Change in Pericardial Fat Volume and Cardiovascular Risk Factors in a General Population of Japanese Men

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Background: Pericardial fat volume (PFV), defined as the volume of ectopic fat in and around the heart, is associated with the atherosclerotic process in coronary arteries. The magnitude of change in PFV over time and the factors affecting this change in a general population, however, have not been investigated.

Methods and Results: Cardiac computed tomography (CT) was carried out at baseline and at follow-up in 623 Japanese men aged 40–79 years without a history of cardiovascular disease who were selected randomly in Kusatsu (Shiga, Japan). PFV was measured on cardiac CT in a qualified laboratory. Age, heart rate, triglycerides, and obesity measurements (weight, body mass index, and waist circumference) were significantly and positively associated with PFV at baseline. Over an average interval of 4.7 years, median PFV increased significantly from 64.1 cm³ (IQR, 47.2–90.0 cm³) to 73.6 cm³ (IQR, 53.3–98.1 cm³; $P<0.001$). Current smoking and heart rate were significantly and independently associated with changes in PFV ($B=3.336$, $P<0.001$ and $B=6.409$, $P=0.003$, respectively).

Conclusions: PFV increased significantly over time in a population-based observational study of Japanese men. PFV change was significantly and independently associated with smoking status and heart rate, suggesting that quitting smoking might help reduce PFV, which could be expected to decrease the risk of coronary artery disease.

Key Words: General population; Longitudinal change; Pericardial fat; Smoking

“Ectopic fat” is defined as excess adipose tissue in locations not classically associated with storage of adipose tissue.¹ It shares a common embryonic origin with abdominal visceral fat.^{2,3} “Pericardial fat” is ectopic fat in and around the heart. It can function as a lipid-storing depot; as an endocrine organ secreting hormones; and as an inflammatory tissue secreting cytokines and chemokines.² Pericardial fat may have a direct role in the atherosclerotic process in coronary arteries through local release of inflammation-related cytokines.⁴ Pericardial fat volume (PFV) has been shown to be associated with coronary atherosclerosis^{3,5–7} or the prevalence of coronary artery disease (CAD)^{4,8,9} or cardiovascular disease (CVD)⁸ in patient-based cohort studies^{3,6–8} and population-based cohort studies.^{4,5,8–10} In Japan, PFV has been reported to be associated with the severity of CAD^{11,12} and

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inflammation of the coronary arteries in CAD patients.¹³ Longitudinal changes in PFV, however, have not been examined in a general population: only one study in the USA, based on the registry of a selected population, has reported longitudinal changes in PFV.^{14,15}

The present study examined longitudinal changes in PFV and associations between PFV changes and classical cardiovascular risk factors in a community-based cohort of Japanese men.

Methods

The aim of the Shiga Epidemiological Study of Subclinical

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Atherosclerosis is to examine the various factors associated with subclinical atherosclerosis. The design of this study is described elsewhere.¹⁶ Briefly, 1,094 Japanese men aged 40–79 years were selected randomly from the Residential Basic Book of Kusatsu in Shiga Prefecture in Japan. The participation rate was 46%. Baseline and follow-up studies were performed from 2006 to 2008 and from 2010 to 2014, respectively. Mean follow-up period was 4.7 ± 1.2 years. A total of 731 participants underwent computed tomography (CT) twice: once at baseline and once at follow-up, until October 2013. Of these, 108 men were excluded due to missing information on PFV ($n=73$) or a history of myocardial infarction/angina pectoris ($n=35$). The remaining 623 participants were enrolled in the present study (**Figure 1**).

Anthropometric measurements (height, body weight [BW], and waist circumference [WC]) were obtained by trained nurses using a standard protocol at baseline and follow-up. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Blood pressure and heart rate were measured twice in a seated position after a 5-min rest using an automated sphygmomanometer (BP-8800; Omron Colin, Tokyo, Japan). The average of 2 measurements was used for analysis. Hypertension was defined as blood pressure $\geq 140/90$ mmHg or current use of antihypertensive drugs. Blood samples were obtained after 12-h fast. Serum was separated by centrifugation ($1,000 \times g$ for 15 min at $4^\circ C$) ≤ 90 min after sample collection. Samples were sent for routine laboratory testing, including lipid profiles and glucose. Total cholesterol and triglycerides were measured using enzymatic assay. High-density lipoprotein cholesterol (HDL-C) was determined using a direct method. Low-density lipoprotein cholesterol (LDL-C) was estimated using the Friedewald formula in participants with triglycerides < 400 mg/dL. Lipid measurements were standardized according to the protocol set by the US Centers for Disease Control and Prevention/Cholesterol Reference Method Laboratory Network. Dyslipidemia was defined as LDL-C ≥ 140 mg/dL, triglycerides ≥ 150 mg/dL, HDL-C < 40 mg/dL, or current use of lipid-lowering drugs. Glycated hemoglobin (HbA1c) was measured using the method suggested by the Japan Diabetes Society and was

