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Hypertension and Smoking Are Associated With Reduced Regional Left Ventricular Function in Asymptomatic Individuals

The Multi-Ethnic Study of Atherosclerosis

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OBJECTIVES This study sought to test the hypothesis that reduced regional left ventricular (LV) function is associated with traditional risk factors including hypertension, hypercholesterolemia, and smoking in asymptomatic individuals.

BACKGROUND Coronary artery disease is the main etiology of congestive heart failure in the U.S. and Europe. However, the relationship between risk factors for coronary artery disease and decreased myocardial function has not been studied systematically in asymptomatic individuals.

METHODS The Multi-Ethnic Study of Atherosclerosis (MESA) is a cohort study designed to investigate the nature of atherosclerosis in asymptomatic individuals. A total of 1,184 participants (45 to 84 years old) underwent tagged cardiac magnetic resonance imaging. Regional LV function was quantified by analyzing peak systolic circumferential strain (Ecc) in regions corresponding to the left anterior descending (LAD), circumflex (LCX), and right coronary (RCA) territories. The association between risk factors and strains was studied using multiple linear regression.

RESULTS Higher diastolic blood pressure (DBP) was associated with lower Ecc ($p \leq 0.002$). The Ecc's in the LAD territory of participants with DBP <80, 80 to 84, 85 to 89, and ≥90 mm Hg were −15.6%, −14.8%, −14.2%, and −13.7%, respectively ($p < 0.001$). Similar results were documented in other territories and after multivariable analysis. Smokers had lower Ecc in the LAD and RCA regions compared with nonsmokers. Furthermore, dose response relationship between cigarette consumption measured in pack-years and regional LV dysfunction by Ecc was noted ($p \leq 0.01$ in LAD and RCA territories). Finally, combined diastolic hypertension and smoking was associated with a greater reduction of regional LV function.

CONCLUSIONS Higher diastolic blood pressure and smoking are associated with decreased regional LV function in asymptomatic individuals. (J Am Coll Cardiol 2006;47:1150–8) © 2006 by the American College of Cardiology Foundation

Coronary artery disease is the main etiologic determinant of left ventricular (LV) dysfunction and congestive heart failure in the U.S. and Europe (1). Risk factors for coronary artery disease such as diabetes mellitus, hypertension, smoking, dyslipidemia, and family history are associated with the development of major cardiovascular events, including congestive heart failure (2,3). In addition, it has been shown that subclinical LV dilation and systolic dysfunction are independent predictors of heart failure (4).

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These previous studies that used LV dilation and systolic dysfunction as subclinical markers of heart failure have clearly shown the crucial importance of defining the pre-clinical stages of this disease process (4). Coronary events including myocardial infarction may be silent, and repeated ischemic injury may also lead to significant LV dysfunction in the absence of discrete clinical events. Relying solely on clinically detected heart failure may thus be limiting for purposes of designing novel strategies of primary prevention in heart failure.

Coronary atherosclerosis is regional in nature. Hence, it is expected that myocardial dysfunction secondary to coronary

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Abbreviations and Acronyms

DBP = diastolic blood pressure
Ecc = circumferential strain
HDL = high-density lipoprotein
LAD = left anterior descending
LCX = left circumflex
LDL = low-density lipoprotein
LV = left ventricle/ventricular
MESA = Multi-Ethnic Study of Atherosclerosis
MRI = magnetic resonance imaging
RCA = right coronary artery
SBP = systolic blood pressure

atherosclerosis would begin as a regional process. Regional LV function can be assessed by a number of invasive and non-invasive techniques that are generally limited by subjective evaluation and reduced reproducibility. Conversely, myocardial tagging by magnetic resonance imaging (MRI) provides objective measurements of myocardial motion and deformation, allowing for a detailed quantification of regional cardiac function (5). However, because the analysis of MRI tagged images is complex, this method was only used in small clinical studies and experimental trials until recently (6). The advent of Harmonic Phase (HARP) imaging (7) has enabled the use of this technique in large epidemiologic studies such as the Multi-Ethnic Study of Atherosclerosis (MESA).

The MESA trial is a prospective, population-based observational cohort study of men and women free of clinical cardiovascular disease at study enrollment (8). As part of the multiple investigations comprising the MESA baseline examination, a large subset of its cohort underwent cardiac MRI with tissue tagging. We therefore used MRI tagging in 1,184 asymptomatic MESA participants to study their regional myocardial function and to test the hypothesis that traditional risk factors for coronary artery disease, including hypertension, hypercholesterolemia, smoking, and diabetes mellitus, are associated with abnormalities of regional LV function.

