

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第 77 回日本循環器学会学術集会（3 月 15～17 日、2013 年、横浜）
<Symposiums>
(SY10: New Biomarkers for Cardiovascular Disease Prevention)

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第 76 回日本循環器学会学術集会（3 月 16～18 日、2012 年、福岡）
<Asian Joint Case-Conference 2>Malaysia and Japan (AJC2) (CAD)

91) Sugimura K, Fukumoto Y, **Satoh K**, Miura Y, Nochioka K, Aoki T, Tatebe S, Yamamoto S, Shimokawa H. Effects of percutaneous transluminal pulmonary angioplasty in patients with distal-type chromic thromboembolic pulmonary hypertension. *Circ J.* 76(Suppl I):I-100,2012.
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Yamamoto S, Tatebe S, Aoki T, Nochioka K, Miura Y, **Satoh K**, Shimokawa H. Recent progress in the management of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. *Circ J.* 76(Suppl I):I-266,2012.
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構（第52回日本脈管学会総会 Japanese College of Angiology Award (JCAA) 受賞講演　2011年10月20日、岐阜）

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Fukumoto Y, Sugimura K, Satoh K, Nochioka K, Miura Y, Aoki T, Tatebe S, Miyamichi-Yamamoto S, Shimokawa H. Percutaneous transluminal pulmonary angioplasty markedly ameliorates pulmonary hemodynamics and long-term prognosis of patients with distal-type chronic thromboembolic pulmonary hypertension.

2) European Society of Cardiology Congress 2012 (August 25-29, Munich, Germany)
Sugimura K, Fukumoto Y, Satoh K, Miura Y, Nochioka K, Aoki T, Tatebe S, Yamamoto S, Shimokawa H.　Remarkable effectiveness of percutaneous transluminal pulmonary angioplasty for hemodynamics and long-term prognosis in patients with distal-type chronic thromboembolic pulmonary hypertension.

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H. 知的所有権の出願・取得状況（予定を含む）

1. 特許取得

【取得】
国際特許
特許名：肺高血圧症のモデル動物作製法、肺高血圧治療法、および治療薬物
発明者：菅村和夫、石井直人、小野栄夫、下川宏明、村田和子、佐藤公雄
出願人：独立行政法人科学技術振興機構
（整理番号 P038P02US, PCT）
国際出願日：2007 年 1 月 17 日
国際出願番号：PCT/JP2004/001063

【出願状況】（計 1 件）
名称：サイクロフィリンAによる心血管疾患の検査方法
発明者：下川宏明、佐藤公雄
権利者：下川宏明、佐藤公雄（国立大学法人東北大学）
種類：特許
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〔その他〕
ホームページ
http://www.cardio.med.tohoku.ac.jp/index.html

2. 実用新案登録

なし

Ⅱ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
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Ⅲ. 研究成果の刊行物・別刷

Circulation Journal
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http://www.j-circ.or.jp

ORIGINAL ARTICLE
Ischemic Heart Disease

Plasma Cyclophilin A Is a Novel Biomarker for Coronary Artery Disease

Kimio Satoh, MD, PhD; Yoshihiro Fukumoto, MD, PhD; Koichiro Sugimura, MD, PhD; Yutaka Miura, MD, PhD; Tatsuo Aoki, MD, PhD; Kotaro Nochioka, MD, PhD; Shunsuke Tatebe, MD; Saori Miyamichi-Yamamoto, MD, PhD; Toru Shimizu, MD; Shizuka Osaki, BSc; Yusuke Takagi, MD, PhD; Ryuji Tsuburaya, MD, PhD; Yoshitaka Ito, MD, PhD; Yasuharu Matsumoto, MD, PhD; Masaharu Nakayama, MD, PhD; Morihiko Takeda, MD, PhD; Jun Takahashi, MD, PhD; Kenta Ito, MD, PhD; Satoshi Yasuda, MD, PhD; Hiroaki Shimokawa, MD, PhD

Background: Oxidative stress induces secretion of cyclophilin A (CyPA) from vascular smooth muscle cells and it plays a crucial role in the pathogenesis of atherosclerosis in mice. Therefore, we tested our hypothesis that plasma CyPA levels are increased in patients with coronary artery diseases (CAD).

Methods and Results: In 320 consecutive patients undergoing coronary angiography, we examined the relationship between plasma CyPA levels and the severity of CAD. We measured plasma CyPA by an immunoassay based on the sandwich technique. Plasma CyPA levels were significantly higher in patients with significant coronary stenosis compared to those without it (P<0.001). A positive correlation was noted between plasma CyPA levels and significant coronary stenosis. The average number of stenotic coronary arteries and the need for coronary intervention were significantly increased in the quartiles of higher CyPA levels (both P<0.001). Indeed, the plasma CyPA level significantly correlated with the presence of CAD (adjusted odds ratio for CAD, 6.20; 95% confidence interval, 3.14–12.27; P<0.001). Interestingly, plasma levels of CyPA increased according to the number of atherosclerotic risk factors, all of which induce oxidative stress. Furthermore, plasma levels of CyPA significantly reduced after medical treatment of risk factors. Finally, CyPA was strongly expressed in coronary atherosclerotic plaque in patients with myocardial infarction.

