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Associations among Lung Function, Arterial Elasticity and Circulating Endothelial and Inflammation Markers: the Multi-Ethnic Study of Atherosclerosis

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Abstract

A parallel physiologic pathway for elastic changes is hypothesized for declines in arterial elasticity and lung function. Endothelial dysfunction and inflammation could potentially decrease elasticity of both vasculature and lung tissue. We examined biomarkers, large (LAE) and small (SAE) arterial elasticity, and forced vital capacity (FVC) in a period cross-sectional design in the Multi-Ethnic Study of Atherosclerosis, which recruited 1,823 women and 1,803 men, age range 45–84 years, black, white, Hispanic, and Chinese, free of clinically recognized CVD. Radial artery tonometric pulse waveform registration was performed and LAE and SAE were derived from diastole. Spirometric data and markers of endothelial dysfunction and inflammation (soluble intracellular adhesion molecule-1, fibrinogen, hs-C-reactive protein, and interleukin-6) were obtained. Mean LAE was 13.7 ± 5.5 ml/mmHgx10 and SAE was 4.6 ± 2.6 ml/mmHgx100. Mean

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FVC was 3,192 ± 956.0 mL and FEV1 was 2,386 ± 734.5 mL. FVC was about 40 ± 5 mL higher per SD of SAE, stronger in men than women. The association was slightly weaker with LAE, with no sex interaction. After regression adjustment for demographic, anthropometric, and cardiovascular risk factors, the biomarkers tended to be related to reduced SAE and FVC, particularly in men. These biomarker associations suggest important CVD risk alterations that occur concurrently with lower arterial elasticity and lung function. The observed positive association of SAE with FVC and with FEV1 in middle-aged to older free-living people is consistent with the hypothesis of parallel physiologic pathways for elastic changes in the vasculature and in lung parenchymal tissue.

Keywords

arterial stiffness; endothelial markers; inflammatory markers; large and small artery elasticity; lung function; MESA Study

Lung function predicts cardiovascular disease (CVD) and mortality[1,2]. Inter-individual variation in lung function in early adulthood is associated with future development of hypertension[3,4,5]. Our recent study in the Coronary Artery Risk Development in Young Adults (CARDIA) cohort showed that forced vital capacity (FVC) change from peak, still within the normal range of FVC, significantly predicted incidence of arterial hypertension during the subsequent 10 year follow-up[6].

Arterial elasticity is a subclinical marker for cardiovascular disease (CVD) morbidity and mortality[7–12]. Arterial elasticity is derived from the continuous blood pressure curve and is therefore related to but conceptually broader than systolic and diastolic blood pressure. We demonstrated in the Multi-Ethnic Study of Atherosclerosis (MESA) that small artery elasticity (SAE) and to a lesser extent large artery elasticity (LAE) predicts the incidence of development of hypertension in normotensive subjects[13].

Although the relationship between lung function decline and the incidence of hypertension is clear, the mechanisms underlying these associations are not. Our hypothesis is that the association between decline in lung function and CVD events and hypertension might be mediated by common changes in elasticity of the lung parenchymal tissue and arterial vasculature that result both in a lower FVC and in a decrease of elasticity of the arterial wall. Furthermore, we assert that common inflammatory pathways link arterial elasticity and lung function. Therefore, the purpose of this study was to examine the relationship between arterial elasticity and lung function measures in MESA using a period cross-sectional design. In light of an observed association between arterial elasticity and lung function, we explored biomarkers of inflammation and endothelial dysfunction that might reflect shared underlying pathways.

METHODS

Study Participants

The MESA study cohort[14] included 6,814 men and women aged 45–84 y of four race/ethnicities, recruited in 2000-2002 in six U.S. communities to study the characteristics of subclinical cardiovascular disease. The sample was free of clinically recognized CVD. The protocols of MESA and all studies described herein were approved by the institutional review boards of all collaborating institutions and the NHLBI and signed informed consent was obtained.

