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Association of cardiorespiratory fitness with characteristics of coronary plaque: Assessment using integrated backscatter intravascular ultrasound and optical coherence tomography

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ABSTRACT

Background: Cardiorespiratory fitness (CRF) can predict future cardiovascular disease. Rupture of vulnerable plaque which often has a large lipid core with a thin fibrous cap causes acute coronary syndrome including sudden cardiac death. We tested our hypothesis that preserved CRF is associated with low lipid composition and thick fibrous cap thickness of coronary lesions.

Methods: We prospectively performed both integrated backscatter intravascular ultrasound (IB-IVUS) and optical coherence tomography (OCT) for 77 non-culprit coronary lesions in 77 consecutive angina pectoris patients who underwent percutaneous coronary intervention (PCI). Percentage of achieved of predicted peak oxygen consumption (%PPeak Vo_2) calculated based on measured peak Vo_2 using a cardiopulmonary exercise test performed post PCI was adapted as an indicator of patient CRF.

Results: Patients were divided into two groups [those with preserved CRF (%PPeak Vo_2 >82%) (Group I) or others (Group II)]. Coronary plaques of Group I patients had significantly smaller lipid volume, greater fibrous volume, and thicker fibrous cap thickness than those of Group II ($32 \pm 14\%$ vs. $45 \pm 13\%$, $p<0.001$; $57 \pm 11\%$ vs. $49 \pm 11\%$, $p<0.001$; and 177.7 ± 20.9 μm vs. 143.7 ± 36.9 μm, $p<0.001$). In multivariate linear regression analysis, %PPeak Vo_2 showed a significantly negative correlation with lipid volume and a positive correlation with fibrous volume and fibrous cap thickness ($\beta = -0.418$, $p = 0.001$; $\beta = 0.361$, $p = 0.006$; and $\beta = 0.339$, $p = 0.008$).

Conclusions: High %PPeak Vo_2 was associated with low lipid volume, high fibrous volume and thick fibrous cap thickness in coronary lesions. These results may well suggest an attenuated risk of cardiovascular events in patients with preserved CRF.

1. Introduction

Cardiorespiratory fitness (CRF) status strongly predicts cardiovascular events [1–3], and improved CRF can prevent coronary heart disease (CHD) and mortality [1,3–5]. Studies have reported that CRF is a more powerful predictor of mortality and CHD death compared to other established risk factors [3,6]. However, it has not been clearly elucidated why patients with high CRF levels have such low morbidity and mortality rates due to CHD.

Recently, characteristics of tissue components of coronary plaque are analyzed by integrated backscatter (IB) intravascular ultrasound (IVUS) [7–10], and the fibrous cap thickness is measured by optical coherence tomography (OCT) [11,12]. A lipid-rich plaque with thin fibrous cap is often associated with vulnerable plaque, which directly relates to a risk of rupture [13,14]. To the best of our knowledge, there has been no report as to whether CRF correlates with characteristics of tissue components and fibrous cap thickness of coronary plaque. Accordingly, we tested our hypothesis that preserved CRF is associated with low lipid composition and thick fibrous cap thickness in coronary plaques, using imaging modalities of IB-IVUS and OCT.

2. Materials and methods

2.1. Study population

This study included 88 consecutive patients undergoing elective percutaneous coronary intervention (PCI) at our institution between November 2009 and May 2010. Enrollment criteria were patients with both stable angina pectoris and statin treatment

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for at least 9 months. Exclusion criteria consisted of: age >80 years; malignant tumor; rheumatoid arthritis; end-stage renal disease on maintenance hemodialysis; severe valvular heart disease diagnosed according to the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines [15]; congestive heart failure (CHF) (left ventricular ejection fraction <45% or signs of CHF defined as admission to hospital necessitated by heart failure and treatment with diuretics for CHF); history of acute coronary syndrome within 6 months; and contraindication of aspirin treatment and/or exercise. As to coronary lesions to be analyzed, enrollment criteria consisted of: previously untreated; non-culprit and mild to moderately stenotic [percent stenosis <50% as determined by quantitative coronary angiography (QCA)]; and >15 mm away from the intervention site. Moreover, when there were more than two plaques to be analyzed and recognized in target vessels, the most proximal one was selected for our analysis. Exclusion criteria were coronary plaques located in the left main trunk, just proximal to the left anterior descending artery or left circumflex, and near the right coronary artery ostium, due to the fact that OCT imaging requires vessel occlusion.