Conclusions: Plasma CyPA level is a novel biomarker for oxidative stress and CAD in humans. (*Circ J* 2013; **77**: 447–455)

Key Words: Biomarker; Coronary artery disease; Oxidative stress

The development of atherosclerosis is initiated by activation of endothelial cells (EC), leading to expression of adhesion molecules for inflammatory cells.[1] A critical step in the progression of atherosclerosis is the development of an oxidizing environment because of the activation of macrophages that have become loaded with oxidized low-density lipoprotein (LDL) and other lipids. These macrophages produce abundant reactive oxygen species (ROS) and secrete several growth factors that contribute to the progression of atherosclerosis.[2] It has been widely recognized that oxidative stress, generated by excessive ROS, promotes coronary artery diseases (CAD).[3] Moreover, ROS induce the secretion of cyclophilin A (CyPA) from vascular smooth muscle cells (VSMC)[4,5] and extracellular CyPA induces EC adhesion molecule expression and promotes VSMC proliferation and migration.[6–8]

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CyPA is a ubiquitously distributed protein belonging to the immunophilin family, and is recognized as the intracellular receptor for the immunosuppressive drug cyclosporin.[9] CyPA possesses peptidyl-prolyl isomerase activity and plays an important role in protein folding and trafficking of extracellular signal-regulated kinase 1/2[10] and apoptosis-inducing factor.[11] Although initially CyPA was thought to function primarily as

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Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan
The Guest Editor for this article was Hiroyuki Daida, MD.
Mailing address: Hiroaki Shimokawa, MD, PhD, Professor and Chairman, Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai 980-8574, Japan. E-mail: shimo@cardio.med.tohoku.ac.jp
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an intracellular protein, recent studies have revealed that it can be secreted by cells in response to ROS. Extracellular CyPA is a potent leukocyte chemoattractant,[12,13] and importantly, plasma CyPA is significantly increased in patients with inflammatory diseases such as rheumatoid arthritis.[14] Furthermore, we have found that CyPA expression in mice is closely associated with the development of intimal thickening, aortic aneurysms, and atherosclerosis.[8,15–17] The secretion of CyPA is regulated by activation of Rho-kinase,[7] which plays a crucial role in inflammation, vascular contraction, and the development of atherosclerosis.[18,19] Thus, it seems plausible that the plasma levels of CyPA may discriminate between subjects at high or low risk for CAD.

An ELISA assay for CyPA has recently been developed, enabling measurement of the plasma levels of CyPA. In the present study, we tested our hypothesis that circulating CyPA is detectable in patients with CAD and that these levels are associated with the number of atherosclerosis risk factors, the severity of CAD and the need for future cardiovascular intervention.

Methods

Study Patients

We conducted a prospective observational study of the prognostic value of CyPA in patients with symptoms or signs of CAD who were referred to the Tohoku University Hospital in Sendai for elective coronary angiography (CAG) from November 2007 through October 2011. If patients underwent angiography more than once, our analysis was based only on data obtained at the time of the first angiographic study. Patients with valvular or congenital heart disease were excluded. A total of 320 consecutive patients who had angina pectoris and evidence of ischemia on exercise ECG or myocardial radionuclide imaging were enrolled. Patients with unstable angina or myocardial infarction (MI) were excluded. The institutional Ethical Review Board approved the study, and written informed consent was given by all participating patients.

Coronary Angiography

At baseline, selective CAG was performed with recordings on the angiographic data system. Two experienced cardiologists, who were blinded to the patients' CyPA plasma levels, evaluated the angiograms. The degree of coronary stenosis was assessed in the direction that showed the most severe stenosis according to the American Heart Association standards. A narrowing of the lumen by more than 51% of the diameter was considered to indicate clinically significant stenosis. The patients were classified according to the severity of CAD as having no clinically significant organic stenosis, or 1-, 2-, or 3-vessel disease. The left anterior descending coronary artery, left circumflex coronary artery, and right coronary artery were examined to evaluate the number of stenotic coronary arteries as 0 to 3-vessel disease. Stenosis of the left main coronary artery was evaluated as 2-vessel disease. The relationship between the plasma CyPA level and the number of stenotic coronary arteries was analyzed using the average number of stenotic arteries to assess the severity of CAD.

Immunostaining

We have described the CyPA immunostaining in detail elsewhere.[6–8] In brief, paraformaldehyde-fixed frozen sections were incubated overnight at 4°C with primary antibody[20] (CyPA polyclonal, 1:1,000 dilution; BIOMOL Research Laboratories). For detection of CyPA, peroxidase-conjugated streptavidin (1:1,000 dilution; Jackson Immuno) and NovaRed substrate kit (SK-4800, Vector Laboratories, Burlingame, CA, USA), were used and counterstained with hematoxylin. As a negative control, species- and isotype-matched IgG were used in place of the primary antibody.