Study Parameters

Large (LAE) and small (SAE) artery elasticity measurements—Arterial elasticity was assessed at baseline in 6,336 of MESA participants[12,13]. Arterial wave forms were recorded using the HDI/PulseWave CR2000 (Hypertension Diagnostics, Inc., Eagan, Minnesota)[15,16]. A tonometer (Arterial PulseWave(tm) Sensor, HDI, Inc.) was placed over the radial artery to achieve a stable 30 second analog tracing of the radial waveform on the supine participant. The waveform was digitized at 200 samples per second. Before the waveform assessment, an automated oscillatory blood pressure measurement (oscillatory device built into the HDI/PulseWave CR2000) was also taken on the contra-lateral arm and systolic and diastolic pressures were recorded and computer stored. The device used the pressure waveform to estimate quantities X=LAE*systemic vascular resistance (SVR) and Y=SAE*SVR. SVR was estimated from physical measures including height, weight, age, heart rate (HR), and mean arterial blood pressure (BP). LAE and SAE were then estimated by dividing X and Y by estimated SVR. Since findings were not substantially different for LAE*SVR and for SAE*SVR, we present only findings for LAE and SAE.

Lung Function—Spirometry was conducted in accordance with American Thoracic Society/European Respiratory Society guidelines[17] on a dry-rolling-sealed spirometer with automated quality checks (Occupational Marketing, Inc., Houston, TX) and over-reading by one investigator[18]. Predicted values were calculated using reference equations from the National Health and Nutrition Examination Survey III[17,19] with an 0.88 correction for Asians[18]. Spirometry was performed in 3965 MESA participants at either MESA examination 3 or 4 (2003–2008), a median of 5 years after measurement of arterial elasticity. Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and FEV_1/FVC ratio were assessed. We excluded anyone with invalid spirometry, failure to perform tonometry and missing values of cigarette pack-years. These exclusions reduced the sample by 230. Further exclusion of those with self-reported COPD (47 severe) using separate items derived from both the MESA Lung and the MESA questionnaires did not greatly affect estimated associations, so participants with signs of COPD were retained in the analysis.

Biomarkers—The following biomarkers were studied: soluble intercellular adhesion molecule-1 (sICAM-1), fibrinogen, high sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6). Assessment of sICAM-1 was in a selection of participants (n=2,622); the characteristics of the selected subset do not differ from those of the entire MESA cohort. Fasting (>8 hours) blood samples were drawn from participants on the day of the radial artery pulse wave registration, and aliquots were stored at −70°C and centrally analyzed at the University of Vermont and the University of Minnesota. sICAM-1 was measured by an ELISA assay (Parameter Human sICAM-1 Immunoassay; R&D Systems, Minneapolis, MN). (Burlington, VT). Fibrinogen antigen is measured using the BNII nephelometer (N Antiserum to Human Fibrinogen; Dade Behring Inc., Deerfield, IL). Intra-assay and inter-assay analytical CVs are 2.7% and 2.6%, respectively, Hs-CRP is measured using the BNII nephelometer (N High Sensitivity CRP; Dade Behring Inc., Deerfield, IL). Intra-assay and inter-assay analytical CVs range from 2.3 – 4.4% and 2.1 – 5.7%, respectively. IL-6 is measured by ultra-sensitive ELISA (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN). The laboratory analytical CV for this assay is 6.3%.

Statistical analysis—We restricted the analysis to those with data available on lung function (n=3,965). After further exclusion of participants with missing biomarker or covariate data, 3,635 participants remained (1,480 for sICAM-1; see Table 1). The study design was period cross- sectional. Lung variables were always used as dependent variables because lung function was measured about 5 years after other variables. Linear regression

