Published in final edited form as:
Nutr Metab Cardiovasc Dis. 2011 May ; 21(5): 332–338. doi:10.1016/j.numecd.2009.10.010.

Pericardial Fat is Associated with Carotid Stiffness in the Multi-Ethnic Study of Atherosclerosis

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Abstract

Background and Aims—Arterial stiffness is a prominent feature of vascular aging and a risk factor for cardiovascular disease (CVD). Fat around the heart and blood vessels (i.e. pericardial fat, Pfat) may contribute to arterial stiffness via a local paracrine effect of adipose tissue on the surrounding vasculature. Thus, we determined the association between Pfat and carotid stiffness in 5,770 participants (mean age 62 yrs, 53% female, 25% African American, 24% Hispanic, and 13% Chinese) from the Multi-Ethnic Study of Atherosclerosis.

Methods and Results—Pfat was measured by computed tomography, and ultrasonography of the common carotid artery was used to calculate the distensibility coefficient (DC) and young's modulus (YM). Lower DC and higher YM values indicate stiffer arteries. Pfat quartile was highly associated with demographic, behavioral, anthropometric, hemodynamic, metabolic, and disease variables in both men and women. After adjusting for height, clinical site, CVD risk factors, and medications, a 1-standard deviation (41.91 cm^3) increment in Pfat was associated with a 0.00007±0.00002 1/mmHg lower DC (p=0.0002) in men and a 48.1±15.1 mmHg/mm higher YM in women (p=0.002). Additional adjustment for C-reactive protein, coronary artery calcification, and carotid intima-media thickness had only modest effects. More importantly, adjusting for body mass index and waist circumference did not significantly change the overall results.

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The authors have no disclosures to report.

Conclusion—Higher Pfat is associated with higher carotid stiffness, independent of traditional CVD risk factors and obesity.

Keywords

pericardial fat; arterial stiffness; distensibility; carotid artery

Introduction

Arterial stiffness, which occurs most notably in the large, elastic arteries (e.g. the aorta and carotid arteries), is a hallmark of the aging process and is characterized by fragmentation and degeneration of elastin, increases in collagen, wall thickening, and progressive dilation [1]. These structural changes are accompanied by increases in the pulse wave velocity, which causes the reflected wave to reach the heart at systole instead of diastole and pulsatile flow to extend further into the microcirculation. The consequences of arterial stiffening include increased systolic and pulse pressure, left ventricular (LV) hypertrophy, impaired myocardial perfusion, and small vessel degeneration in the brain and kidneys [2]. Accordingly, arterial stiffness is emerging as a key risk factor for atherosclerosis, myocardial infarction, stroke, dementia, renal disease, and mortality [1].

The mechanistic basis for age-related arterial stiffness is not well understood; however the presence of cardiovascular disease (CVD) risk factors, such as obesity, may accelerate vascular changes that contribute to arterial stiffening [1]. Indeed, arterial stiffness is higher in obese persons, and this association appears to be driven not by the total amount of fat mass, but by the location of the accumulated fat. While the focus has largely been on visceral fat accumulation in the abdominal region, it has been hypothesized that increased fat deposition around the heart and blood vessels (i.e. pericardial fat, Pfat) may affect cardiovascular structure and function [3]. For example, several studies show that increased Pfat is associated with LV hypertrophy and impaired cardiac function [4–6]. Pfat is also associated with CVD risk factors, coronary artery calcification (CAC), and metabolic syndrome [7–9]. However, to our knowledge, no studies have examined whether Pfat is related to arterial stiffness. Thus, we examined the association between Pfat and carotid artery stiffness in a large community-based cohort.