Baseline Measurements

Information on vital status and data were obtained from the department's database system by means of a computerized search performed on December 7, 2011.[21] No patients were lost to follow-up and all patients had a recorded medical history that included details of any previous MI, previous revascularization, angina pectoris, hypertension, previous stroke or transient ischemic attacks, diabetes, and smoking status. The cardiovascular risk was assessed in terms of hypertension, diabetes, smoking, aging and dyslipidemia. Patients with hypertension were assessed as being at risk if their blood pressure was ≥140/90 mmHg or they had a history of antihypertensive drug use. Patients with diabetes mellitus were assessed as being at risk if their fasting glucose level was ≥126 mg/dl or they had a history of hypoglycemic drug or insulin use. Patients with dyslipidemia were assessed as being at risk if their LDL cholesterol was ≥140 mg/dl or their high-density lipoprotein cholesterol was ≤40 mg/dl, or they were taking a lipid-lowering drug. Before CAG, fasting blood samples for the measurement of CyPA were drawn from the antecubital vein of the patients who were resting supine. Plasma samples were collected using EDTA and centrifuged for 10 min at 2,500 g within 30 min of collection, and aliquots were stored at −80°C. CyPA was measured with use of an immunoassay based on the sandwich technique according to the protocol (Human Cyclophilin A ELISA Kit, CSB-E09920h, Cusabio). The detection limit was 0.78 ng/ml. Across the entire analysis, duplicate measures of plasma CyPA level were highly correlated (r=0.92, **Figure S1A**). The values of high-sensitivity CRP (hsCRP) were measured with a sandwich technique (Roche Diagnostics). The values of other laboratory parameters were obtained from samples assayed in an autoanalyzer in the hospital.

Statistical Analysis

Baseline characteristics of the study patients, grouped according to quartiles of CyPA, are presented as frequencies and percentages, and continuous variables as means and standard deviations, or medians and interquartile ranges for variables with skewed distributions. Baseline characteristics were compared among quartiles with use of the chi square test for discrete variables and the Wilcoxon or Kruskal-Wallis rank-sum test for continuous variables when appropriate.

Additional CyPA analyses were performed in subgroups defined according to the results of angiography. A Student's t-test was used for comparisons between 2 groups and Dunnett's multiple comparison of means was used for multi-group comparison after analysis of variance (ANOVA). Receiver-operating-characteristic (ROC) curves were constructed to assess the sensitivity and specificity of plasma CyPA measurements obtained before CAG and to compare the ability to diagnose the existence and severity of CAD.

Logistic regression was used to estimate the association between plasma CyPA levels and CAD status after adjustment for age, sex, smoking status, presence or absence of diabetes, presence or absence of hypertension, and LDL cholesterol level. hsCRP levels were added in subsequent models. Adjusted odds ratios (ORs) are reported both for plasma CyPA levels >15 ng/ml and across quartiles. Model performance was as-