models included SAE and LAE predicting FVC, followed by parallel analyses in which FEV1 was predicted. Because of high correlation between FVC and FEV1, findings for FEV1 are similar to those for FVC (data not shown). There were no associations with FEV1/FVC (data not shown). We performed all analyses separately for men and for women for two reasons: we observed much higher coefficients predicting FVC and FEV1 in men than in women for two important covariates: height and heart rate (HR), and associations of SAE with lung function were stronger in men than in women. Predictor variables were modeled as continuous; goodness of fit of linear models was found to be adequate by visual examination of associations in which predictors were modeled in gender-specific quartiles. Where indicated, continuous variables were reported in standard deviation units. We tested interactions with a t-test comparing the gender-specific regression coefficients. Covariates in regression models were age, race/ethnicity, gender, clinical site, height, HR, BP and medication, body mass index (BMI), waist circumference, cigarette smoking, and blood lipids (LDL-cholesterol, HDL-cholesterol, and triglycerides). Inclusion of both BMI and waist (r= 0.88 in women and 0.91 in men) as covariates removes a small amount of confounding beyond a model that included only one of them. Because they are highly correlated, we verified that collinearity was not a problem, that is, that the coefficient and standard error of the coefficient of the predictor of interest in each model changed by a reasonable amount in the model that included both BMI and waist compared to models that included only one of them. We considered statistical significance when $p<0.05$.

RESULTS

Men and women differed on height, HR, diastolic BP, mean arterial BP, pulse pressure (PP) (Table 1). Smoking status and hs-CRP. LAE, SAE, FVC and FEV1 were higher in men compared to women, while FEV1/FVC was lower in men than women. The correlation between FEV1 and FVC was r=0.93. Fibrinogen, hs-CRP and IL-6 were higher in women than men, while there was no gender difference regarding s-ICAM. In Table 2, FVC, LAE, and SAE correlated similarly with age, height, HR, and BP, but oppositely with BMI and waist circumference (waist data not shown).

Associations of Lung Function with Arterial Elasticity

Estimates pooled across gender were that both FVC and FEV1 (data not shown) were about 20–80 mL higher per SD of LAE or SAE. The SAE difference was substantially larger in men than in women, while the LAE difference did not vary significantly by gender (Table 3). Associations of arterial elasticity with FEV1 were similar to those shown in Table 3 (data not shown). Associations were similar in those with and without hypertension and across race/ethnicity groups (data not shown).

Associations of Lung Function with Arterial Elasticity with Endothelial and Inflammatory Markers

Table 4 summarizes the gender-specific distributions of the endothelial marker and three inflammatory markers. Means of all biochemistries were within the normal range. In men, SAE was 4–6% of a standard deviation of lower per SD of the biomarker, significant for hs-CRP and for IL-6. No associations of the biomarkers with SAE were seen in women, although no test for sex-interaction achieved statistical significance. No biomarker was associated with LAE. FVC was about 3–4% of a standard deviation (about 30–40 mL) lower per biomarker standard deviation in both sexes, achieving statistical significance except for sICAM-1 in men.

DISCUSSION

In this study of Caucasian, African-Americans, Hispanics and Chinese with an age range of 45 – 84 years, SAE and LAE were associated with FVC and FEV1 measured 5 years later independently of measured confounding factors. Neither measure was associated with FEV1/FVC. This study was performed as part of a series of linked studies on associations among lung function and blood pressure. We described in the CARDIA study cohort that a decline in lung function within the normal range predicted arterial hypertension[6]. We also demonstrated in MESA that SAE and to a lesser LAE predicted arterial hypertension in normotensive asymptomatic subjects[13]. Therefore we hypothesized that arterial elasticity was also associated with lung function.

There is very limited information regarding the association of lung function and arterial elasticity (or its inverse, arterial stiffness) in generally healthy adults. Jankowich et al.[20] studied the relationship between pulse pressure, a surrogate marker of arterial stiffness, and FEV1 in a well-defined cohort of 13,090 men and women examined in the NHANES study, demonstrating a significant inverse relationship in those over 40 years old. In a substudy of Whitehall II[21], the investigators found an inverse association between the carotid-femoral pulse wave velocity (cfPWV) and lung function (n = 4234 participants, 55–78 years old) even after adjustment for age, gender, ethnic group, PP, mean arterial BP, HR, antihypertensive treatment and chronic disease. Neither of these studies provided gender-specific findings. In 194 men free of coronary heart disease, age range 30–70 years, Zureik et al.[22] found that cfPWV was significantly, negatively, and independently associated with FVC and FEV1. The Caerphilly Prospective Study[23] also found FVC and FEV1 to be inversely associated with cfPWV but the measures in mid-life were the stronger predictors compared to later life.