A blood sample was obtained prior to PCI and various lipids, glucose, and inflammatory profiles were measured. Immediately prior to PCI, IVUS and OCT imaging were performed in the coronary artery. To determine CRF of patients without inducible ischemia a cardiopulmonary exercise test (CPX) was performed between 14 days and a month post-PCI. Prior to CPX, an echocardiogram was taken. The study protocol and chart reviews were approved by the Nagoya University institutional ethics committee. Written informed consent was obtained from each patient.

2.2. Definitions

Patients classified as having diabetes mellitus were given fasting plasma glucose concentration >126 mg/dl, hemoglobinA1c levels ≥6.5%, and/or a history of any anti-hyperglycemic medication or previous diagnosis with diabetes. Hypertension was defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or having received treatment for Hypertension. Daily aspirin (100 mg) was administered at least a week prior to PCI. A bolus of 10,000 U heparin was intravenously administered immediately prior to PCI. An intracoronary infusion of 5 mg isosorbide dinitrate was given immediately prior to angiography for QCA, IVUS and OCT.

2.3. QCA

Coronary angiograms were obtained prior to PCI. Angiogram showing the maximal degree of stenosis was selected for QCA. QCA was analyzed using a contour detection minimum cost algorithm (QCA-CMS Version 3.0, MEDIS, Leiden, The Netherlands).

2.4. Gray-scale IVUS

A commercially available system (Clear View, Boston Scientific, Natick, Massachusetts for imaging, and SCIMED, Freemont, California for a motored pull-back device and commercial scanner) and a 40-MHZ IVUS catheter were used for gray-scale IVUS analysis. In accordance with ACC guidelines [16], the external elastic membrane (EEM) and lumen were traced by manual planimetry. CSA of EEM was measured by tracing the leading edge of the adventitia. Plaque plus media CSA was calculated as (EEM − lumen CSA). Percent plaque area was defined as: [(EEM area − lumen area)/EEM area] × 100. Gray-scale 3-dimensional IVUS image analysis was performed to compute vessel volume, lumen volume, and total plaque volume (sum of EEM, lumen CSA, Plaque plus media CSA at 1-mm axial intervals for the analysis segments). Percent plaque volume (%) was calculated as (plaque volume/vessel volume) × 100.

2.5. IB-IVUS

IB signals were obtained with a commercially available system connected to the IVUS system (IB-IVUS, YD Co., Ltd., Nara, Japan). IB values for three histological categories (fibrous area, lipid area, and high signal area; calcification) were calculated as average power of the ultrasound backscattered signal using a fast Fourier transform, measured in decibels (dB). Analysis for 3-dimensional IVUS images including lipid volume, fibrous volume, and high signal volume was calculated as the sum of the fibrous, lipid, and high signal area in each CSA at 1-mm axis intervals, respectively. The percentage of fibrous, lipid, and high signal area (volume) [fibrous, lipid, and high signal area (volume)/plaque area (volume) × 100] was automatically calculated.

2.6. OCT

OCT imaging was performed as follows: an over-the-wire occlusion balloon catheter (Helios®, St. Jude Medical, Inc., St. Paul, Minnesota, USA) was advanced to the distal end of the target plaque, under the guidance of a 0.014 inch guidewire. The guidewire was then removed and the OCT imaging probe (ImageWire®, St. Jude Medical, Inc., St. Paul, Minnesota, USA) was inserted through the over-the-wire lumen of the occlusion balloon. With the ImageWire held in place, the occlusion balloon was withdrawn proximal to the plaque. To remove blood from the imaging site, the occlusion balloon was inflated to 0.5 atm, and lactated Ringer's solution was infused from the distal tip of the occlusion balloon at a rate of 0.5 ml/s. Imaging was performed with an automatic pullback device at a rate of 1 mm/s. Obtained images were analyzed using proprietary off-line software provided by LightLab Imaging Inc., according to previously defined criteria for plaque characterization [12]. Target plaque location was determined based on distance from predominant landmarks (e.g. major branches, calcification, stent edge). If target plaque was an OCT-determined lipid plaque (identified as signal-poor and attenuating), the thickness of the thinnest component of the fibrous cap was measured [11].