METHODS

Study population. The MESA trial was designed to evaluate the mechanisms underlying the development and progression of subclinical cardiovascular disease in asymptomatic individuals of diverse ethnicities (8). Individuals with symptoms or a history of cardiovascular disease were excluded. A total of 6,814 men and women, 45 to 85 years of age, from four ethnicities (non-Hispanic white, African American, Hispanic, and Chinese) were enrolled in the study at six field centers (Wake Forest University, Winston Salem, North Carolina; Columbia University, New York, New York; Johns Hopkins Hospital, Baltimore, Maryland; University of Minnesota, Minneapolis, Minnesota; Northwestern University, Chicago, Illinois; and UCLA, Los Angeles, California). On entry, all participants underwent extensive evaluation, including clinical questionnaire, physical examination, and laboratory tests including fasting plasma glucose, triglycerides, and total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol. The MESA protocol was approved by the institutional review boards of all participating centers. Informed consent was obtained from all participants.

Tagged MRI studies. In an ancillary study, 1,184 randomly selected MESA participants underwent tagged MRI studies at enrollment (from September 2001 to September 2002) in the six centers. Images were acquired in whole-body scanners (1.5 CVi, General Electric Medical Systems, Waukesha, Wisconsin, and Sonata/Symphony Siemens Medical Solutions, Germany) using electrocardiogram-triggered segmented k-space fast spoiled gradient-echo (spoiled gradient recalled acquisition or fast low angle shot) pulse sequences during breath holds. Three tagged short-axis slices (base to apex) were obtained with parallel striped tags prescribed in two orthogonal orientations (0° and 90°) using electrocardiogram-triggered fast gradient echo sequences with spatial modulation of magnetization (SPAMM).

Parameters for tagged images were: field of view, 40 cm; slice thickness 7 to 8 mm; repetition time, 6 ms; echo time, 3 ms; flip angle, 10° to 12°; phase encoding views, 128 with 6 phase encoding views per segment; temporal resolution, 40 ms; tag spacing, 7 mm.

All MRI studies were submitted to the major MRI reading center of the MESA trial located in Johns Hopkins Hospital. The analyses of all acquired images were performed in the core laboratory of the MRI reading center.

Strain analysis. Short-axis tagged slices were analyzed by the harmonic phase method. Harmonic phase (Diagnosoft, Inc., Palo Alto, California) is a new technique that enables a fast determination of strain (7,9,10). In the present study, peak systolic mid-wall circumferential strain (Ecc) was determined in 16 segments in three slices (six basal, six mid-cavity, and four apical slices). The Ecc from the most apical segment could not be analyzed because a cavity has to be seen for accurate analysis. Thus, 16 segments of the 17-segment model were used.

Systolic Ecc values are conventionally negative to express circumferential shortening, i.e., circumferential length reduction that occurs during systole. Therefore, a less negative Ecc indicates reduced regional function. Regional circumferential shortening was analyzed for the three coronary perfusion territories according to published standard criteria (11), i.e., left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA).

Risk factors for coronary artery disease. An elevated blood pressure was defined as diastolic blood pressure (DBP) ≥90 mm Hg, systolic blood pressure (SBP) ≥140 mm Hg, or receiving treatment for hypertension. High-normal DBP was defined as <90 mm Hg and ≥85 mm Hg. Total cholesterol ≥240 mg/dl (6.2 mmol/l), LDL cholesterol ≥160 mg/dl (4.1 mmol/l), and triglycerides ≥150

mg/dl (1.7 mmol/l) were considered as elevated. HDL <40 mg/dl (1.0 mmol/l) was defined as low. Hyperlipidemic patients were defined as either participants with abnormal lipid levels or receiving lipid-lowering therapy. Diabetic individuals were defined as either having fasting plasma glucose ≥126 mg/dl (7.0 mmol/l) or treated for diabetes. Smoking status was defined as current smoking, former smoking, or never smoked.

Statistical analysis. Regional strains (Ecc in LAD, RCA, and LCX regions), DBP, SBP, total cholesterol, LDL and HDL cholesterol, triglycerides, and plasma glucose levels had a normal distribution. The distribution of values was assessed by the Kolmogorov-Smirnov test for a normal distribution.

The associations between strains and continuous variables were studied by the Pearson linear correlation. Multiple linear regression was used to study relationships between Ecc and different risk factors (defined as categorical variables in the risk factor subsection in the previous text). Variables entered into the regression model included age, gender, ethnicity, site of the study, scanner model (GE vs. Siemens), DBP, SBP, total cholesterol, LDL cholesterol, diabetes mellitus, body mass index, and smoking status (never smoked, former and current smokers). The associations between regional strains and risk factors after multivariable adjustment are displayed as regression coefficients (or adjusted mean change in systolic strains), whereas the first value (e.g., DBP <80 mm Hg) serves as reference. Therefore, their values are dependent on the units of the dependent and independent variables. A dose-response relationship between Ecc and number of pack-years was studied after including all of the abovementioned covariates (except smoking status) in the model. Interactions between different risk factors were studied to evaluate the effect of combined risk factors on regional function. The trend across the increasing levels of risk factors was tested for statistical significance by scoring each risk factor category by its median value and entering the score as a continuous term in the regression model. To explore further the nature of the relationship between regional LV function and the different risk factors, additional adjustments for LV mass and coronary calcium scores in the corresponding coronary territories were performed.