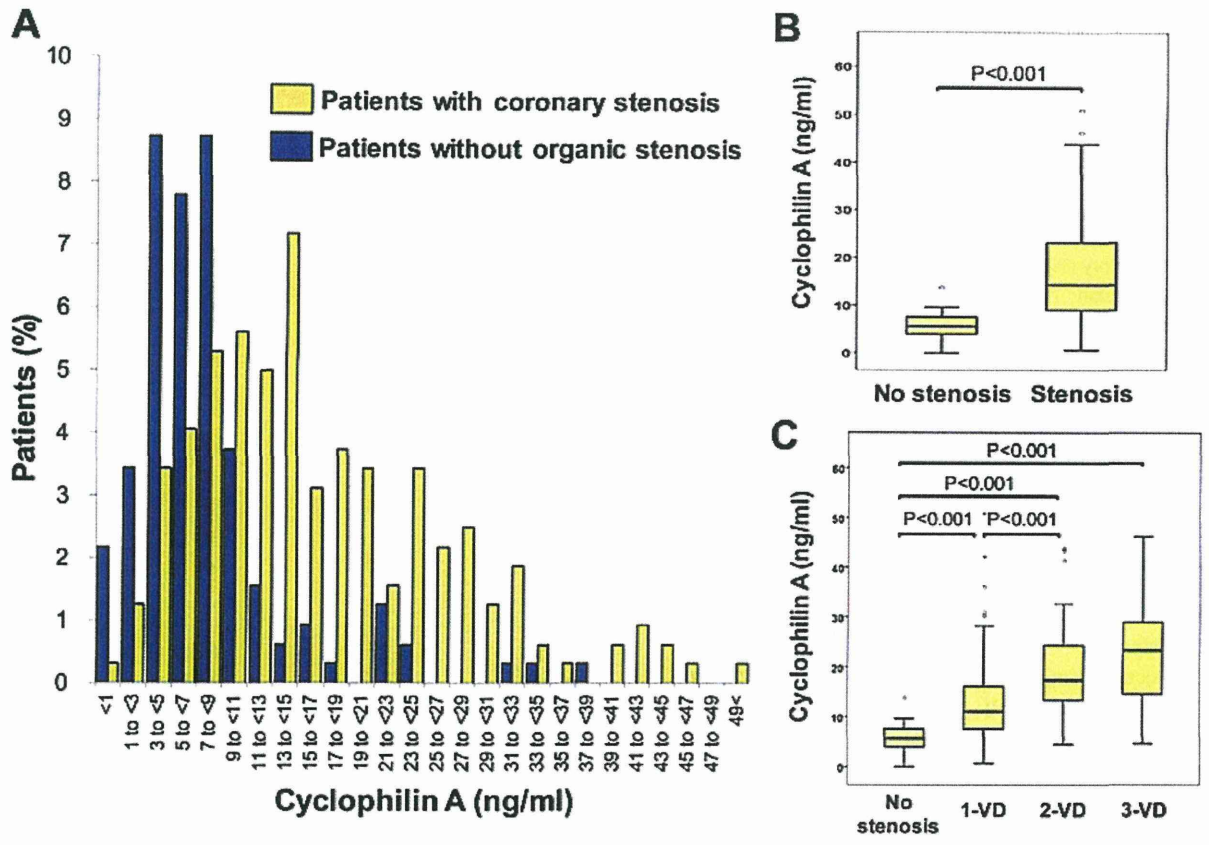

Figure 1. Circulating cyclophilin A (CyPA) levels in patients with 1-, 2-, or 3-vessel disease. (**A**) Green bars represent the number of patients with coronary artery stenosis and blue bars that of those without it. (**B**) Data are shown as box-and-whisker plots of CyPA in patients with organic stenosis (>51%, n=189) and patients with no organic stenosis (n=131). CyPA was elevated in patients with coronary stenosis (P<0.001) compared with patients without stenosis. (**C**) CyPA was elevated in patients with 1-, 2-, or 3-vessel disease (all P<0.001) compared with the control group (no organic stenosis/no vasospastic angina). CyPA increased sequentially within the coronary stenosis group as the number of stenotic vessels increased (P value for trend <0. 001).

sessed according to discrimination, by means of the area under the ROC (c-statistic); calibration, as indicated by the Hosmer-Lemeshow goodness-of-fit statistic.[22] Analyses were performed with CyPA as a categorical variable with the lowest quartile serving as reference for the other 3 quartiles. All reported P values are 2-tailed, with P<0.05 indicating statistical significance. Analyses were performed with SPSS, version 19.0 (Chicago, IL, USA) and JMP, version 9.02 (Cary, NC, USA).

Results

Plasma Levels of CyPA and Angiographic Status

Figure 1A shows the distribution of patients with and without coronary artery stenosis by the plasma level of CyPA. The plasma levels of CyPA were significantly higher in patients with coronary organic stenosis compared with those without stenosis (Figure 1B). Moreover, the CyPA level increased with the severity of angiographic CAD (P<0.001, Figure 1C).

All the cases were divided into quartile groups based on the plasma level of CyPA to examine its correlation with the number of stenotic coronary arteries. Table 1 shows the patients' clinical background and laboratory data according to the quartiles of CyPA. Patients with CyPA in the upper quartile were older and were more likely to have clinically significant CAD (P<0.001, Table 1). The prevalence of both hypertension and diabetes was higher in the 4th quartile, and these patients showed a slightly reduced estimated glomerular filtration rate (eGFR). The number of stenotic coronary arteries was significantly increased in the higher quartiles of CyPA (P<0.001, Figure 2A). Furthermore, the requirement for cardiovascular intervention, such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), was significantly increased in the 4th quartile compared with the lower quartiles (P<0.001, Figure 2B). We calculated the ROC curves and c-statistic on the basis of the plasma CyPA levels. The ROC curves demonstrated that the plasma level of CyPA is useful for the diagnosis of coronary organic stenosis (c-statistic=0.802) and the requirement for cardiovascular intervention (c-statistic=0.793) (Figures 2C,D).

Plasma Levels of CyPA and the Severity of CAD

CyPA was elevated in patients with traditional cardiovascular risk factors such as hypertension, diabetes, smoking, dyslipidemia and advanced age (all P<0.001, Figure 3). Division of the cohort into quartiles according to plasma CyPA level provided additional evidence of an association between plasma