2.7. CPX

Exercise stress testing was performed according to the ACC/AHA guidelines [17]. A symptom limited CPX, using an electromagnetically braked cycle ergometer, was used to estimate CRF. Patients were required to stop taking beta-blockers two days prior to CPX if such were administered daily. A ramp protocol with an exercise regimen of a 3-minute warm-up at 10 W at a cycle ergometer velocity of 50 rpm, followed by linear increase in the work load at a rate of 10 W/min was used. Breath-by-breath oxygen consumption (Vo_2), carbon dioxide production (VCo_2), and minute ventilation (VE) were measured throughout the test using an Ergospirometry Oxycon Pro (Viasys Healthcare Inc., Washington, USA). Peak Vo_2 (ml/min/kg) was defined as the average of maximum 30 second attained Vo_2 at the end of the exercise period. Percentage of achieved of predicted peak Vo_2 (%PPeak Vo_2) which was calculated as [obtained peak Vo_2/age-, gender-, and weight-adjusted predicted peak Vo_2 ml/min/weight (kg)] × 100 [18,19] was adapted as an indicator of patient CRF.

2.8. Statistical analysis

SPSS ver. 18 (SPSS, Chicago, IL, USA) was used for all statistical analysis. Continuous variables were presented as mean ± standard deviation, and differences between the 2 groups were evaluated by the Student unpaired *t*-test. When their distribution was abnormal the Mann Whitney *U*-test was used. Categorical variables were presented as numbers (%), and comparisons across the 2 groups were performed by the chi-square test or Fisher exact test. To analyze the relationship between %PPeak Vo_2 and other confounders and characteristics of coronary plaques univariate linear regression analysis was used. And then, multivariate linear regression analysis was performed to adjust for these variables with p value <0.1 at univariate linear regression analysis. A two-tailed p value of <0.05 was considered statistically significant.

3. Results

We tried to perform IVUS and OCT imaging immediately prior to PCI for 88 patients. Of them, IVUS and/or OCT catheters could not be placed appropriately within the coronary artery in 4 patients due to bending or calcification of vessels. Further 7 patients were excluded because of the absence of coronary lesion which met the inclusion criteria, thus, leaving 77 patients with 77 lesions eligible for this study. Representative analyzed images of serial intra coronary images of the study patients are shown in Fig. 1. A total of 30 randomly selected images of target lesions were measured for the evaluation of inter- and intra-observer agreement. Inter- and intra-observer variabilities of lipid volume and fibrous volume in 3-dimensional IVUS images were well correlated [r = 0.97 (p<0.001) and r = 0.96 (p<0.001), and r = 0.94 (p<0.001) and r = 0.95 (p<0.001)]. Inter- and intra-observer variabilities of fibrous cap thickness in OCT analysis were also well correlated [r = 0.86 (p<0.001) and r = 0.84 (p<0.001)].

According to the cutoff points of 82% of %PPeak Vo_2 which were 3rd tertile of obtained %PPeak Vo_2, they were divided into two groups [patients with preserved CRF (Group I) or others (Group II)]. Among enrolled patients, 26 (34%) had %PPeak Vo_2 ≥82, and 51 (66%) had %PPeak Vo_2 <82%. Table 1 shows clinical characteristics of both groups. The rate of previous angioplasty was significantly lower in patients of Group I than those of Group II (15% vs. 59%, p = 0.001). HDL-C levels were significantly higher in patients of Group I than those of Group II (53.9 ± 17.4 mg/dl vs. 44.5 ± 10.3 mg/dl, p = 0.016). Fewer patients had a prescription of beta-blocker in Group I than Group II (8% vs. 37%, p = 0.006).