converted to the National Glycohemoglobin Standardization Program (NGSP) equivalent value.¹⁷ Diabetes mellitus was defined as HbA1c (NGSP) $\geq 6.5\%$, fasting blood glucose ≥ 126 mg/dL, or current use of anti-diabetic drugs. We obtained information on cigarette smoking, alcohol drinking, medical history, and disease history from self-administered questionnaires at baseline and follow-up. Smoking status was categorized into 3 groups: “never”, “ex”, and “current” smoker. Participants who had never smoked were defined as “never smokers” and participants who smoked in the last 30 days were defined as “current smokers”. Drinking status was categorized into 3 groups: “never”, “ex”, and “current” drinker. Participants who had never consumed alcohol were defined as “never drinkers” and participants who consumed alcohol habitually were defined as “current drinkers”.

This study was conducted in accordance with the principles contained in the Declaration of Helsinki and approved by the Institutional Review Board of Shiga University of Medical Science (17-19, 17-83). Written informed consent was obtained from all participants.

Non-contrast CT was acquired using electron-beam CT with a C-150 scanner (Imatron, San Francisco, CA, USA) or using 16-channel multi-detector row CT (MDCT) at baseline and on MDCT at follow-up. Slice thickness was 3 mm. PFV was measured using the same method as that of the Multi-Ethnic Study of Atherosclerosis (MESA) at Harbor University of California-Los Angeles Medical Center.^{4,18} PFV was measured on axial images starting 15 mm above the superior extent of the left main coronary artery to 30 mm below that slice. Volume analysis software (GE Healthcare, Waukesha, WI, USA) was used to identify adipose tissue based on a corresponding threshold of -190 HU to -30 HU (mean, -120 HU).^{4,18} According to a report from MESA, the intra-class correlation coefficients of intra-reader and inter-reader reliability for pericardial fat are 0.99 and 0.89, respectively.⁴ We defined “pericardial fat” as adipose tissue inside and outside the pericardial sac. Change in PFV (cm^3) was calculated as PFV (cm^3) at follow-up minus PFV (cm^3) at baseline.

Table 1. Baseline Male Participant Characteristics (SESSA; Shiga, Japan; 2006–2008)

Variables	
n	623
Follow-up time (years)	4.7±1.2
Age (years)	66.5±6.8
Age range (years)	40–79
Body weight (kg)	64.2±8.9
BMI (kg/m ²)	23.4±2.9
WC (cm)	85.0±8.0
SBP (mmHg)	137.7±18.3
DBP (mmHg)	80.4±10.7
Heart rate (beats/min)	64.5±10.1
Smoking status	
Never	18.6
Ex	52.3
Current	29.1
Drinking status	
Never	16.1
Ex	5.1
Current	78.8
Total cholesterol (mg/dL)	209.8±32.9
Triglyceride (mg/dL)	104.0 (75.8–146.0)
HDL-C (mg/dL)	59.5±17.4
LDL-C (mg/dL)	125.6±30.7
FBG (mg/dL)	97.0 (91.0–107.3)
Hemoglobin A1c (%)	5.9 (5.6–6.3)
Hypertension	57.9
Medication for hypertension	32.6
Dyslipidemia	55.1
Medication for dyslipidemia	14.2
Diabetes	19.4
Medication for diabetes	10.1
PFV (cm ³)	64.1 (47.2–90.0)

Data given as mean±SD, median (IQR) or %. BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; PFV, pericardial fat volume; SBP, systolic blood pressure; SESSA, Shiga Epidemiological Study of Subclinical Atherosclerosis; WC, waist circumference.