The mechanistic underpinning of these associations is largely unknown. The most plausible explanation is that alterations in lung function and arterial function stem at least in part from the same pathophysiological process. A common process could be a loss of arterial elasticity, particularly in the small arteries, and of elastic recoil of the lung tissue. Recently we found in the CARDIA (Coronary Artery Risk Development in Young Adults) study that a decline in FVC from peak at average age 29.4 years to average age 35 predicted incident hypertension between average ages 35 and 45[6]. These results increased our understanding of the association between lung function and CVD by postulating arterial hypertension as an important intermediary. Consistent with our prior work, the current study found the addition of arterial elasticity provided an additional predictor to the model that already included blood pressure and antihypertensive treatment, moving us beyond the findings in CARDIA. SAE is not only predictive for CVD events in asymptomatic subjects[12], but in a previous study performed in MESA, we demonstrated that SAE has a predictive value for the development of arterial hypertension[13] and of decline of kidney function[24]. The Malmö study[25] has also shown associations of lung function with incident heart failure, which is often the result of hypertension. A composite judgment plausibly links lung function, arterial elasticity, hypertension, and future CVD.

In the limited available information in the literature regarding the inverse association of arterial stiffness/elasticity and lung function, the majority of the studies were done exclusively in men, thus generally without explicit information about gender difference. The association between SAE and lung function was more prominent in men than in women. Height and heart rate were important variables that also differed by gender in their levels and in their prediction of lung function.

In this multi-ethnic study population free of overt CVD, biomarkers of inflammation and endothelial dysfunction were inversely associated with SAE and FVC. Although our data were period cross-sectional, this pattern of findings whereby markers of inflammation and endothelial dysfunction relate to both SAE and FVC invokes the concept that there are common changes in the lung tissue and arterial vasculature. It is possible that these changes, in turn, may precede and contribute to CVD events that have been reported to be associated with SAE[12] and with lung function[1,2].

We hypothesized that endothelial dysfunction and inflammation might be common causes that were correlated with both SAE and FVC. These associations were confirmed in this manuscript, strengthening the assertion of a common pathway of inflammation at the level of the vasculature and the lung tissue.

Systemic inflammation associated with reduced lung function and adhesion molecules figure prominently in initiating the inflammatory response. ICAM-1 is expressed on the surface of pulmonary vascular endothelial cells and type II pneumocytes[26]. ICAM-1 plays a key role in the recruitment of neutrophils to activated endothelial cells, contributing in this way to the inflammatory response[27]. Ongoing lung injury and vascular inflammation both result in increased secretion of pro-inflammatory cytokines. Inflammation causes vascular dysfunction and perpetuates proatherosclerotic processes. In our study IL-6 was inversely associated with SAE in men and FVC. The Framingham Study assessed twelve circulating inflammatory biomarkers in relation to tonometry variables including central pulse pressure, mean arterial pressure, forward pressure wave, reflected pressure wave, cfPWV and augmentation index[28]. Of these circulating inflammatory biomarkers, IL-6 was positively associated with cf PWV. In a sample of untreated hypertensive patients, Mahmud and Feely showed that IL-6 was positively associated with cfPWV and augmentation index[29].

Hs-CRP is the most frequently studied biomarker in association with arterial stiffness in health and disease. Our study demonstrated a significant inverse association of hs-CRP with SAE in men and FVC. Several studies found similar results. For example, hs-CRP is associated with cfPWV and augmentation index in younger and older apparently healthy subjects[30]. In the Rotterdam study, hs- CRP was positively associated with cfPWV but not with the carotid distensibility among asymptomatic subjects older than 55 years[31]. A cross sectional study of Japanese healthy subjects has demonstrated that brachial ankle PWV was independently correlated with serum hs-CRP levels after adjustment for other established cardiovascular risks factors[32].