Table 2 shows the angiograms, QCA, IVUS and OCT data. The analyzed target (non-culprit) lesions were more frequently located in the left descending artery in Group I than in Group II (62% vs. 24%, p = 0.001). There was no significant difference about percentages of plaque volume at analyzed lesion (p = 0.466). In the IB-IVUS assessment, at the minimum luminal area section, patients of Group I had a significantly lower percentage of lipid area and a significantly greater percentage of fibrous area of target plaques compared to those of Group II (32 ± 14% vs. 45 ± 13%, p<0.001 and 57 ± 11% vs. 49 ± 11%, p = 0.001). Furthermore, in the volumetric analysis, patients of

Group I had a significantly lower percentage of lipid volume and a significantly greater percentage of fibrous volume of target plaques compared to those of Group II (32 ± 11% vs. 45 ± 11%, $p<0.001$ and 58 ± 8% vs. 50 ± 9%, $p<0.001$). Of the 77 target lesions, 59 had fibrous cap detected using OCT [13 (50%) of Group I vs. 46 (90%) of Group II, $p<0.001$]. The average fibrous cap thickness was significantly greater in Group I than in Group II (177.7 ± 20.9 μm vs. 143.7 ± 36.9 μm, $p<0.001$). %PPeak Vo_2 was significantly higher in patients of Group I than those of Group II (100 ± 18% vs. 62 ± 12%, $p<0.001$). VE/Vco_2 slope was significantly lower in patients of Group I than those of Group II (28.6 ± 3.9 vs. 32.0 ± 6.1, $p=0.005$) (Table 3). Univariate linear regression analysis showed %PPeak Vo_2 had a significantly negative correlation with percent lipid volume and a significantly positive correlation with percent fibrous volume ($r=-0.429$, $p<0.001$ and $r=0.376$, $p=0.001$) and thickness of fibrous cap ($r=0.370$, $p=0.004$). HDL-C levels also had a significantly positive correlation with percent lipid volume ($r=-0.239$, $p=0.036$) (Table 4). Using multivariate linear regression analysis after adjustment for confounders, %PPeak Vo_2 still had a significantly negative correlation with percent lipid volume and a significantly positive correlation with percent fibrous volume ($\beta=-0.418$, $p=0.001$ and $\beta=0.361$, $p=0.006$) and fibrous cap thickness ($\beta=0.339$, $p=0.008$) (Table 5).

4. Discussion

It is well known that a lower incidence of cardiac event is observed in patients with preserved CRF [1–3], although the underlying mechanisms are not well established. We investigated the relationship between CRF and characteristics of tissue components and fibrous cap thickness of coronary plaque. As a result, preserved CRF indicated by high %PPeak Vo_2 was associated with a low percentage of lipid volume, high percentage of fibrous volume and thick fibrous cap thickness.

A high percentage of lipid volume, low percentage of fibrous volume and thin fibrous cap are usually associated with vulnerability of plaque which directly relates to risk of rupture [13,14]. Rupture of vulnerable plaques causes acute coronary syndrome, including sudden cardiac death. Eighty-six percent of vulnerable plaques reportedly evolve from mild to moderately stenotic plaques, resulting in myocardial infarction [13]. Moreover, plaque rupture frequently occurs relatively proximal to coronary arteries [20]. These were why we evaluated not severe stenotic (culprit), but mild to moderately stenotic (non-culprit) plaques at as proximal as possible, although culprit lesions had the greatest plaque burden and perhaps the largest lipid core. The results of the present study could help explain why patients with high CRF have a decreased risk of cardiovascular events.

Peak Vo_2 is a more accurate and reproducible variable evaluating not only cardiac reserve but also peripheral adaptations [3–5,19,21] Age, gender, build, skeletal muscle, respiratory, hematological factors, underlying chronic disease, as well as cardiac output response have effect on it [3,22]. In this study, CRF levels were indicated by %PPeak Vo_2 which was an age-, gender-, and weight-adjusted value based on directly measured peak Vo_2 using CPX. No significant difference was seen regarding underlying chronic disease which might influence on results of CPX or cardiac function measured by echocardiogram.