Methods

Study Population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective study of men and women from four different ethnic groups (Caucasian, African-American, Hispanic, Chinese) aged 45 to 84 years old and free of clinical CVD at baseline [10]. A total of 6,814 participants were recruited from Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and St. Paul, MN from 2000–2002. The study was approved by institutional review boards at participating institutions and all participants gave written informed consent. There were 468 participants missing Pfat measurements and 271 missing carotid stiffness measures. An additional 305 participants were missing data on pertinent covariates. Thus, the present analysis is based on the remaining 5,770 participants. The participants who were excluded from the analyses were similar with respect to gender, smoking status, and education, but were more likely to be Black (40% vs. 26%, $p<0.0001$), hypertensive (52% vs. 44%, $p<0.0001$), diabetic (18% vs. 12%, $p<0.0001$), and obese (42% vs. 30%, $p<0.0001$).

Pericardial Fat

Pfat encasing the coronary arteries was measured by computed tomography as described previously [11]. The superior extent of the left main coronary artery was identified in a cross-sectional scan and slices within 15 mm above and 30 mm below this slice were included in the measurement. Volume Analysis software (GE Healthcare, Waukesha, WI) was used to discern fat from the remaining portions of the heart with a threshold of −190 to −30 Hounsfield units.

Carotid Stiffness

High resolution B-mode ultrasound imaging of the carotid arteries was performed in the supine position using a GE scanner [12]. Every effort was made to examine the participants in the morning after an overnight fast and smoking cessation. The best acoustic window was identified with the jugular vein above the common carotid artery and a series of images was acquired over a 20 second period. On average 5 to 6 cardiac cycles were used for the estimation of carotid diameters. Blood pressure (BP) was determined by upper arm sphygmomanometry during acquisition of carotid artery measurements. These data were used to calculate the distensibility coefficient (DC) and young's modulus (YM) according to the approach described by Gamble et al. [13]:

$$\text{Distensibility Coefficient (DC)} = \frac{2\Delta D}{\Delta P D_s}$$

$$\text{Young's Modulus (YM)} = \frac{D\Delta P}{\Delta D h}$$

ΔD is the difference between systolic and diastolic diameter; ΔP is the difference between systolic and diastolic BP measured in the brachial artery; D_s is the systolic diameter; D is the average carotid artery diameter; and *h* is the wall thickness of the arterial segment. Stiffer arteries have low DC and high YM values.

Anthropometry

Weight was measured with a Detecto Platform Balance Scale (Detecto, Webb City, MO). Height was measured with an Accu-Hite Measure Device Stadiometer with level bubble (Seca, Hamburg, Germany). Waist circumference was measured at the umbilicus using a steel measuring tape with standard 4 ox tension (Gulick II, 150-cm anthropometric tape). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Other Covariates

Standard questionnaires were used to collect information on demographics, alcohol use, smoking status, medical history, and medication use. Physical activity was calculated as the total minutes of all moderate and vigorous activity multiplied by their respective metabolic equivalents (MET-min/wk). BP was measured in the right arm after 5 min in a seated position using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, FL). High-density lipoprotein (HDL) cholesterol levels were determined enzymatically on a Hitachi-911 instrument (GMI, Inc., Ramsey, MN). Low-density lipoprotein (LDL) cholesterol was estimated by the Friedewald equation. Glucose levels were measured on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Rochester, NY). C-reactive protein (CRP) was measured using the BNII nephelometer (Dade Behring, Deerfield, IL). Carotid intima-media thickness (IMT) was measured between lumen-intima and media-adventitia interfaces of near and far walls of the common and internal carotid arteries. A maximum IMT for each of these two segments was standardized, and the mean of the standardized IMT for the common and the internal carotid maxima was used in the

analysis. CAC was measured using either electron-beam or multidetector computed tomography [14]. The amount of calcium averaged from 2 scans was quantified using the Agatston scoring method [15]. The presence of CAC was defined as Agatston score > 0.