Table 1. Baseline Clinical Characteristics According to Quartiles of CyPA

	1st quartile (n=80)	2nd quartile (n=80)	3rd quartile (n=80)	4th quartile (n=80)	P value
CyPA level (ng/ml)	0.0–6.1	6.2–9.6	9.7–17.4	17.5–50.9	
Age (years)					<0.001
Median	58	63	68	68	
Interquartile range	50–68	55–71	60–75	60–74	
Male sex (%)	60	61	66	76	0.122
Family history of IHD (%)	11	18	4	10	0.046
Medical history (%)					
Hypertension	56	59	75	88	<0.001
Diabetes	36	34	48	55	0.022
Dyslipidemia	51	51	70	80	<0.001
Current smoker (%)	28	34	49	59	<0.001
Angiographic findings (%)					<0.001
No coronary artery stenosis	71	61	20	13	
1-vessel disease	23	31	41	29	
2-vessel disease	3	4	24	31	
3-vessel disease	4	4	11	28	
Requirement for PCI or CABG during follow-up (%)	8	8	23	40	0.019
BMI*					0.003
Median	25	24	24	23	
Interquartile range	23–27	22–26	21–26	21–25	
eGFR ($ml \cdot min^{-1} \cdot 1.73m^{-2}$)	54±17	59±19	51±20	49±19	<0.001
Left ventricular ejection fraction (%)	65±10	66±8	59±12	63±12	0.090
Lipid status (mg/dl)					
LDL cholesterol	105±36	105±29	96±35	97±33	0.078
HDL cholesterol	47±13	49±12	49±12	49±14	0.837
Triglycerides	127±69	147±95	130±73	132±100	0.576
Hemoglobin A_{1c}	6.4±1.4	6.3±0.8	6.4±0.9	6.6±1.2	0.067
hsCRP (mg/L)	2.3±3.2	1.7±2.6	2.3±3.1	1.8±2.8	0.103
Medication (%)					
Aspirin	16	30	51	71	<0.001
β-blocker	25	29	46	55	<0.001
Statin	39	35	56	70	<0.001
ACE inhibitor	28	24	31	39	0.212
ARB	24	26	28	33	0.654
Calcium-channel blocker	51	55	61	58	0.550

Data are shown as mean±SD unless otherwise shown.
*BMI=weight in kg/(height in m)^2.
ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CyPA, cyclophilin A; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IHD, ischemic heart disease; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention.

CyPA and CAD (**Table 2**). In the analysis adjusted for age, sex, and traditional cardiovascular risk factors (smoking, diabetes, hypertension, dyslipidemia), quartiles 2, 3, and 4 of plasma CyPA were associated with an increased risk of CAD as compared with the quartile of lowest CyPA (OR, 1.73, 9.94, and 10.29; P-value for trend <0.001). This result remained significant after adjustment for traditional cardiovascular risk factors plus hsCRP levels (OR, 1.84, 10.53, and 10.78; P-value for trend <0.001). Several known cardiovascular risk factors were associated with CAD in logistic-regression models adjusted for age, sex, and body mass index (BMI) (**Figure 4**). Diabetes and hypertension were each linked to an increased risk of CAD. Each of the known risk factors, in addition to plasma CyPA, was combined in a single logistic-regression analysis (**Figure 4**). In this model, which included the hsCRP level, plasma CyPA >15 ng/ml remained highly related with disease status (OR 6.20, P<0.001). Multivariable analysis demonstrated that, in addition to the established risk factors (age, sex, smoking, hypertension, diabetes and hsCRP), CyPA >15 ng/ml was significantly correlated with CAD (**Table 3**).

The inclusion of plasma CyPA resulted in significant improvement of the overall performance of the logistic-regression model. The c-statistic increased from 0.807 to 0.870 when plasma CyPA was added to known cardiovascular risk factors (age, sex, smoking, hypertension, diabetes, dyslipidemia). When the hsCRP level was included in the baseline model, the c-statistic increased from 0.807 to 0.873. The addition of plasma CyPA did not reduce model discrimination as assessed by goodness-of-fit statistics. CyPA added prognostic information above and beyond that provided by age, sex, family history