Demographic characteristics and cardiovascular risk factors were compared using Student *t* test and one-way analysis

Table 1. Demographic and Risk Factor Data

	n (%)	Range
Demographic data		
Gender		
Men	635 (53.6)	
Women	549 (46.4)	
Total	1,184	
Ethnicity		
Non-Hispanic white	364 (30.7)	
Chinese	135 (11.4)	
African American	322 (27.2)	
Hispanic	363 (30.7)	
Age (yrs)	66.4 ± 10	45–85
BMI (kg/m^2)	27.7 ± 4.6	15.4–45.9
Risk factors		
Blood pressure		
SBP (mm Hg)	129 ± 21	78–205
DBP (mm Hg)	72 ± 10	44–119
Self-reported hypertension	526 (44.4)	
Treatment for hypertension	398 (33.6)	
Lipids		
Total cholesterol, mg/dl (mmol/l)	194 ± 35 (5.0 ± 0.9)	85–456 (2.2–11.8)
LDL cholesterol, mg/dl (mmol/l)	118 ± 30 (3.1 ± 0.8)	38–270 (0.9–7.0)
HDL cholesterol, mg/dl (mmol/l)	51 ± 15 (1.3 ± 0.4)	21–119 (0.5–3.1)
Triglycerides, mg/dl (mmol/l)	130 ± 80 (1.5 ± 0.9)	21–831 (0.2–9.4)
Treatment for hyperlipidemia	234 (19.8)	
Smoking		
Never smoked	606 (51.5)	
Former smoking	441 (37.5)	
Current smoking	130 (11.0)	
Glucose		
Plasma glucose, mg/dl (mmol/l)	107 ± 27 (5.9 ± 1.5)	44–353 (2.4–19.6)
History of diabetes mellitus	132 (11.2)	
Insulin-treated	16 (1.4)	
Major Q-wave abnormalities in ECG	22 (1.9)	

Data are presented as n, mean ± SD, or range. Percentages are in parentheses.

BMI = body mass index; DBP = diastolic blood pressure; ECG = electrocardiogram; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SBP = systolic blood pressure.

Table 2. Strains (Mean ± SD) According to Traditional Risk Factors

	LAD (%)	LCX (%)	RCA (%)
Age (yrs)			
45–54	−14.9 ± 3.7	−16.8 ± 3.9	−11.5 ± 3.6
55–64	−15.0 ± 4.5	−16.7 ± 5.4	−11.9 ± 4.6
65–74	−15.6 ± 4.0	−17.2 ± 4.7	−12.1 ± 4.0
≥75	−15.3 ± 4.4	−16.7 ± 4.9	−11.7 ± 4.1
p Value (for trend: age vs. Ecc)	0.2	0.4	0.07
Gender			
Female	−15.5 ± 4.6	−16.7 ± 5.4	−12.1 ± 4.4
Male	−15.1 ± 3.8	−17.1 ± 4.3	−11.9 ± 3.9
p Value (male vs. female)	0.12	0.09	0.13
Hypertension category			
Normal (n = 674)	−15.5 ± 4.1	−16.9 ± 4.7	−11.9 ± 4.1
Borderline isolated systolic hypertension (n = 185)	−15.1 ± 4.0	−17.2 ± 4.9	−12.1 ± 4.1
Isolated systolic hypertension (n = 271)	−15.3 ± 4.4	−17.2 ± 4.9	−12.3 ± 4.1
Diastolic hypertension (n = 54)	−13.7 ± 4.5	−15.1 ± 4.9	−10.0 ± 4.6
p Value for trend	**0.01**	**0.02**	**0.003**
Diabetes mellitus			
Normal glucose (n = 875) (<100 mg/dl [5.6 mmol/l])	−15.4 ± 4.2	−16.9 ± 4.8	−12.0 ± 4.1
Impaired fasting glucose (n = 185) (≥100 and <126 mg/dl [5.6 and 7.0 mmol/l])	−14.9 ± 4.3	−17.1 ± 5.0	−11.6 ± 4.1
Diabetes mellitus (n = 102) (≥126 mg/dl [7.0 mmol/l], or treated)	−15.3 ± 4.1	−17.2 ± 4.6	−12.0 ± 4.2
p Value for trend	0.6	0.6	0.7
Total cholesterol category			
Desirable (<200 mg/dl [5.2 mmol/l]) (n = 687)	−15.3 ± 3.4	−16.9 ± 4.9	−11.8 ± 4.1
Borderline (>200 and <240 mg/dl [5.2 and 6.2 mmol/l]) (n = 390)	−15.2 ± 4.4	−16.8 ± 4.7	−12.1 ± 4.0
High (≥240 mg/dl [6.2 mmol/l]) (n = 107)	−15.4 ± 4.2	−17.0 ± 4.9	−12.4 ± 4.4
p Value for trend	0.8	0.7	0.2
HDL cholesterol category			
High (≥60 mg/dl [1.6 mmol/l]) (n = 281)	−15.0 ± 4.6	−16.3 ± 5.2	−11.8 ± 4.5
Normal (≥40 and <60 mg/dl [1.0 and 1.6 mmol/l]) (n = 627)	−15.4 ± 4.14	−16.8 ± 4.8	−11.9 ± 4.2
Low <40 mg/dl [1.0 mmol/l]) (n = 275)	−15.4 ± 3.8	−17.7 ± 4.2	−12.1 ± 3.6
p Value for trend	0.1	**0.0001**	0.1
Smoking history			
Never (n = 606)	−15.6 ± 4.2	−17.1 ± 4.9	−12.3 ± 4.1
Former (n = 441)	−15.1 ± 4.1	−16.9 ± 4.6	−11.7 ± 4.2
Current (n = 130)	−14.6 ± 4.2	−16.4 ± 4.8	−11.4 ± 4.2
p Value for trend	**0.02**	**0.02**	0.45