Statistical Analyses

All analyses were performed using SAS version 9.1. Chi-square tests and analysis of variance were used to compare differences in categorical and continuous variables, respectively, by gender-specific quartiles of Pfat. Pearson correlation coefficients were used to describe the relationship between fat measures. Linear regression models were used to quantify the association of Pfat with carotid stiffness. Interaction terms were examined to determine whether the association with carotid stiffness is modified by gender or race/ethnicity. Based on these findings, all models were stratified by gender (interaction $p \leq 0.03$). Models were initially adjusted for height (to account for the effect of body size on Pfat), demographics (i.e. age, race/ethnicity, education, and site), and behavioral factors (i.e. smoking status, alcohol use, and exercise). Subsequent models were adjusted for metabolic factors (i.e. lipids and glucose), systolic and diastolic BP, and medication use (i.e. lipid-lowering, anti-hypertensive, and anti-diabetic medications). Further analyses were conducted to determine whether Pfat is associated with carotid stiffness, independent of inflammation (i.e. CRP) and subclinical atherosclerosis, as assessed by CAC and carotid IMT. We also examined whether the association between Pfat and carotid stiffness is independent of BMI and waist circumference in models adjusted for demographics, behavior, BP, metabolic factors, and medication use. Associations with carotid stiffness were reported as a 1-standard deviation (SD) increment in fat measure. A p-value ≤ 0.05 was considered statistically significant.

Results

Subject Characteristic

The mean age of the participants was 62.1±10.2 yrs, 52.9% were female, and 25.3% were African American, 23.8% Hispanic, and 13.0% Chinese. Subject characteristics by gender-specific quartile of Pfat are shown in Table 1. Individuals in the highest quartile of Pfat were more likely to be older, less educated, obese, hypertensive, and diabetic, and less likely to be African American. In addition, Pfat quartile was associated with all demographic, behavioral, anthropometric, hemodynamic, metabolic, and disease variables. In both men and women, Pfat was associated with waist circumference ($r=0.46$, $p<0.0001$) and BMI ($r=0.53$, $p<0.0001$).

Multivariate Analyses

Regression analyses describing the association between Pfat and carotid stiffness are shown in Table 3. In men after adjusting for height, demographics, and behavioral factors, a 1-SD increment in Pfat was associated with a 38.7±10.8 mmHg/mm higher YM ($p=0.0003$) and a 0.00011±0.00002 1/mmHg lower DC ($p<0.0001$). After further adjustment for BP, metabolic factors, and medication use, the association between Pfat and carotid stiffness remained significant for DC ($p=0.0002$), but not YM ($p=0.06$). Additional adjustment for CRP and subclinical atherosclerosis had little effect on the relationship with DC ($p=0.0003$), although it slightly strengthened the association with YM ($p=0.01$). As shown in Table 3, adjusting for BMI and waist circumference strengthened the association between Pfat and YM ($p=0.006$), while the association with DC was attenuated, but remained significant ($p=0.02$). BMI and waist circumference were not independently associated with either stiffness measure.

In women after adjusting for height, demographics, and behavioral factors, a 1-SD increment in Pfat was associated with a 78.7±15.1 mmHg/mm higher YM ($p<0.0001$) and a 0.00014±0.00002 1/mmHg lower DC ($p<0.0001$). After further adjustment for BP, metabolic factors, and medication use, the association between Pfat and carotid stiffness remained significant for YM ($p=0.002$), but not DC ($p=0.06$). Additional adjustment for CRP and subclinical atherosclerosis had little effect on the relationship with YM ($p=0.003$). After adjusting for BMI and waist circumference, the association between Pfat and YM remained significant ($p=0.007$). As in men, BMI and waist circumference were not related to carotid stiffness in women (Table 3).

In an exploratory analysis, we examined whether the relationship between Pfat and carotid stiffness was altered by total obesity (non-obese vs. obese) or abdominal obesity (normal vs. high waist) (Table 4). Obese was defined as BMI >30 kg/m^2. A high waist circumference was defined as >102 cm in men and >88 cm in women. After adjustment for height, demographics, behavior, BP, metabolic factors, and medications, similar relationships between Pfat and carotid stiffness were found in men, regardless of the obesity subgroup. In contrast, the association between Pfat and carotid stiffness generally appeared to be ~2-fold stronger in women who were non-obese or had a normal waist circumference.