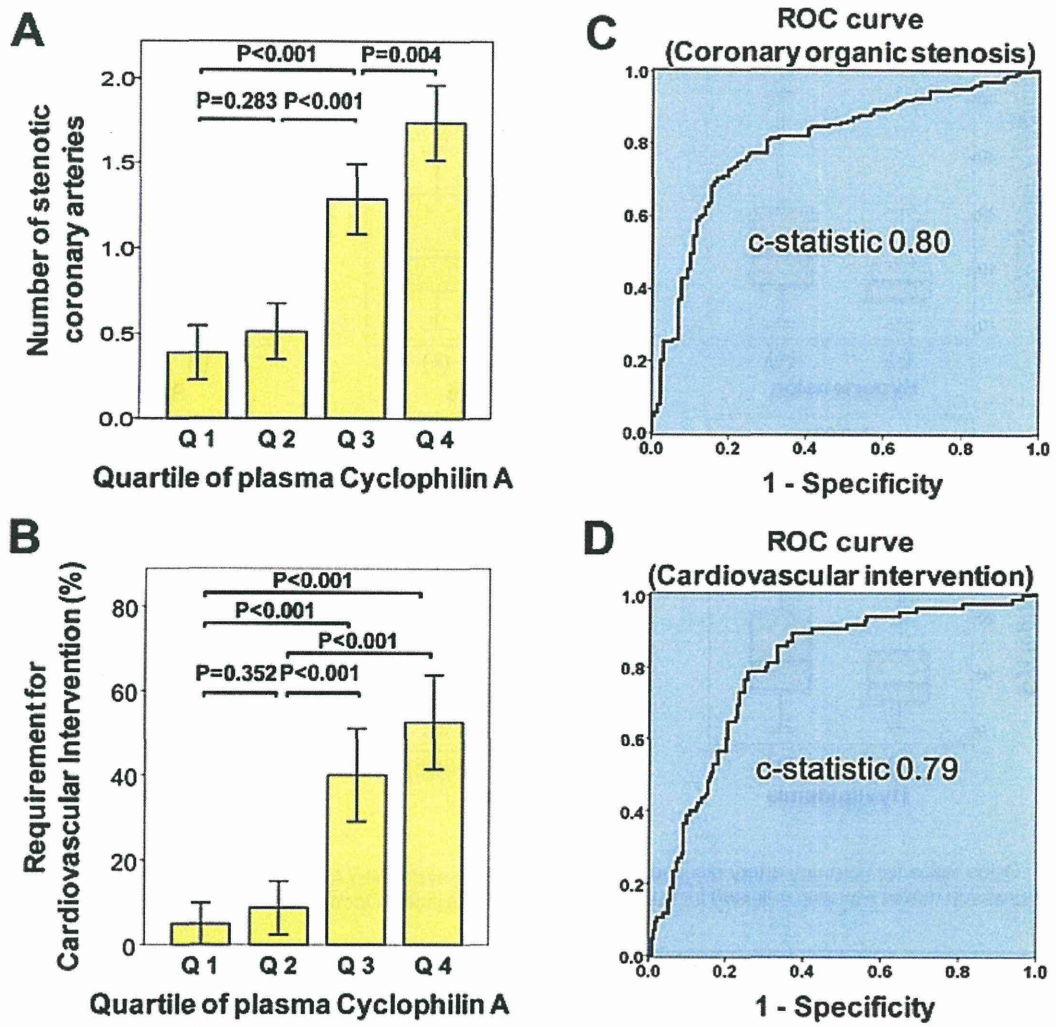

Figure 2. Number of stenotic coronary arteries and requirement for cardiovascular intervention according to quartiles of cyclophilin A (CyPA). Data from 320 patients with and without coronary stenosis are divided according to the quartiles of plasma CyPA levels. The CyPA levels were as follows: 1st quartile (Q1), <6.1 ng/ml; 2nd quartile (Q2), 6.2–9.6 ng/ml; 3rd quartile (Q3), 9.7–17.4 ng/ml; 4th quartile (Q4), >17.5 ng/ml. P<0.001 by the log-rank test for the overall comparison among the groups. (**A**) Number of stenotic coronary arteries according to quartiles of CyPA. CyPA was elevated in patients in Q3 (P<0.001) and Q4 (P<0.001) compared with Q1. The number of stenotic coronary arteries increased sequentially as the quartiles increased. (**B**) Requirement for cardiovascular intervention according to quartiles of CyPA. The requirement was higher in patients with Q4 compared with Q1 (P<0.001) and Q2 (P<0.001). Cardiovascular intervention included percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). (**C,D**) Receiver-operating-characteristic curves (ROC) and c-statistic for baseline measurements of CyPA. Also shown are the sensitivity and specificity of these measures. (**C**) ROC curve describing the diagnostic performance of CyPA to identify coronary organic stenosis >50% in at least 1 vessel as compared with the reference standard of invasive quantitative coronary angiography (CAG). The c-statistic was 0.80 (95% CI, 0.75–0.85). (**D**) ROC curve describing the diagnostic performance of CyPA to identify the requirement for future cardiovascular intervention as compared with the reference standard of invasive quantitative CAG. The c-statistic was 0.79 (95% CI, 0.74–0.85). CI, confidence interval.

with respect to ischemic heart disease, presence or absence of hypertension, diabetes, smoking status, BMI, eGFR, and plasma lipid level. Excluding the 141 patients with high hsCRP did not significantly change the results. In patients with hsCRP <1.000, the adjusted OR for CAD in the 4th quartile of CyPA, as compared with the 1st quartile, was 13.2 (95% confidence interval, 3.2–53.9, P<0.001). Additionally, CyPA (>15 ng/ml) remained a strong prognostic marker, with an adjusted OR of 5.9 (95% confidence interval, 2.3–14.8, P<0.001). Among patients with hsCRP >1.000, the same trend was observed, suggesting the potential usefulness of combining these biomarkers for CAD.