Significant values are in **boldface** type.
Ecc = circumferential strain; LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery; other abbreviations as in Table 1.

of variance. Data are presented as mean ± SD. Differences between variables were considered significant if $p < 0.05$. All reported p values are two-sided. Analyses were done using STATA-7 software (Stata Inc., College Station, Texas).

RESULTS

Demographic characteristics and risk factor profile. The study included 1,184 individuals, of whom 54% were men (Table 1); 44% of the participants reported having hypertension and one-third of the participants were treated for hypertension. Approximately 20% were treated for hypercholesterolemia, and one-half of all participants were either former or current smokers.

Regional myocardial functional indexes. A marked regional variation in myocardial strain was found for the entire cohort as shown in Table 2. The LCX territory had the highest absolute values of circumferential shortening (Ecc), whereas in the RCA region Ecc had the lowest magnitude (Ecc in RCA vs. LCX or LAD, $p < 0.001$). No relationship between Ecc and gender or age were documented. Mean Ecc at the LV base was markedly lower than mean Ecc at the mid- and apical LV levels (−9.5 ± 5.5% vs. −12.8 ± 4.7% and −12.3 ± 5.0%, base versus mid- or apex $p < 0.001$).

Regional function and risk factors for coronary artery disease. BLOOD PRESSURE. A strong inverse association between increased diastolic blood pressure and regional myocardial function was noted (Fig. 1A). In the LAD territory, Ecc values for individuals with DBP <80, 80 to 84, 85 to 89 and ≥90 mm Hg were −15.6%, −14.9%,

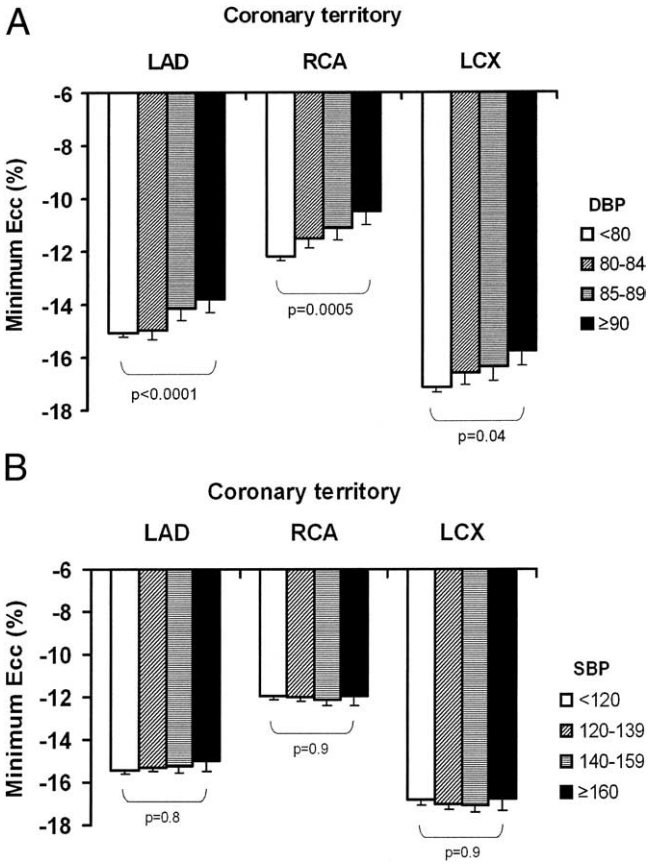

Figure 1. Strain in different territories (left anterior descending artery [LAD], left circumflex [LCX], and right coronary artery [RCA] territories) according to categories of diastolic blood pressure **(A)** and systolic blood pressure **(B)**. Relationships between strain and blood pressures presented in this figure are unadjusted. Testing for trend (analysis of variance) indicates presence of significant relationship between diastolic blood pressure and strains (p values indicate significance for such a trend). No such relationship exists between systolic blood pressure and regional left ventricular (LV) function. Mean + standard error (SE) are presented.