Discussion

Arterial stiffness is the most consistent manifestation of vascular aging, and occurs even in healthy individuals without any clinical CVD [1]. However, some individuals exhibit unsuccessful vascular aging characterized by increased arterial stiffness beyond that which occurs due to normal aging. The presence of CVD risk factors, such as increased visceral fat, may accelerate vascular changes that result in arterial stiffening [1]. Pfat is a visceral fat depot that potentially poses a significant risk for arterial stiffness due to its close proximity to the vasculature. Thus, in the present study we investigated the association between Pfat and carotid stiffness and found that 1) higher Pfat is associated with higher carotid stiffness in both men and women, and 2) the relationship between Pfat and carotid stiffness is independent of BMI and waist circumference.

There is strong evidence that Pfat affects cardiovascular structure and function. For example, Pfat has not only been associated with LV hypertrophy and impaired LV function, but is also a stronger predictor of LV mass than abdominal visceral fat, BMI, and waist circumference [4–6]. Similarly, Pfat was found to be a stronger predictor of coronary artery [4–6] disease in Japanese men than other measures of obesity [16]. In the Framingham study investigators reported that Pfat is highly associated with CAC, independent of abdominal visceral fat [17]. We and others have confirmed the association with CAC [9,11]. While Pfat is highly correlated with a number of metabolic factors [5,9,16–18], our data suggest that Pfat has independent effects on the vascular wall. In the present study we also observed strong associations between Pfat and CVD risk factors. Even after adjusting for these risk factors, Pfat was strongly associated with carotid stiffness. More importantly, Pfat was a stronger predictor of carotid stiffness than either BMI or waist circumference.

We also found that when stratifying by obesity, the association between Pfat and carotid stiffness was generally stronger in women, but not men, who were non-obese or had a normal waist circumference. Similar findings have been reported with other outcomes. Taguchi et al. found that the association between Pfat and coronary artery disease is stronger in lean vs. obese men [16]. Gorter et al. found that Pfat is associated with coronary artery disease severity and CAC only in patients with a BMI<27 kg/m^2 [7]. These findings suggest that having excess Pfat is more detrimental when the overall amount of body fat is low or normal. On the other hand, in obese persons the increased amount of fat mass throughout the

body may have cumulative effects that outweigh the risk of having excess fat in a more localized area.

It has been hypothesized that increased Pfat may compress the adjacent blood vessel and mechanically impair vascular function [19]. Another potential mechanism underlying the association between Pfat and arterial stiffness is altered adipokine-mediated signaling between adipose tissue and blood vessels, which may contribute to arterial stiffness and subsequent CVD through pathways involving oxidative stress, endothelial dysfunction, and inflammation. Pfat is highly lipolytic and has a high expression of chemokines and inflammatory cytokines [18,20]. Fat around blood vessels has also been shown to promote vascular smooth muscle cell growth, vasoconstriction, and inflammatory cell recruitment [21–23]. Thus, in the presence of excess Pfat, these pro-inflammatory activities are likely to be increased and thereby promote the development of vascular dysfunction. We were surprised to find that adjustment for CRP, CAC, and carotid IMT generally did not alter the relationship between Pfat and carotid stiffness. However, systemic levels of inflammatory markers do not correlate well with local inflammation at the tissue level. In addition, although arterial stiffness and atherogenesis share common pathological processes, their etiologies are very distinct.

There are a few limitations in this study. First, this study was cross-sectional and therefore we cannot determine whether an increase in Pfat causes carotid stiffness. Second, carotid stiffness indices were calculated using brachial BP rather than carotid BP. This approach is generally considered less accurate due to pulse pressure amplification between central and peripheral arteries, which can be altered with aging. However, we do not believe that this would differentially affect the observed associations with Pfat in this population of middle-aged and older men and women. Third, because we did not measure adipokines in this study, we cannot address whether they play a mediating role in the association between Pfat and carotid stiffness. Fourth, waist circumference was used as a measure of abdominal obesity, which provides no distinction between subcutaneous and visceral fat areas. Although waist circumference is highly correlated with abdominal visceral fat, we cannot determine whether the association between Pfat and carotid stiffness is independent of visceral fat. Similarly, we cannot rule out the possibility that fat adjacent to the carotid arteries is driving the association between Pfat and carotid stiffness, as these fat depots are likely to be highly correlated. Nevertheless, we are the first to describe the association between Pfat and arterial stiffness in a large, multi-ethnic population of men and women. We found that higher Pfat is associated with higher carotid stiffness, independent of traditional CVD risk factors and obesity. Although more studies are needed to address whether fat around the heart and blood vessels is a distinct risk factor or simply a marker of visceral fat, this fat depot may prove to be a therapeutic target in reducing CVD morbidity and mortality.