Plasma Levels of CyPA as a Biomarker of Therapeutic Outcome

Interestingly, the plasma level of CyPA increased according to the atherosclerotic risk factors such as sex, hypertension, diabetes mellitus, dyslipidemia, and smoking, all of which are

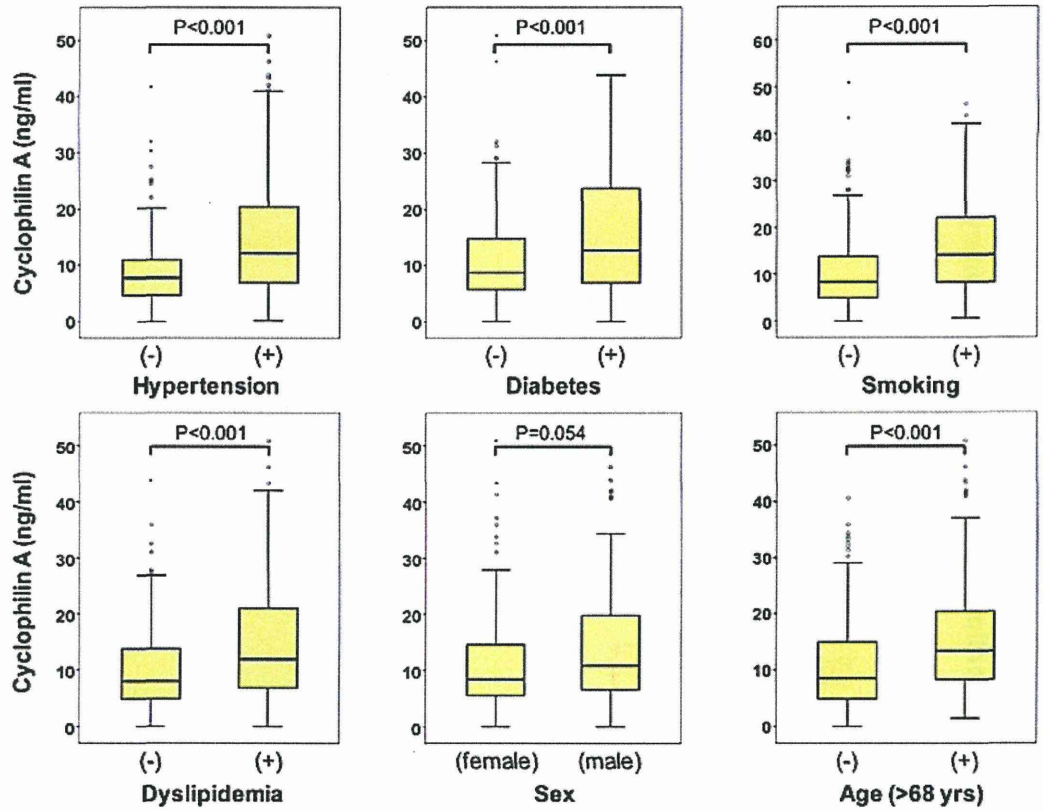

Figure 3. Odds ratios for coronary artery disease according to plasma cyclophilin A (CyPA) level and selected risk factors. The logistic-regression model was also adjusted for age, sex, and body mass index. Odds ratios for continuous variables are per 1-SD increase.

Table 2. CAD Status According to Quartiles of Plasma CyPA

	No. of patients	OR for CAD (95% CI)*	
		Adjusted for cardiovascular risk factors	Adjusted for cardiovascular risk factors and hsCRP
Quartile 1	80	1.00	1.00
Quartile 2	80	1.73 (0.78–3.85)	1.84 (0.82–4.14)
Quartile 3	80	9.94 (3.98–24.83)	10.53 (4.16–26.63)
Quartile 4	80	10.29 (3.95–26.79)	10.78 (4.13–28.14)
P value for trend		<0.001	<0.001

*Cardiovascular risk factors included in the logistic-regression model were age, sex, smoking status, presence or absence of diabetes, presence or absence of hypertension, and presence or absence of dyslipidemia.
CAD, coronary artery disease; CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

oxidative stress inducers (**Figure 3**). Therefore, plasma CyPA may be important as a biomarker of therapeutic outcome after controlling risk factors. To further confirm the role of plasma CyPA, we performed a follow-up study after the addition of drugs to control risk factors. After treatment in several individuals (n=42), the plasma obtained at baseline and follow-up (mean follow-up, 273 days) revealed a significant reduction after treatment (P=0.003, **Figure 5A**). Medical treatments that control atherosclerotic risk factors decreased plasma CyPA levels in patients with stable CAD, suggesting that plasma CyPA is useful for the evaluation of systemic oxidative stress and the therapeutic effect of medication.

CyPA and Atherosclerotic Unstable Plaque

As demonstrated, ROS-induced secretory protein CyPA is a useful biomarker of CAD, so we hypothesized that secreted CyPA is highly accumulated in atherosclerotic plaque of coronary arteries. Indeed, we observed strong CyPA expression in coronary arteries in patients with MI (**Figures 5B,C**). Importantly, the strong expression of CyPA was localized just beneath the thin fibrous cap of atherosclerotic plaque.