−14.1%, and −13.7%, respectively ($p < 0.0001$ for trend). Similar relationships were also documented for the LCX and RCA territories (Fig. 1A). Increased DBP was associated with significantly lower (absolute) strains in the LAD, LCX, and RCA regions before adjustment (correlation coefficient, $r = 0.15$, 0.09, and 0.11, respectively; $p \leq 0.002$ for all regions).

Table 3 provides the adjusted mean change (95% confidence interval) in systolic strain (regression coefficients) derived from multiple linear regression analyses with increasing blood pressure categories having DBP <80 and SBP <120 mm Hg as the reference groups, respectively. These analyses were performed after multivariable adjustment for age, gender, ethnicity, total cholesterol, LDL cholesterol, diabetes mellitus, body mass index, smoking status, and drug treatment for hypertension. Significant associations between lower (absolute) systolic strains and increased DBP were seen in all regions. By using a chi-square log-likelihood ratio test and comparing nested models, we found that the addition of a quadratic term did not improve the model assessing the association between strains and DBP levels, indicating a linear relationship. In contrast, no such relationships were evident with higher SBP categories. Peak systolic circumferential strains in participants with SBP ≥160 mm Hg were not different from Ecc in normotensive individuals either before or after multivariable adjustment (Fig. 1B, Table 3).

Importantly, as compared with individuals without hypertension, only those with isolated diastolic hypertension had a significantly lower adjusted mean change (95% confidence interval) in systolic strain (regression coefficients), whereas no such differences were observed with either borderline isolated hypertension as well as systolic hypertension (Table 4).

In subgroup analyses, despite the limited number of individuals in each ethnic subgroup, significant relationships between DBP and regional strains were seen in white and Hispanic individuals, whereas only a trend toward reduced (absolute) Ecc was seen in African Americans.

In contrast, conflicting results were evident when the relationships between SBP and regional LV function were analyzed by ethnic subgroups. There was a general tendency toward reduced Ecc in white individuals ($p = 0.017$ in the LAD territory), whereas in Chinese Americans, an opposite trend was noted in all regions, i.e., increased Ecc in individuals with higher SBP ($p = 0.065$, 0.027, and 0.04 in the LAD, LCX, and RCA regions).

When different LV levels were analyzed separately, a significant relationship between Ecc and DBP was noted in the apex and mid-ventricular level, whereas no significant associations were observed at the LV base (data are not shown). Moreover, DBP/regional function relationships in the subendocardial as well in the subepicardial layers were parallel to those seen in the mid-wall. Importantly, these associations remained unchanged after adjustment for coronary calcium in the corresponding coronary regions, but were attenuated after adjustment for LV mass. Finally, results did not change after excluding participants who had Q-wave abnormalities in their electrocardiograms.

CIGARETTE SMOKING. Current or former smokers had lower (absolute) strains in the LAD and RCA regions (Table 2). The LAD region Ecc values for non-smokers, former smokers, and current smokers were −15.6 ± 4.2, −15.1 ± 4.1, and −14.6 ± 4.2, respectively ($p = 0.02$ for trend). Importantly, in the adjusted analyses, current smokers had a significantly lower adjusted mean change in systolic strain when compared with never-smokers in the LAD and RCA regions (Table 4).

Figure 2B shows the dose response relationship between cigarette consumption expressed in pack-years and Ecc for both the RCA and LAD territories ($p \leq 0.01$ for trends). In the LCX region, lower Ecc was noted only in participants who consumed ≥40 pack-years when compared with those who consumed less. As shown previously for DBP, the relationships between smoking and regional LV function were seen in the mid-wall and at the LV apical levels, and remained unaltered after adjustment for coronary calcium in

Table 3. Multivariable Regression Coefficients (95% Confidence Intervals) for Myocardial Strain According to Categories of DBP and SBP

	DBP (mm Hg)				Trend Test
	<80	80–84	85–89	≥90	(p Value)
LAD	Ref	0.55 (−0.22 to 1.32)	1.48§ (0.52 to 2.46)	1.83‖ (0.81 to 2.86)	<0.001
LCX	Ref	0.52 (−0.36 to 1.41)	0.95* (−0.17 to 2.07)	1.62‡ (0.43 to 2.82)	0.002
RCA	Ref	0.65* (−0.11 to 1.41)	1.20† (0.24 to 2.16)	1.71‖ (0.70 to 2.72)	<0.001
	SBP (mm Hg)				Trend Test
	<120	120–139	140–159	≥160	(p Value)
LAD	Ref	0.07 (−0.52 to 0.66)	0.24 (−0.49 to 0.96)	0.56 (−0.52 to 1.65)	0.3
LCX	Ref	−0.27 (−0.94 to 0.41)	−0.32 (−1.14 to 0.51)	0.13 (−1.12 to 1.38)	0.7
RCA	Ref	−0.02 (−0.60 to 0.56)	−0.26 (−0.97 to 0.45)	0.01 (−1.06 to 1.07)	0.7