Abbreviations

BMI	body mass index
BP	blood pressure
CAC	coronary artery calcification
CRP	C-reative protein
CVD	cardiovascular disease
DC	distensibility coefficient
HDL	high-density lipoprotein

IMT	intima-media thickness
LDL	low-density lipoprotein
LV	left ventricular
Pfat	pericardial fat
YM	young's modulus

Acknowledgments

This work was supported by an individual grant R01-HL-085323 and contracts N01-HC-95159 through N01-HC-95169 and from the National Heart, Lung, and Blood Institute. The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

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Nutr Metab Cardiovasc Dis. Author manuscript; available in PMC 2012 May 1.

Table 1

Subject characteristics by gender-specific pericardial fat quartile

Characteristic	Quartile 1 (n=1441)	Quartile 2 (n=1443)	Quartile 3 (n=1443)	Quartile 4 (n=1443)	P-value
Age, yrs	58.5±0.3	61.3±0.3	63.8±0.3	65.1±0.3	<0.0001
Female, %	52.9	52.9	52.9	52.9	--
Race, %					<0.0001
Caucasian	35.0	34.9	37.9	46.2	
African American	37.3	27.1	22.7	15.3	
Hispanic	15.3	21.0	26.8	28.7	
Chinese	12.4	17.0	12.6	9.8	
Education, %					<0.0001
Less than high school	11.2	16.7	20.8	23.6	
High school diploma	15.1	16.6	19.1	21.2	
Some college/technical school	28.8	29.3	28.5	27.4	
College graduate and beyond	44.8	37.4	31.6	27.8	
Alcohol use, %					0.009
Never	17.6	20.5	22.6	21.3	
Former	22.6	22.7	23.3	24.9	
Current	59.8	56.8	54.1	53.9	
Smoking status, %					<0.0001
Never	53.3	52.5	51.4	46.0	
Former	32.1	34.7	35.7	42.2	
Current	14.6	12.8	12.9	11.9	
Exercise, MET-min/wk	1947±62	1610±62	1501±62	1250±62	<0.0001
BMI, kg/m^2	24.9±0.1	26.9±0.1	28.8±0.1	31.8±0.1	<0.0001
Waist circumference, cm^2	87.6±0.3	94.4±0.3	100.1±0.3	108.4±0.3	<0.0001
Height, cm	167.0±0.3	166.2±0.3	165.9±0.3	165.8±0.3	0.007
Systolic BP, mmHg	120.4±0.6	124.0±0.6	128.4±0.6	131.5±0.6	<0.0001
Diastolic BP, mmHg	70.9±0.3	71.4±0.3	72.0±0.3	72.6±0.3	<0.0001
LDL cholesterol, mg/dL	114.4±0.8	119.1±0.8	119.2±0.8	116.9±0.8	<0.0001
HDL cholesterol, mg/dL	56.2±0.4	52.1±0.4	49.8±0.4	46.8±0.4	<0.0001

Characteristic	Quartile 1 (n=1441)	Quartile 2 (n=1443)	Quartile 3 (n=1443)	Quartile 4 (n=1443)	P-value
Triglycerides, mg/dL	101.2±1.7	120.1±1.7	132.2±1.7	151.6±1.7	<0.0001
Glucose, mg/dL	90.3±0.8	94.0±0.8	98.2±0.8	104.1±0.8	<0.0001
Diabetes, %	6.6	8.8	12.8	18.4	<0.0001
Hypertension, %	31.1	37.3	48.7	57.0	<0.0001
C-reactive protein, mg/L	2.8±0.2	3.2±0.2	4.1±0.2	4.6±0.2	<0.0001
Maximum IMT - internal carotid, μm	0.95±0.02	1.02±0.02	1.09±0.02	1.19±0.02	<0.0001
Maximum IMT - common carotid, μm	0.81±0.01	0.86±0.01	0.90±0.01	0.91±0.01	<0.0001
Presence of CAC, %	37.1	45,3	53.1	63.1	<0.0001

Table values are means±SE or percentage.