Recently a few studies have been published regarding the association of CRP with lung function. In the Women's Health and Aging Studies I and II, a combined elevation of IL-6 and hs-CRP was associated with the lowest pulmonary function levels in older women[33]. Gimeno et al.[34] examined hs-CRP and I1–6 and the change in their concentrations over 12 years after baseline in relation to FVC and FEV1 in 1500 participants, free from self-reported respiratory problems in the Whitehall II Study. Higher baseline levels of hs-CRP and IL-6 were strongly associated with lower FVC and FEV, independent of potential cofounders. A 10% increase in serum hs-CRP from baseline to follow-up was associated with lower values of FVC and FEV1 at follow-up, 4.7 ml and 3.0 ml respectively. The corresponding values for a 10% increase in IL-6 were 12.6 ml for FVC and 7.3 ml FEV1. In the Caerphilly Prospective Study, the association between lung function parameters, hs-CRP and CRP polymorphisms were assessed[35]. Serum hs-CRP at baseline was inversely associated with contemporaneous FEV1 and FVC as well as at follow-up even after adjustment for conventional confounders. As was seen in relation to PWV[36], there were no clear associations of the polymorphisms or haplotypes with lung function or with lung function decline, again casting doubt on whether hs-CRP is causally related to lung function.

In the current study, fibrinogen was inversely associated with SAE in men and FVC. Fibrinogen is a well known coagulation factor but, in addition it is an important acute-phase protein and influences several processes such as inflammation and matrix interactions. Vlachopoulos et al.[36] found in normotensive and untreated hypertensive subjects that fibrinogen level was not correlated with carotid-radial PWV and lost its association with augmentation index after multivariable adjustment. However, even in multivariable analysis, an independent association was established between fibrinogen level and carotid-femoral PWV. In the Caerphilly prospective study the only independent baseline predictor of the augmentation index after 20 years was fibrinogen[37]. In the CARDIA study by Thyagarajan et al.[38] fibrinogen was associated with a modest deterioration in lung function (decrease in FVC and FEV1 but unrelated to their ratio) after 5 and 10 year follow-up.

Strengths and limitations

The results of this study should be viewed in light of several limitations. First, common to all observational studies, unmeasured confounding could be a problem. Although lung function was assessed several years after arterial elasticity assessment, we regard the study as period cross-sectional in nature, and do not feel confident in inferring the direction of the relationship between lung function and SAE and LAE in time. The strength of the present analysis is the large number of generally healthy men and women of different ethnicities and the high-quality of the spirometric, arterial elasticity, and biomarker data. We have no direct comparison of LAE and SAE with carotid-femoral pulse wave velocity. However the strong predictive value of SAE of CVD generally and of LAE for heart failure as reported by the MESA study should be taken into consideration (12, 13), even by those who criticize the Windkessel model itself.

In conclusion, this study suggested that there is a positive and independent association of SAE and FVC in a multi-ethnic population free of overt cardiovascular and lung disease. Markers of inflammation and endothelial dysfunction are related to lower arterial elasticity (in men) and to lung function (in men and women). This finding supports the hypothesis that a common pathway exists in the development of arterial stiffness, hypertension and decline in lung function. Longitudinal and interventional studies are needed to establish the directionality of these relationships and whether they reflect common pathways as we propose here.

Perspectives

Although the vasculature and the lung are distinct body systems, early detection of decrease in arterial elasticity and lung function can each be helpful diagnostic steps in preventing both future cardiovascular and pulmonary disease. Inflammation and endothelial dysfunction seem to be the common pathological pathway in deterioration of these body systems. This pathway which should be targeted by new preventive therapeutic strategies. Accelerated aging is the end consequence of inflammation and endothelial dysfunction, which promotes subclinical conditions including arterial stiffening and lung function decline. We speculate that the process of fibrosis plays a key role in these pathological processes. Systolic hypertension, diastolic heart failure with preserved ejection fraction and chronic obstructive pulmonary disease are likely to be major health economic burdens for the next decades. To delay the processes of cardiovascular and pulmonary aging that are suggested in the present paper, the study of fibrotic markers in relation to arterial stiffness and decline in lung function should be investigated, with a goal towards development of potential anti-inflammatory and anti-fibrotic therapy in early stages of cardiovascular and lung disease.