Increase in one standard deviation of DBP was significantly associated with reduced strains in LAD (regression coef: 0.62, $p < 0.001$), LCX (0.52, $p < 0.001$) and RCA (0.45, $p = 0.001$). Using a chi-square log-likelihood ratio test, we found that addition of a quadratic term did not improve the model assessing the relationship between strains and DBP, indicating a linear relationship. Variables included in the regression model in addition to DBP and SBP: age, gender, ethnicity, total cholesterol, LDL cholesterol, diabetes mellitus, body mass index, smoking status, and drug treatment for hypertension. *$p < 0.1$; †$p < 0.05$; ‡$p < 0.01$; §$p < 0.005$; ‖$p \leq 0.001$ compared with reference.

Ref = reference; other abbreviations as in Table 2.

the corresponding coronary regions or after excluding from the analysis participants with Q-wave abnormalities. However, they were diminished after adjustment for LV mass.

COMBINED EFFECTS OF DBP AND SMOKING. The combination of increased DBP with smoking was associated with a substantially lower mid-wall circumferential strain in the LAD territory when compared with the relationships with each risk factor individually. As shown in Figure 3, the association between DBP and Ecc was stronger in heavy smokers (≥20 pack-years) than in non-smokers. Conversely, the association between smoking and Ecc was more prominent in hypertensive than in normotensive participants. This effect remained after adjustment for age and gender. A similar combined effect of DBP and cigarette smoking was noted for the RCA region, although of borderline significance. Such synergistic patterns were not seen for other risk factor combinations.

HYPERLIPIDEMIA AND DIABETES MELLITUS. No associations between regional strain and total cholesterol or glucose levels were seen before or after adjustment for treatment of hypercholesterolemia or diabetes, respectively (Table 2). Furthermore, neither LDL cholesterol nor triglyceride levels were correlated with regional strains (data not shown). There was, however, a negative and significant correlation between HDL cholesterol and Ecc in the LCX region (correlation coefficient, $r = -0.11$, $p < 0.001$), i.e., greater levels of HDL cholesterol were associated with lower regional LV function. Such a relationship remained after multivariate adjustment and was not present in other coronary territories.

DISCUSSION

We show in this study that diastolic blood pressure and cigarette smoking are associated with decreased regional myocardial function based on tagged MRI analyses in 1,184 MESA participants without symptoms or history of ischemic heart disease or heart failure. These relationships were consistent and documented in all major coronary territories for DBP and in two (LAD and RCA) for smoking. Moreover, a dose response relationship between the extent

Table 4. Multivariate Regression Coefficients (95% Confidence Intervals) for Myocardial Strain According to Categories of Traditional CHD Risk Factors

	LAD (%)	LCX (%)	RCA (%)
Hypertension category			
Normal (n = 674)	Ref	Ref	Ref
Borderline isolated systolic hypertension	0.56 (−0.15 to 1.28)	−0.58 (−1.40 to 0.24)	−0.28 (−0.98 to 0.42)
Isolated systolic hypertension	0.30 (−0.34 to 0.95)	−0.47 (−1.22 to 0.27)	−0.54 (−1.18 to 0.10)
Diastolic hypertension	1.79§ (0.56 to 3.02)	1.78† (0.35 to 3.21)	1.70‡ (0.49 to 2.90)
Smoking history			
Never	Ref	Ref	Ref
Former	0.41 (−0.13 to 0.95)	0.17 (−0.44 to 0.79)	0.50* (−0.03 to 1.03)
Current	0.93† (0.11 to 1.76)	0.78 (−0.17 to 1.72)	0.83† (0.02 to 1.64)

Regression coefficients indicate the magnitude of reduction of Ecc with any risk factor vs. the reference as noted in the table. Variables included in the regression model included: age, gender, ethnicity, DBP, SBP, total cholesterol, LDL cholesterol, diabetes mellitus, body mass index, smoking status, and drug treatment for hypertension. *$p < 0.1$; †$p < 0.05$; ‡$p < 0.01$; §$p < 0.005$; ‖$p \leq 0.001$ compared with reference.

Abbreviations as in Tables 2 and 3.