Table 2. PFV and Baseline Variables: Spearman's Correlation Coefficients in 623 Men Aged 40–79 Years (SESSA; Shiga, Japan; 2006–2008)

Variables	r
Age (years)	0.147*
Body weight (kg)	0.625**
BMI (kg/m ²)	0.684**
WC (cm)	0.746**
SBP (mmHg)	0.135*
DBP (mmHg)	0.170**
Heart rate (beats/min)	0.100*
Total cholesterol (mg/dL)	0.038
Triglyceride (mg/dL)	0.345**
HDL-C (mg/dL)	–0.352**
LDL-C (mg/dL)	0.124*
FBG (mg/dL)	0.223**
Hemoglobin A1c (%)	0.169**

*P<0.05; **P<0.01. Abbreviations as in Table 1.

Statistical Analysis

Data are expressed as mean±SD for normally distributed continuous variables, or median (IQR) for non-normally distributed continuous variables. To compare paired data between 2 time-points, paired t-test was used for continuous variables and chi-squared test for categorical variables. Spearman's correlation analysis was used for continuous variables and analysis of variance for categorical variables to examine associations between classical cardiovascular risk factors and PFV at baseline and the change over time. Multivariable linear regression analysis was performed to examine the independent association between classical cardiovascular risk factors at baseline and PFV or its change. We selected confounders on multivariate analysis based on variables that were associated significantly with PFV on univariate analysis and from literature review. An age-adjusted model for each risk factor was estimated and multivariate regression analysis with backward selection was performed using a previous study for reference.¹⁹ We included the follow-up time and CT type as covariates in all models. We performed a stratified analysis by age (<65, ≥65 years). Statistical significance was defined as P<0.05. All statistical analyses were conducted using SAS v9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline participant characteristics are listed in **Table 1**. Mean age was 66.5±6.8 years and mean BMI was <25 kg/m². Mean BMI decreased slightly from 23.4±2.9 kg/m² to 23.2±2.9 kg/cm². Mean heart rate did not change during follow-up (64.5±10.1 beats/min at baseline and 64.3±10.6 beats/min at follow-up, P=0.684). The percentage of ex-smokers was higher than that of current smokers. Approximately 80% of participants were current drinkers. Prevalence of hypertension, dyslipidemia, and diabetes was 57.9%, 55.1%, and 19.4%, respectively.

PFV was strongly and positively associated with obesity measurements (BW, BMI, and WC) at baseline (**Table 2**). PFV was also significantly and positively associated with age, heart rate, blood pressure as well as the level of triglycerides, LDL-C, fasting blood glucose, and HbA1c. HDL-C was inversely associated with PFV (**Table 2**). On multivariable linear regression analysis, age, heart rate, and current smoking were significantly and positively associated with PFV after adjustment for age and CT type (**Table 3**). In the backward selection model, BMI and dyslipidemia in addition to age and heart rate were significantly and positively associated with PFV. When adjusted for BW or WC instead of BMI, both BW and WC were significantly and positively associated with PFV (data not shown).

Over an average interval of 4.7 years, median PFV increased significantly from 64.1 cm³ (IQR, 47.2–90.0 cm³) to 73.6 cm³ (IQR, 53.3–98.1 cm³; P<0.001). PFV change is given in **Figure 2**. The change in PFV was positively associated with heart rate at baseline and inversely associated with age (**Table 4**). These associations were significant but were not so strong (r=0.100, P=0.013 and r=–0.106 and P=0.008, respectively). The change in PFV was not associated with baseline BW, BMI, or WC. The PFV change in current smokers was significantly higher than that in ex-smokers and never smokers (20.5±29.0 cm³ vs. 11.4±23.4 cm³, P=0.001; and vs. 8.1±20.7 cm³, P<0.001, respectively). Drinking status was not associated with PFV change (P=0.569). On multivariable linear regression analysis,

Table 3. Multivariate Baseline Indicators of PFV in 623 Men Aged 40–79 Years (SESSA; Shiga, Japan; 2006–2008)

	Adjusted for age, CT type		Backward selection	
	B	P-value	B	P-value
Age (years)	0.642	0.002	1.069	<0.001
BMI (kg/m ²)	−0.094	0.669	8.029	<0.001
Heart rate (beats/min)	0.145	0.020	0.479	<0.001
Hypertension (Y/N)	0.847	0.511		
Dyslipidemia (Y/N)	0.044	0.972	4.261	0.032
Diabetes mellitus (Y/N)	2.069	0.174		
Smoking status				
Never	Ref.			
Ex	−0.431	0.734		
Current	4.118	0.003		
Drinking status				
Never	Ref.			
Ex	−3.031	0.249		
Current	0.107	0.944		

R² for the backward selection model: 0.536. CT, computed tomography. Other abbreviations as in Table 1.