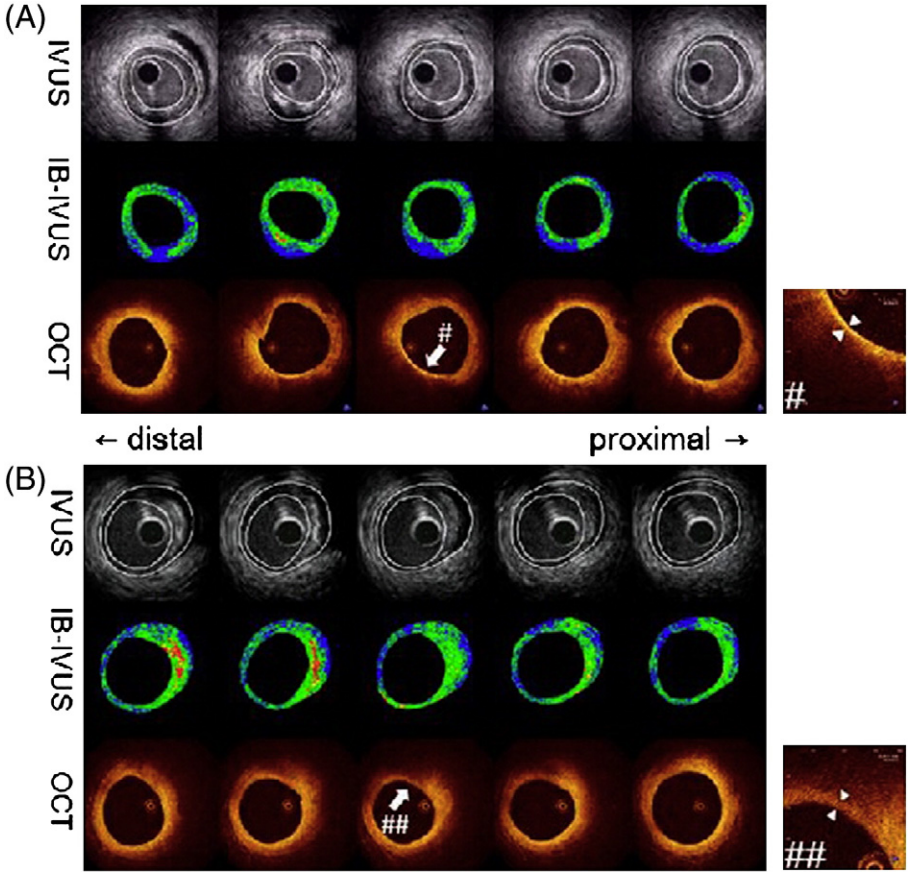

Fig. 1. Example of analyzed images of serial gray-scale intravascular ultrasound (IVUS), integrated backscatter (IB) IVUS, and optical coherence tomography (OCT) of the studied patients. (A) In a patient with 119% of achieved of predicted peak oxygen consumption (%PPeak Vo_2) (Group I), the percentages of lipid and fibrous volume were 33% and 52% (Blue = lipid; green and yellow = fibrous; red = high signal), and fibrous cap thickness was 200 μm (arrow and magnified picture in #). (B) In a patient with 62% of %PPeak Vo_2 (Group II), the percentages of lipid and fibrous volume were 53% and 43%, respectively, and fibrous cap thickness was 90 μm (arrow and magnified picture in ##).

Table 1
Patient characteristics.