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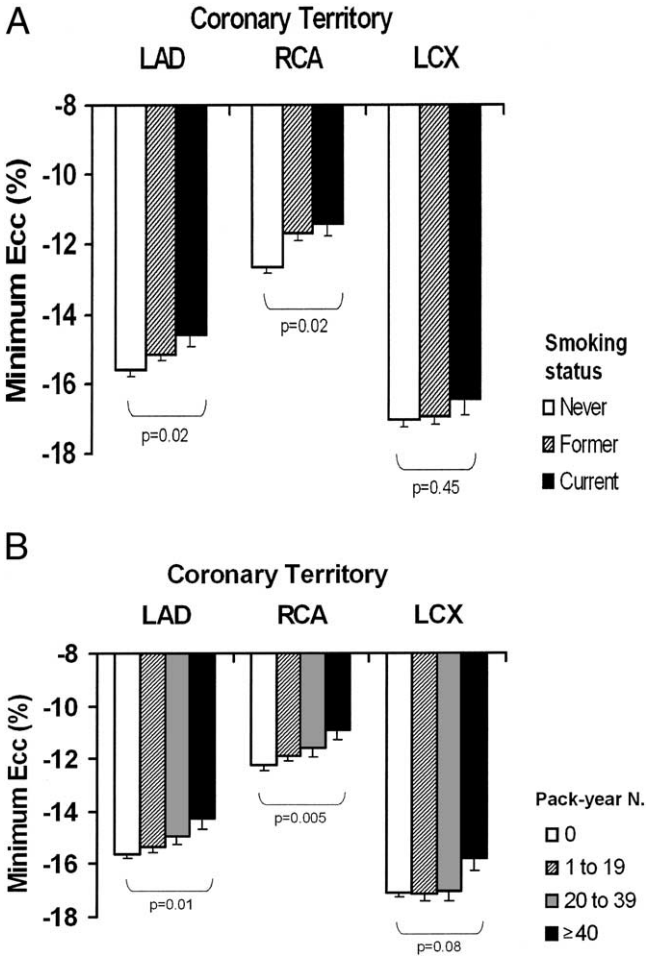

Figure 2. **(A)** Relationship between regional left ventricular (LV) function and smoking status. The relationship between strain and smoking status presented here is unadjusted. **White bars** = non-smokers; **ruled bars** = former smokers; **black bars** indicate current smokers. There is a reduction (absolute) of circumferential strain (Ecc) in left anterior descending (LAD) and right coronary (RCA) in current smokers, as compared with former and non-smokers. Mean + SE are shown. **(B)** Relationship between cigarette consumption (pack-years) and regional LV function. The relationship between strain and pack-years presented here is unadjusted. **White bars** = non-smokers (0 pack-years); **ruled bars**, **gray bars**, and **black bars** = 1 to 19, 20 to 39, 40 and more pack-years, respectively. Testing for trend is significant for the LAD and RCA territories. Mean + standard error (SE) are shown.

of cigarette consumption expressed by pack-years and regional LV function was also found. The association between DBP and reduction in Ecc was augmented in the presence of cigarette smoking and vice versa in the LAD and RCA regions.

Reduction of regional myocardial strain or LV function can be caused by increased cardiac load, myocardial dysfunction attributable to hypertrophy, and coronary artery disease manifested as myocardial infarction or ischemia, as well as combinations of two or more of these mechanisms. The association between reduced regional LV function and higher DBP as well as smoking did not change after adjustment for regional coronary calcium score, but was substantially attenuated after controlling for LV mass, underscoring the importance of LV hypertrophy in the development of regional LV dysfunction.

Previous studies have shown in normal volunteers a gradient of increasing circumferential strain from the base to the apex (12,13). Regional LV dysfunction expressed as reduced intramural circumferential and longitudinal shortening has been reported by Palmon et al. (14) in hypertensive patients with a normal ejection fraction and LV hypertrophy. In that study, the base-to-apex gradient of circumferential strain was found to be blunted in patients with hypertension and LV hypertrophy. In the present study, similarly, there was a significant difference between myocardial shortening at the LV base versus the LV mid-ventricular level, but no differences relative to shortening at the apex were noted.

In the Framingham study, hypertension was found to be the most prominent factor associated with the development of congestive heart failure (15). However, in that study, the effects of SBP and pulse pressure were more prominent than those of diastolic blood pressure (16). In our study, by contrast, increased SBP was not independently associated with reduced regional function. There are several potential explanations for these dissimilarities. First, in this cross-sectional analysis, the relationship between MRI-defined LV function and risk factors was studied in asymptomatic individuals, whereas in the report from the Framingham study the end point was incident heart failure (16). It is therefore possible that increased systolic blood pressure may have led to overt failure and exclusion from the MESA trial. Secondly, the MESA trial is characterized by a heterogeneous demography with substantial participation of African American, Hispanic, and Chinese in addition to white individuals. It is possible that DBP plays a more important role in the pathogenesis of regional dysfunction in non-white individuals. In this regard, the relationship between SBP and regional LV function was somewhat complex. Whereas in white patients, a general tendency toward lower regional LV function in individuals with higher SBP was