Figure 2. Distribution of change in pericardial fat volume (PFV).

change in PFV was significantly and independently associated with heart rate and current smoking in the model adjusted for age, CT type, and follow-up time (**Table 5**). The result was similar in the model with backward selection including all variables (**Table 5**). We divided the participants into 2 groups by age (<65, ≥65 years) and found no interactions between these age groups and PFV change ($P=0.790$ for interaction). When adjusted for BW or WC as other obesity measurements instead of BMI, heart rate and current smoking were also significantly and positively associated with PFV change ($B=0.133$, $P=0.037$ and $B=6.841$, $P=0.001$ for BW; $B=0.0173$, $P=0.007$ and $B=4.433$, $P=0.002$ for WC, respectively). When the analysis was limited to those who did not change smoking status ($n=546$), the results did not change (**Table S1**).

Finally, we considered change in BMI. On multivariable linear regression analysis with the backward selection model including all variables, change in PFV was significantly and independently associated with change in BMI

Table 4. Change in PFV and Baseline Variables: Spearman's Correlation Coefficients in 623 Men Aged 40–79 Years (SESSA; Shiga, Japan; 2006–2008 for Baseline and 2010–2014 for Follow-up)

Variables	r
Follow-up time (years)	0.115**
Age (years)	−0.106**
Body weight (kg)	0.040
BMI (kg/m ²)	0.024
WC (cm)	0.004
SBP (mmHg)	0.031
DBP (mmHg)	0.063
Heart rate (beats/min)	0.100*
Total cholesterol (mg/dL)	0.002
Triglyceride (mg/dL)	−0.040
HDL-C (mg/dL)	0.064
LDL-C (mg/dL)	−0.023
FBG (mg/dL)	0.009
Hemoglobin A1c (%)	0.013
PFV at baseline (cm ³)	0.004

* $P<0.05$; ** $P<0.01$. Abbreviations as in Table 1.

($B=8.79$, $P<0.001$) and current smoking ($B=3.69$, $P=0.001$). The association between change in PFV and heart rate weakened slightly and showed marginal significance ($B=0.09$, $P=0.061$).

Discussion

This is the first study to examine longitudinal changes in PFV in a community-based cohort. We found that PFV increased significantly over time. The change in PFV was significantly and independently associated with smoking status and heart rate.

On cross-sectional analysis, PFV significantly and positively correlated with heart rate, triglycerides, and obesity measurements (BW, BMI, and WC). PFV has been found to

Table 5. Multivariate Indicators of Change in PFV in 623 Men Aged 40–79 Years (SESSA; Shiga, Japan; 2006–2008 for Baseline and 2010–2014 for Follow-up)

	Adjusted for age, CT type and follow-up time		Backward selection	
	B	P-value	B	P-value
Age (years)	−0.274	0.546		
BMI (kg/m ²)	−0.101	0.647		
Heart rate (beats/min)	0.148	0.021	0.930	0.037
Hypertension (Y/N)	0.838	0.519		
Dyslipidemia (Y/N)	−0.011	0.993		
Diabetes mellitus (Y/N)	2.084	0.178		
Smoking				
Never	Ref.			
Ex	−0.385	0.080	3.064	0.070
Current	4.109	0.004	6.841	0.001
Drinking				
Never	Ref.			
Ex	−3.087	0.243		
Current	0.120	0.938		
Follow-up time (years)	−0.498	0.854		
PFV at baseline (cm ³)	−0.013	0.501		

R² for the backward selection model: 0.05. Abbreviations as in Tables 1,3.

be positively associated with obesity measurements.^{3,5,10,11,15,20} Studies in Japanese populations with a lower prevalence of obesity have also reported a positive association between PFV and obesity measurements.¹² Although CAD patients were examined specifically in those studies, the present results are consistent with these.