	Group I n = 26	Group II, n = 51	P
Age (year)	69 ± 6	66 ± 9	0.138
Male	19 (73)	38 (75)	1.000
Body mass index (kg/m^2)	25.4 ± 3.7	23.8 ± 3.5	0.063
Clinical history			
Hypertension	18 (69)	39 (76)	0.585
Diabetes	12 (46)	19 (37)	0.472
Current smoker	2 (8)	12 (24)	0.122
Previous angioplasty	4 (15)	30 (59)	0.001
Previous bypass surgery	1 (4)	6 (12)	0.412
Previous myocardial infarction	2 (8)	9 (18)	0.316
Multiple vessel disease	13 (50)	33 (65)	0.230
Familial history of CHD	11 (42)	16 (31)	0.449
Peripheral arterial disease	1 (4)	3 (6)	1.000
Chronic obstructive pulmonary disease.	0	1 (2)	1.000
Total cholesterol (mg/dl)	197.1 ± 42.1	167.9 ± 39.4	0.110
Low-density lipoprotein cholesterol (mg/dl)	104.5 ± 32.1	98.5 ± 30.8	0.432
High-density lipoprotein cholesterol (mg/dl)	53.9 ± 17.4	44.5 ± 10.3	0.016
Low- to High-density lipoprotein cholesterol ratio	2.0 ± 0.81	2.3 ± 0.81	0.212
Triglyceride (mg/dl)	159.2 ± 104.3	146.7 ± 87.2	0.581
HemoglobinA1c (%)	6.1 ± 0.9	6.5 ± 1.2	0.142
High-sensitivity C-reactive protein (mg/l)	1.2 ± 1.2	1.8 ± 1.8	0.144
Medication			
Aspirin	26 (100)	57 (100)	
Statins	26 (100)	57 (100)	
Angiotensin converting enzyme inhibitors	0	5 (10)	0.161
Angiotensin II receptor blockers	13 (50)	31 (61)	0.466
Beta-blockers	2 (8)	19 (37)	0.006
Insulin	2 (8)	6 (12)	0.710
Oral diabetes medication	3 (12)	11 (22)	0.360

Values are mean ± standard deviation or number (%). CHD = coronary heart disease.

Table 2
Data on angiograms, quantitative coronary angiography, and intravascular imaging.

	Group I n = 26	Group II n = 51	P
Target lesion location			
Left anterior descending artery	16 (62)	12 (24)	0.001
Left circumflex artery	6 (23)	14 (27)	0.787
Right coronary artery	4 (15)	25 (49)	0.006
QCA of target lesions			
Minimum lumen diameter (mm)	1.8 ± 0.44	1.9 ± 0.47	0.431
Reference vessel diameter (mm)	2.4 ± 0.53	2.6 ± 0.58	0.262
Diameter stenosis (%)	24 ± 11	25 ± 9.8	0.552
Lesion length (mm)	6.5 ± 1.6	6.9 ± 1.7	0.291
Gray-scale IVUS			
MLA (mm^2)	4.7 ± 2.3	4.9 ± 1.8	0.606
EEM area of MLA (mm^2)	11.4 ± 5.7	12.3 ± 4.1	0.420
Plaque area of MLA (mm^2)	6.5 ± 4.0	7.3 ± 3.4	0.391
Percent plaque area of MLA (%)	58 ± 11	57 ± 13	0.931
Lumen volume (mm^3)	43.1 ± 21.5	50.2 ± 22.1	0.182
EEM volume (mm^3)	88.4 ± 43.6	103.4 ± 45.9	0.172
Plaque volume (mm^3)	45.3 ± 25.3	53.2 ± 28.4	0.235
Percent plaque volume (%)	53 ± 11	51 ± 10	0.466
IB-IVUS			
Lipid area of MLA (%)	32 ± 14	45 ± 13	<0.001
Fibrous area of MLA (%)	57 ± 11	49 ± 11	0.001
High signal area of MLA (%)	11 ± 7	6 ± 5	0.005
Percent lipid volume (%)	32 ± 11	45 ± 11	<0.001
Percent fibrous volume (%)	58 ± 8	50 ± 9	<0.001
Percent high signal volume (%)	10 ± 5	5 ± 4	0.001
OCT			
Fibrous cap	13 (50)	46 (90)	<0.001
[a]Fibrous cap thickness (μm)	177.7 ± 20.9	143.7 ± 36.9	<0.001

Values are mean ± SD or number (%).
QCA = quantitative coronary angiography; IVUS = intravascular ultrasound; MLA = minimum luminal area; EEM = external elastic membrane; IB = integrated backscatter; OCT = optical coherence tomography.
[a] Group I, n = 13, Group II, n = 46.

Table 3
Echocardiogram and cardiopulmonary exercise test findings.