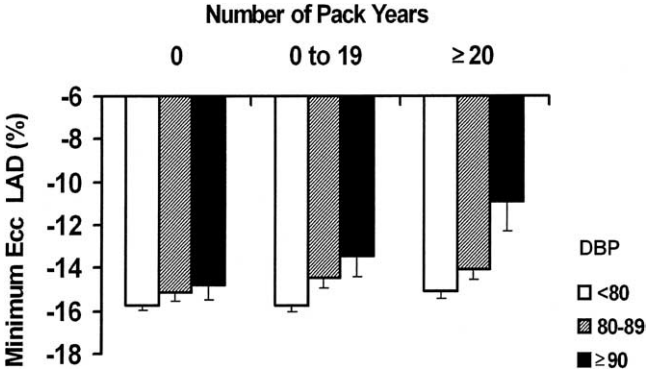

Figure 3. Combined effect of diastolic blood pressure and smoking status on circumferential strain (Ecc) in left anterior descending (LAD) region. The relationships between strain, diastolic blood pressure (DBP), and smoking shown here reflect unadjusted values. Note that the effect of reduced Ecc in the presence of increased DBP is more pronounced in heavy smoking (≥20 pack-years). Mean + standard error (SE) are shown.

detected, in Chinese American individuals those with a higher SBP tended to have higher regional strains. These analyses are limited by the small number of participants in each ethnic subgroup, especially the Chinese American group. Tagged MR studies of most Chinese American individuals included in this cohort have been performed in one study center (UCLA). Despite this, we do not believe that technical or methodological issues (such as image acquisitions) contributed to these differences, because the results and the trend noted in another major subgroup scanned in this center (Hispanic patients) were not significantly different from the entire population.

A second important risk factor related to reduced regional myocardial function was cigarette smoking. A dose response association with cigarette smoking as well as an interaction with the effects of DBP was noted. As discussed earlier, not only this relationship but also the association between DBP and reduced regional LV function may result from occult myocardial infarction or ischemia caused by epicardial atherosclerosis. However, the small number of individuals with significant Q-wave abnormalities (1.9%) does not support this notion. Importantly, the relationship between DBP or smoking and regional LV function remained unaltered after excluding individuals who had electrocardiogram Q-wave abnormalities or after controlling for coronary calcium as an indicator of subclinical atherosclerosis. Celermajer et al. (17) have shown that both active and passive smoking were related to impaired endothelial-dependent vascular relaxation. This early manifestation of endothelial dysfunction may be related to subclinical atherosclerosis and possibly regional myocardial dysfunction. This possibility is still speculative, and should be validated by further studies. On the other hand, the possibility that smaller and/or repeated injury caused by emboli and/or repeated transient ischemia cannot be ruled out, and in fact represent a plausible mechanism for the associations noted in this study.

The associations between smoking and lower myocardial strain in the RCA and LAD territories but only a trend in the LCX region are also noteworthy. Lack of finding of statistical differences in this region might reflect lack of statistical power to detect changes in this territory, rather than a pathophysiologic phenomenon. Increased variation has been noted in the LCX region, and may be related to the distance between the posterior wall and the surface coil with reduced signal-to-noise ratio. Interestingly, previous studies have also shown a relationship between smoking and the specific development of coronary atherosclerosis in the right coronary artery with subsequent inferior myocardial infarction (18–20).

In our study, the combination of smoking and elevated diastolic blood pressure had an additive effect and was associated with greater reduction in regional myocardial function. Other risk factors, including hypercholesterolemia and diabetes mellitus, are known to be associated with an increased risk for coronary events and congestive heart failure (2,21,22). However, we did not find independent associations between regional LV function and these risk factors. This could be related to the cross-sectional design of our study and/or to the MESA study design, precluding the presence or history of heart disease. Paradoxically, we found an inverse relationship between HDL cholesterol and myocardial shortening, but only in the LCX region. The question of whether this represents an incidental or a significant finding remains to be elucidated.

Methodological considerations. This study is cross-sectional, a factor that prevents making conclusions regarding the risks of developing regional LV dysfunction in the presence of different risk factors. In addition, because of the parent MESA study design, symptomatic individuals were excluded. This might explain in part the lack of significant relationships between regional LV function and systolic blood pressure, diabetes, or hypercholesterolemia. In the MESA trial, study participants do not undergo coronary angiography or contrast-enhanced MRI. Thus, their coronary anatomy is unknown and the presence of occult coronary stenoses or silent myocardial infarctions could not be confirmed or excluded (23,24).

We analyzed 1,184 tagged images in the present study, making this, to our knowledge, the largest tagged MRI study ever performed. The harmonic phase tool is a reliable and fast method for strain analysis and has been validated against other well-established methods of assessing myocardial function (10). It provides a detailed quantitative description of regional wall function expressed as myocardial strains. We combined different segments of the LV wall to analyze regional function in specific coronary territories similar to previous echocardiographic and nuclear studies (11).

CONCLUSIONS

Reduced regional left ventricular function is associated with diastolic hypertension and cigarette smoking in a population of asymptomatic individuals without a history of cardiac disease. This relationship is strongest with the combination of diastolic blood pressure and cigarette smoking.

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