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Abbreviations

BMI	body mass index
BP	blood pressure
CVD	cardiovascular disease
hs-CRP	high sensitivity C-reactive protein
FVC	Forced Vital Capacity
FEV1	Forced expiratory volume in 1 second
FEV1/FVC	Ratio of FEV1 to FVC
HDL	high density lipoprotein
HR	heart rate
sICAM-1	soluble intercellular adhesion molecule
IL-6	interleukin 6
LAE	large artery elasticity
LDL	low density lipoprotein
SAE	small artery elasticity
SD	standard deviation
SVR	systemic vascular resistance

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Novelty and Significance

What is New?

Markers of inflammation and endothelial function are inversely associated with arterial elasticity and lung function in multi-ethnic participants free of clinical cardiovascular disease.

What is Relevant?

Supporting our previous finding that a small decline in lung function at young age precedes development of arterial hypertension, common pathways of inflammation relate to changes in both lung and vasculature.

Summary

Our study adds new cross-organ system insights into the etiology of hypertension. In this way, our findings could ultimately contribute to prevention or treatment of hypertension.

Table 1

Sex-specific distributions of demographics, variables involved in the estimation of arterial elasticity, endothelial and inflammation markers, and lung function: The MESA Study, 2000–2002.

Characteristics	Female (N=1832)		Male (N=1803)		
	Mean or %	SD	Mean or %	SD	p-value
Age (yr)	65.3	9.7	65.4	9.8	0.73
Race/ethnicity					
White (column %)	35		36		0.68
Chinese (column %)	16		17		
Black (column %)	25		25		
Hispanic (column %)	24		23		
Height (cm)	159.2	7.2	172.8	7.5	<0.001
Heart rate (beats/min)	64.9	9.6	62.0	10.1	<0.001
Systolic blood pressure (mmHg)	124.1	21.2	124.8	17.9	0.32
Diastolic blood pressure (mmHg)	68.5	10.0	75.1	8.9	<0.001
Hypertension (%≥140/90/Rx)	45		45		1.00
Body mass index (kg/m^2)	28.5	6.2	27.7	4.5	<0.001
Waist (cm)	97.1	16.0	99.0	12.4	<0.001
Cigarette smoking					
Current (%)	11		14		<0.001
Former (%)	26		46		
	Median	IQR	Median	IQR	
Endothelial Marker					
sICAM-1, ng/mL	266.8	228.8–310.3	263.5	226.0–305.0	0.56
Inflammatory/Hemostatic marker					
Fibrinogen, mg/dL	350	306.5–400	320	282.0–367.0	<0.001
General Inflammatory Markers					
hs-C-reactive protein (CRP), mg/L	2.4	0.9–5.4	1.3	0.7–2.8	<0.001
Interleukin-6 (IL-6), pg/mL	1.2	0.8–1.9	1.1	0.7–1.7	0.001
	Mean or %	SD	Mean or %	SD	
Arterial elasticity					
Large artery elasticity (ml/mmHg*10)	12.0	5.0	15.3	5.5	<0.001
Small artery elasticity (ml/mmHg*100)	3.9	2.4	5.4	3.1	<0.001
Lung Function					
Forced Vital Capacity (FVC) (mL)	2590	612	3813	842	<0.001
Forced Expiratory Volume (FEV1) (mL)	1978	497	2806	701	<0.001
FEV1/FVC Ratio (%)	76.0	8.0	74.0	9.0	<0.001

BMI, body mass index; sICAM-1, soluble intercellular adhesion molecule; hs-CRP, high sensitive C-reactive protein; IL-6, Interleukin-6; Rx = treatment for hypertension; IQR, Inter-quartile range; FVC, Forced Vital Capacity; FEV, Forced expiratory volume in 1 second; FEV1/FV, Ratio of FEV1 to FVC; LAE, large artery elasticity; SAE, small artery elasticity; SD, standard deviation; SVR, systemic vascular resistance

Sample size for sICAM-1: 805 women and 675 men; for IL-6 1800 women and 1755 men

Table 2

Correlations (r) of large and small arterial elasticity and Forced Vital Capacity (FVC) with several variables, n = 3635.