Higher heart rate was associated significantly with higher PFV at baseline. We did not find other studies that examined the association between heart rate and PFV. It has been reported that PFV is related to heart rate recovery, which was used as an index of cardiac autonomic nervous dysfunction.^{21,22} Autonomic nervous dysfunction has been reported to be caused by fat accumulation in visceral adipose tissue in an animal model.²³ PFV shares a common embryonic origin with abdominal visceral fat,²⁴ and has a positive correlation with abdominal obesity. A higher heart rate has also been reported to be a predictor of CVD²⁵ and all-cause mortality.²⁶ The positive relationship between heart rate and PFV might be suggestive of cardiac autonomic dysfunction in the present study. We did not detect a change in heart rate during follow-up because heart rate was recorded with high accuracy, and was measured after a 5-min rest using an automated sphygmomanometer in the present study.

The mechanisms through which smoking increases PFV are complex and incompletely understood. Cigarette smokers tend to have lower BMI²⁷ in the short term because nicotine can reduce appetite and increase energy expenditure.²⁸ Paradoxically, smokers have also been reported to gain BW in a longitudinal study²⁹ and to have increased abdominal adiposity.^{30,31} Nicotine is a sympathomimetic agent and promotes the release of catecholamine.²⁸ Nicotine is also a strong activator of the hypothalamic-pituitary-adrenal axis,³² and increases energy expenditure by increasing the metabolic rate, leading to insulin resistance, which affects fat distribution.²⁸ Another biologic explanation is that smoking may reduce the testosterone concentration,³³ which is a determinant of changes in body

composition.³⁴ In addition, smokers tend to have unfavorable lifestyle habits, such as higher alcohol consumption and lower physical activity.^{35,36} Therefore, smokers tend to have a greater volume of visceral adipose tissue. We have already reported that smoking status is cross-sectionally associated with a greater degree of abdominal obesity.³⁷ We assume that the same mechanism could explain the association between PFV and smoking. In addition, a significant association between smoking status and resting heart rate was noted by Linneberg et al.³⁸ We suggest that smoking and increasing resting heart rate might contribute (at least in part) to the risk of CVD.

Some studies in which PFV was evaluated on ultrasound^{39,40} and only one study in which PFV was evaluated on MDCT¹⁵ reported a similar result to that of the present study: PFV change is associated with BMI change. In morbidly obese patients, bariatric surgery reduces BMI significantly and cardiac ectopic fat volume also decreases significantly after bariatric surgery.⁴¹ A change in BW or BMI influences a change in PFV because visceral adipose tissue is readily influenced by changes in BW or BMI rather than subcutaneous adipose tissue.⁴² The clinical importance of the change in PFV (rather than baseline PFV itself) is poorly understood. Additional studies are needed to clarify which parameter would be more important clinically.

Study Limitations

This study had 4 main limitations. First, the study cohort consisted only of Japanese men, which limits the applicability of the results to women and to other ethnicities. In particular, there is a difference in body fat distribution according to sex.⁴³ Second, smoking parameters were based on self-report, which could lead to potential misclassification and could underestimate the true association. Third, we could not examine the longitudinal influence of change in PFV according to change in smoking status because of the small size of the cohort and the short duration of observation. And finally, we could not examine the longitudinal influ-

ence of change in PFV according to change in heart rate because of the short duration of observation and small change in heart rate. Heart rate was recorded with high accuracy: it was measured after a 5-min rest using an automated sphygmomanometer unattended by medical staff. We examined the association between different variables at baseline and change in PFV. Next, we will attempt to elucidate the longitudinal effect of change in variables on PFV change.

Conclusions

PFV increased significantly over time in a cohort of Japanese men. The change in PFV was significantly and independently associated with smoking status and heart rate, suggesting that quitting smoking might reduce PFV. Further studies that examine the influence of increased PFV on cardiovascular disease (CVD) outcome are needed to contribute to CVD prevention.

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Disclosures

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Supplementary Files

Supplementary File 1

Table S1. Multivariate indicators of change in PFV in 546 men aged 40–79 years who did not change smoking status (SESSA; Shiga, Japan; 2006–2008 for baseline and 2010–2014 for follow-up)

Please find supplementary file(s);
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