	Group I n = 26	Group II n = 51	p
Echocardiogram			
Asynergy	3 (12)	6 (12)	1.000
Left ventricular ejection fraction (%)	65 ± 9	63 ± 10	0.280
Peak E/peak A	1.0 ± 1.2	0.99 ± 0.92	0.944
Cardiopulmonary exercise test			
Rest heart rate (beats/min)	72 ± 11	74 ± 11	0.357
Peak exercise heart rate (beats/min)	123 ± 14	118 ± 17	0.239
Peak Vo_2 (ml/min/kg)	18.2 ± 4.1	17.5 ± 3.4	0.444
%PPeak Vo_2 (%)	100 ± 18	62 ± 12	<0.001
VE/Vco_2 slope	28.6 ± 3.9	32.0 ± 6.1	0.005

Values are mean ± SD or number (%). Vo_2 = oxygen consumption; %PPeak Vo_2 = percent achieved of predicted peak Vo_2; VE = minute ventilation; Vco_2 = carbon dioxide production.

However, higher VE/Vco_2 slope indicating impaired ventilatory efficiency during exercise was obtained from patients with unpreserved CRF than those with preserved. It has been hypothesized that in weak and insufficient skeletal muscle, increased metabolic products during exercise cause an abnormal peripheral muscle ergorecepter activation resulting in an abnormal VE/Vco_2 slope associated with breathlessness and fatigue [23,24]. Therefore, we considered that untrained peripheral skeletal muscle due to low physical activity or exercise might be one of the possible reasons of low CRF indicated by low %PPeakVo_2, although the above mentioned theory is argued only in patients with CHF. Further investigations are warranted.

On the other hand, coronary plaques were well analyzed with IB-IVUS and OCT. Coronary risk factors including high insulin levels, metabolic syndrome, diabetes, and/or chronic kidney disease are associated with plaque morphology analyzed by IB-IVUS and/or OCT [8,9,25–27]. Cross-sectional areas of vessels, plaques and lumen are clinically well evaluated by gray-scale IVUS. Color-coded tissue maps of plaque components analyzed by IB-IVUS have a good correlation with histological and angioscopic findings. However, IVUS is limited by resolution (100 μm), and cannot precisely evaluate fibrous cap thickness [7]. In contrast, high resolution OCT facilitates (10 μm) detection and measurement of fibrous caps, yet is limited in evaluating the size of a lipid-core of a plaque compared to IB-IVUS due to relatively low signal penetration depths [7,12]. Therefore, these modalities may have qualities that redeem their mutual defects.

There may be several mechanisms underlying the present observations. Increased CRF by regular physical activity and exercise training beneficially modifies cardiovascular risk factors [6]. Regular exercise reportedly increases HDL-C which has antiatherogenic properties, such as reverse cholesterol transport, low-density lipoprotein antioxidation, endothelial protection, antiplatelet activity, and anticoagulation [28]. In this study, patients with preserved CRF had significantly higher HDL-C levels than the others. In univariate regression analyses, HDL-C levels had significantly negative correlation with percent lipid volume detected by IB-IVUS. Increased CRF also provides an anti-inflammatory effect [29]. Inflammation contributes to the atherosclerotic process [30]. Li et al. showed inverse linear correlation between high-sensitivity C-reactive protein and fibrous cap thickness [26]. A similar tendency was also obtained from our studied patients. In addition, patients with preserved CRF had a tendency to have lower levels of high-sensitivity C-reactive protein. Thus, attenuated inflammatory, as well as increased HDL-C levels might have a beneficial effect on coronary plaque composition and fibrous cap thickness in patients with preserved CRF. However, because the association of increased CRF with decreasing mortality is independent of the other risk factors [6], this favorable effect cannot be explained only by reduction of coronary risk factors. The functional enhancement of the endothelium to respond to increased blood flow and shear stress reportedly can predict atherosclerotic disease

Table 4
Univariate linear regression analyses.