Table 2

Gender-stratified regression models for the association between pericardial fat and carotid stiffness

	Men (n=2719)		Women (n=3051)	
Model	**β±SE**	**P-value**	**β±SE**	**P-value**
Young's modulus				
Unadjusted	33.5±10.4	0.001	131.5±14.5	<0.0001
Adjusted for height, demographics, and behavior	38.7±10.8	0.0003	78.7±15.1	<0.0001
Plus BP, metabolic factors, and medications	20.7±11.2	0.06	48.1±15.8	0.002
Plus CRP, CAC, and carotid IMT	28.3±11.1	0.01	46.8±15.7	0.003
Distensibility coefficient				
Unadjusted	−0.00013±0.00002	<0.0001	−0.00030±0.00002	<0.0001
Adjusted for height, demographics, and behavior	−0.00011±0.00002	<0.0001	−0.00014±0.00002	<0.0001
Plus BP, metabolic factors, and medications	−0.00007±0.00002	0.0002	−0.00004±0.00002	0.06
Plus CRP, CAC, and carotid IMT	−0.00007±0.00002	0.0003	−0.00004±0.00002	0.13

Regression coefficients are reported per 1 SD increment in pericardial fat (41.91 cm^3).

Table 3

Gender-stratified regression models for the association between pericardial fat and carotid stiffness, after adjustments for demographics, behavioral factors, BP, metabolic factors, medications, BMI, and waist circumference

	Men		Women	
	β±SE	**P-value**	**β±SE**	**P-value**
Young's Modulus				
Pericardial fat	38.3±13.9	0.006	50.2±18.5	0.007
BMI	−55.5±33.4	0.10	2.1±20.6	0.92
Waist circumference	9.9±31.9	0.76	−6.2±20.4	0.76
Distensibility Coefficient				
Pericardial fat	−0.00005±0.00002	0.02	0.00003±0.00003	0.29
BMI	−0.00002±0.00005	0.73	−0.00006±0.00003	0.07
Waist circumference	−0.00001±0.00005	0.77	−0.00004±0.00003	0.14

Table values are regression coefficient ± SE reported per 1 SD unit increment in fat measure. The population SD was used as follows: pericardial fat, 41.91 cm^3; BMI, 5.35 kg/m^2; and waist circumference, 14.23 cm.

Table 4

Relationship between pericardial fat and carotid stiffness in men and women stratified by obesity subgroup

	Men		Women	
	Obese (n=720)	**Non-Obese (n=1999)**	**Obese (n=1038)**	**Non-Obese (n=2013)**
Young's Modulus	21.3±18.4	26.0±16.7	33.3±24.4	68.4±24.6[a]
Distensibility Coefficient	−0.00004±0.00003	−0.00006±0.00003[b]	0.00002±0.00003	−0.00005±0.00007
	High Waist (n=989)	**Normal Waist (n=1730)**	**High Waist (n=2072)**	**Normal Waist (n=979)**
Young's Modulus	27.5±16.4	14.9±19.7	43.5±18.8[b]	88.7±41.4[b]
Distensibility Coefficient	−0.00007±0.00003[b]	−0.00006±0.00003	−0.000004±0.00003	−0.00005±0.00007

Table values are regression coefficients ± SE per 1 SD increment in pericardial fat, adjusting for height, demographics, behavior, BP, metabolic factors, and medications. Obese is defined as BMI >30 kg/m^2. High waist is defined as >102 cm in men and >88 cm in women.

Statistically significant, [a]$p \leq 0.01$,

[b] $p \leq 0.05$.