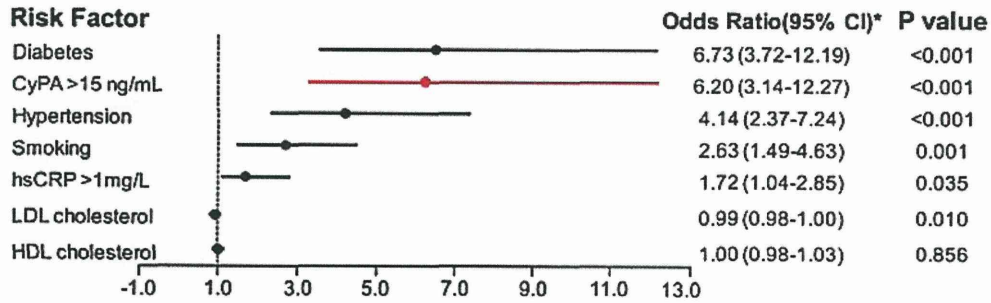

Figure 4. Plasma levels of cyclophilin A (CyPA) and cardiovascular risk factors. Plasma levels of CyPA were significantly increased by the presence of hypertension, diabetes, smoking, dyslipidemia and advanced age of 68 years or older but not by sex difference. *Adjusted with age, sex, and BMI.

Table 3. Correlated Risk Factors for Coronary Stenosis

	Univariable analysis			Multivariable analysis*		
	OR	95% CI	P value	OR	95% CI	P value
Age	1.08	1.05–1.10	<0.001	1.07	1.04–1.10	<0.001
Men	1.76	1.10–2.82	0.018	1.58	0.81–3.09	0.184
BMI	0.95	0.89–1.01	0.085			
Hypertension	5.34	3.19–8.93	<0.001	1.85	0.95–3.63	0.073
Smoking	2.44	1.52–3.90	<0.001	1.82	0.95–3.49	0.072
Dyslipidemia	4.03	2.49–6.51	<0.001	2.37	1.23–4.55	0.010
Diabetes	5.87	3.50–9.86	<0.001	4.71	2.53–8.78	<0.001
Family history of IHD	0.663	0.33–1.35	0.258			
CyPA >15 ng/ml	7.58	4.00–14.38	<0.001	4.14	2.00–8.57	<0.001
hsCRP >1 mg/L	1.77	1.12–2.79	0.014	1.58	0.87–2.86	0.135

*Analysis was performed on 8 variables including age, sex, hypertension, smoking, dyslipidemia, diabetes mellitus, CyPA >15 ng/ml and hsCRP >1 mg/L.
Abbreviations as in Tables 1,2.

Discussion

Our study demonstrated that the plasma level of CyPA in patients with stable CAD provides prognostic information on the severity of CAD and the requirement for cardiovascular intervention. The findings of the present study support our previous results in mice suggesting that CyPA augments the development of atherosclerosis.[8,17,23] Patients with high CyPA levels had a significantly higher prevalence of CAD on CAG than those with low levels of CyPA. A possible role for CyPA in atherosclerosis is becoming increasingly apparent. We have shown that knock-down of CyPA in EC reduced apoptosis induced in vitro by tumor-necrosis factor-α and that CyPA deficiency was associated with a marked decrease in EC apoptosis in the early stages of atherosclerosis.[17] The increase in vascular oxidative stress requires CyPA[15] which thereby sensitizes EC to apoptosis. In addition, CyPA secretion is regulated by Rho-kinase activation, which is important for VSMC contraction and atherosclerosis.[19] Consistently, plasma levels of CyPA were significantly increased in patients with CAD.

In the present study, plasma levels of CyPA were elevated in patients with angiographically verified coronary atherosclerosis. We have previously demonstrated that ROS inducers, such as mechanical stress, angiotensin II and dyslipidemia, promote the secretion of CyPA[8,15,17] in a Rho-kinase-dependent manner.[19,24] It is well known that Rho-kinase is associated with activation of the NADPH oxidases, with resultant ROS production,[25] which plays a crucial role in the development of several cardiovascular diseases. In support of this notion, CyPA was elevated in patients with hypertension, diabetes, smoking, dyslipidemia, and advanced age in the present study. This is the first study that has examined the association between CyPA and ROS inducers, all of which are atherosclerotic risk factors in humans.

Plasma CyPA and Atherosclerotic Risk Factors

In the present study, we further examined the prognostic importance of CyPA in patients with stable CAD. We found that CyPA is a prognostic marker for requirement of cardiovascular intervention such as PCI and CABG. The increased severity of CAD we observed among patients with elevated CyPA may be a consequence of a higher frequency of risk factors for atherosclerosis, all of which promote ROS production and CyPA secretion. All these mechanisms, while promoting an environment of oxidative stress, are likely to contribute to the increased plasma levels of CyPA in patients with severe CAD. Vascular ROS formation can be stimulated by mechanical stretch, pressure, shear stress, environmental factors such as hypoxia, and secreted factors such as angiotensin II.[27-31] In addition, extracellular CyPA induces ROS production in VSMC