Characteristics	Large artery elasticity (ml/mmHg*10)	Small artery elasticity (ml/mmHg*100)	Forced Vital Capacity (mL)
Age (years)	−0.36	−0.43	−0.45
Height (cm)	0.29	0.26	0.49
Heart rate (beats/minute)	−0.27	−0.05	−0.11
Systolic blood pressure (mmHg)	−0.36	−0.36	−0.25
Hypertension (%≥140/90 mmHg or using medication)	−0.24	−0.26	−0.25
Body Mass Index (kg/m^2)	0.06	0.14	−0.08

*Adjusted for sex; all statistically significant correlation at p<0.006.

Table 3

Multivariable linear regression of the relationship of small and large arterial elasticity (SAE, LAE) (standard deviation units) with forced vital capacity (FVC) as the dependent variable.

Characteristics	FVC, mL					
	Female (n=1,832)			Male (n=1,803)		
	b	SE	p	b	SE	p
SAE (per SD = 2.9 ml/mmHg *100)	28.3	13.4	0.03	78.0	15.4	<0.001
LAE (per SD = 5.6 ml/mmHg*10)	33.3	13.0	0.01	21.3	17.5	0.22

Each row is a separate regression model. Gender specific models were run independently for each arterial elasticity variable and adjusted for age, race/ethnicity, site, height, waist circumference, body mass index, heart rate, systolic and diastolic blood pressure, antihypertensive medications, smoking status, cholesterol, high density lipoprotein cholesterol, triglycerides, lipid lowering medication, and diabetes. P for interaction between genders for SAE and for SAE*SVR was <0.015, for LAE and for LAE*SVR was >0.5.

Table 4

Multivariable linear regression of biomarkers of inflammation status with small and large arterial elasticity (SAE, LAE) and forced vital capacity (FVC).

Biomarkers	Female (n=1,832)			Male (n=1,803)		
	b	SE	p	b	SE	p
	Dependent variable					
	SAE (per SD = 2.9 ml/mmHg *100)					
sICAM-1 (per SD = 78.5 ng/mL)	−0.008	0.031	0.78	−0.047	0.039	0.23
Fibrinogen (per SD = 70.3 mg/dL)	−0.004	0.018	0.82	−0.040	0.024	0.10
hs-CRP (per SD = 5.41 mg/L)	−0.002	0.018	0.93	−0.050	0.022	0.02
IL-6 (per SD = 1.15 pg/mL)	−0.018	0.018	0.30	−0.056	0.023	0.02
	Dependent variable					
	LAE (per SD = 5.6 ml/mmHg*10)					
sICAM-1 (per SD = 78.5 ng/mL)	−0.007	0.029	0.80	0.001	0.034	0.97
Fibrinogen (per SD = 70.3 mg/dL)	−0.011	0.019	0.57	0.013	0.021	0.55
hs-CRP (per SD = 5.41 mg/L)	−0.005	0.018	0.80	−0.017	0.020	0.38
IL-6 (per SD = 1.15 pg/mL)	−0.005	0.018	0.77	−0.003	0.020	0.90
	Dependent variable					
	FVC (per SD = 956 mL)					
sICAM-1 (per SD = 78.5 ng/mL)	−0.042	0.018	0.02	−0.027	0.024	0.26
Fibrinogen (per SD = 70.3 mg/dL)	−0.044	0.011	<.0001	−0.044	0.016	0.007
hs-CRP (per SD = 5.41 mg/L)	−0.033	0.011	0.002	−0.036	0.015	0.02
IL-6 (per SD = 1.15 pg/mL)	−0.031	0.011	0.003	−0.042	0.016	0.007

Abbreviations - SD: Standard deviation, LAE: Large artery elasticity (SD = 5.6 ml/mmHg*10), SAE: Small artery elasticity (SD = 2.8 ml/mmHg*100), FVC: Forced Vital Capacity (mL), sICAM-1: soluble intercellular adhesion molecule; Hs-CRP: high sensitivity C-reactive protein; IL-6: Interleukin-6

Sample size for sICAM-1: 805 women and 675 men; for IL-6: 1800 women and 1755 men.

*Each row represents 2 separate, sex-specific regression analyses, adjusted for age, race/ethnicity, site, height, waist circumference, body mass index, heart rate, antihypertensive medications, systolic and diastolic blood pressure, smoking status, cholesterol, high density lipoprotein cholesterol, triglycerides, lipid lowering medication, and diabetes.