Variables	Percent lipid volume regression coefficient	P	Percent fibrous volume regression coefficient	P	Fibrous cap thickness regression coefficient	P
Age (year)	−0.174	0.131	0.189	0.099	0.189	0.152
Male	0.032	0.782	−0.047	0.687	0.133	0.316
Body mass index (kg/m^2)	−0.002	0.987	−0.033	0.779	−0.016	0.905
Hypertension	0.113	0.329	−0.102	0.375	−0.131	0.324
Diabetes	0.067	0.563	−0.083	0.475	0.140	0.291
Current smoker	−0.035	0.762	0.107	0.353	−0.002	0.986
Total cholesterol (mg/dl)	−0.195	0.089	0.182	0.113	0.011	0.937
Low-density lipoprotein cholesterol(mg/dl)	−0.059	0.611	0.058	0.618	−0.010	0.941
High-density lipoprotein cholesterol (mg/dl)	−0.239	0.036	0.190	0.099	0.113	0.393
Low- to high-density lipoprotein cholesterol ratio	−0.028	0.809	0.045	0.698	−0.052	0.694
Triglyceride (mg/dl)	−0.019	0.867	0.023	0.842	−0.169	0.200
HemoglobinA1c (%)	0.051	0.657	−0.038	0.745	−0.123	0.353
High-sensitivity C-reactive protein (mg/l)	0.123	0.288	−0.074	0.520	−0.248	0.058
%PPeak Vo_2 (%)	−0.429	<0.001	0.376	0.001	0.370	0.004

Vo_2 = oxygen consumption; %PPeak Vo_2 = percent achieved of predicted peak Vo_2.

progression and clinical outcome in patients at risk for CHD [31,32]. In the present study, %PPeak Vo_2 was an independent predictor for coronary plaque composition and fibrous cap thickness, suggesting that the atheroprotective effects of enhanced endothelial function via regular physical activity and exercise possibly play a pivotal role on coronary plaque component and fibrous cap thickness. Medical treatment with statins also reduces the lipid volume detected by IB-IVUS and increases fibrous cap thickness measured using OCT [10,33]. Therefore, lifestyle changing intervention to preserve or increase CRF by regular physical activity and exercise training, as well as medical treatment might be extremely useful to patients with low CRF. Increased CRF has beneficial effects on angiographical regression or retardation of progression of coronary stenosis [34]. However, limited information has been available regarding the effect of CRF on coronary plaque stabilization. We speculated that CRF might play an important role in plaque stabilization. Further data on the effects of CRF on the attenuation of the plaque vulnerability should be collected in future studies and would have great clinical importance.

Study limitations need to be addressed. This study consisted of a relatively small number of patients from a single center. In the present study, patients with acute coronary syndrome were excluded. Furthermore, only mild to moderate stenotic coronary plaques located where we could visualize were evaluated, because we considered that a passage of IVUS and occlusion balloon catheter into severe stenotic lumen may cause injury to the surface of coronary plaques, resulting in a bias. However, severe stenotic plaque (>90%) is one of the major criteria for defining vulnerable plaque [35]. These factors may affect the results. Thus, plaques, as well as patients that met the exclusion criteria of this study should be evaluated in any future study. No thin fibrous cap, generally defined as <65 μm [12], was observed. However, we considered that a thinner fibrous cap was associated with greater plaque vulnerability. Finally, clinical outcomes including cardiovascular events must be collected in future studies to confirm our speculations.

Table 5
Multivariate linear regression analyses.

Variables	Regression coefficient	Beta coefficient	P
Percent lipid volume			
Total cholesterol (mg/dl)	−0.030	−0.100	0.416
High-density lipoprotein cholesterol (mg/dl)	0.026	0.028	0.840
%PPeak Vo_2 (%)	−0.229	−0.418	0.001
Percent fibrous volume			
Age (year)	0.130	0.114	0.305
High-density lipoprotein cholesterol (mg/dl)	−0.013	−0.019	0.883
%PPeak Vo_2 (%)	0.150	0.361	0.006
Fibrous cap thickness			
High-sensitivity C-reactive protein (mg/l)	−38.155	−0.193	0.123
%PPeak Vo_2 (%)	0.543	0.339	0.008

Vo_2 = oxygen consumption; %PPeak Vo_2 = percent achieved of predicted peak Vo_2.

In summary, the present study demonstrated that high %PPeak Vo_2 was markedly associated with low percentage of lipid volume, high percentage of fibrous volume and thick fibrous cap thickness of the coronary plaques. Our findings might be one reason why decreased risks of cardiovascular events are seen in patients with preserved CRF.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [36].

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