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Brachial Flow-Mediated Dilation and Incident Atrial Fibrillation: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Objective—It is unknown if endothelial dysfunction precedes atrial fibrillation (AF) development. The objective of this study was to examine the association of brachial flow-mediated dilation (FMD) with incident AF.

Approach and Results—A total of 2,936 participants (mean age 61 ± 9.9; 50% women; 66% non-whites) from the Multi-Ethnic Study of Atherosclerosis with available ultrasound brachial FMD measurements who were free of baseline AF were included in this analysis. Baseline (2000-2002) FMD was computed from the percent difference (%FMD) in brachial artery diameter and maximum diameter during measured vasodilator response. AF was ascertained from hospitalization data including Medicare claims during a median follow-up of 8.5 years. Probability-weighted Cox proportional-hazards regression was used to compute hazard ratios (HR) and 95% confidence intervals (95%CI) for the association between FMD as a continuous variable (%FMD values per 1-SD increase) and incident AF. Incident AF was detected in 137

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(4.7%) participants. Those with %FMD values below the sex-specific median value (median %FMD; males=3.6%, females=4.2%) (Incidence rate per 1000 person-years=7.3, 95%CI=5.9, 9.0) were more likely to develop AF than persons whose %FMD values were above the median value (Incidence rate per 1000 person-years=4.5, 95%CI=3.4, 5.8) (log-rank p=0.0043). In a multivariable Cox regression analysis, 1-SD increase in %FMD values (SD=2.8%) was associated with less incident AF (HR=0.84, 95%CI=0.70, 0.99). These results were consistent across subgroups stratified by age, sex, and race/ethnicity.

Conclusions—Smaller brachial FMD values are associated with higher rates of AF, suggesting a role for endothelial dysfunction in AF pathogenesis.

Keywords

atrial fibrillation; endothelial dysfunction; epidemiology

INTRODUCTION

Arterial flow-mediated dilation (FMD) is an indirect measurement of endothelial nitric oxide (NO) release.[1] Impaired FMD represents systemic vascular endothelial dysfunction that is commonly associated with cardiovascular disease (CVD).[2, 3] Additionally, the association of FMD with CVD is evidenced by its ability to predict future CVD events in population-based studies.[4, 5]

Endothelial dysfunction, defined by impaired FMD, has been reported in patients with atrial fibrillation (AF).[6, 7] Also, abnormalities in NO signaling have been implicated in atrial ectopy near the pulmonary veins.[8, 9] These findings suggest a potential role for endothelial dysfunction in the development of AF. However, data from population-based studies to support this claim are lacking. The purpose of this study was to examine the association of FMD with incident AF in the Multi-Ethnic Study of Atherosclerosis (MESA).

MATERIALS AND METHODS

Materials and Methods are available in the online-only Data Supplement.

RESULTS

Of the 3,026 participants from the FMD ancillary study with available FMD measurements, 28 participants had a diagnosis of AF before enrolment in MESA. These cases were detected by Centers for Medicare & Medicaid Services linkage and were not detected in the baseline study electrocardiogram. Of those that remained, 3 participants with missing follow-up data and 59 participants missing either baseline characteristics or medication data were excluded. A total of 2,936 study participants (mean age 61 ± 9.9; 50% women; 66% non-whites) were included in the final analysis.

FMD was computed from the percent difference (%FMD) in brachial artery diameter and maximum diameter during measured vasodilator response. Baseline characteristics stratified by sex-specific median %FMD are shown in Table 1. Participants with %FMD values below the median were more likely to be older, diabetic, and non-white, and to have lower

educational attainment and income compared with higher %FMD values. Persons with %FMD values below the median value were more likely to have increased values for systolic blood pressure and high-density lipoprotein cholesterol, and lower values for total cholesterol than those with %FMD values above the median value. Higher rates of antihypertensive medications, aspirin, lipid-lowering therapies, and left ventricular hypertrophy also were observed in persons with %FMD values below the median value.

A total of 137 (4.7%) participants developed AF during the study period. Median follow-up for study participants was 8.5 years (interquartile range=7.9, 8.7). Unadjusted cumulative incidence curves stratified by median %FMD are shown in Figure 1. Participants with %FMD less than the median value (incidence rate per 1000 person-years=7.3, 95%CI=5.9, 9.0) were more likely to develop AF compared with participants who had %FMD values greater than the median value (incidence rate per 1000 person-years=4.5, 95%CI=3.4, 5.8) (log-rank p=0.0043).

In a multivariable Cox proportional hazards analysis, 1-SD increase in %FMD values (SD=2.8%) was associated with less incident AF (Table 2). The association between FMD and AF remained significant after further adjustment of Model 2 with amino-terminal-pro-brain natriuretic peptide (HR=0.83, 95%CI=0.69, 0.99). These results were consistent across subgroups of MESA participants stratified by age, sex, and race/ethnicity (Table 2).

DISCUSSION

In this analysis from MESA, lower brachial FMD values were associated with increased rates of AF. These findings suggest that endothelial dysfunction, as measured by brachial FMD, plays a role in the pathogenesis of AF.

To our knowledge, only 2 studies have examined the association of brachial FMD with AF. A study of chronic AF participants showed that FMD measurements are significantly impaired compared with sinus rhythm controls.[6] Another case-control study showed that participants with persistent AF have impaired FMD and that FMD improves after the restoration of sinus rhythm.[7] However, both studies examined FMD among participants who already had AF. The current study examined FMD among participants without diagnosed AF and showed that abnormal FMD values are associated with an increased risk of AF development. Additionally, participants with lower %FMD values were observed to have a higher incidence of AF than those in the general population.[10] Therefore, we provide evidence that impaired FMD precedes the development of AF, suggesting a role for endothelial dysfunction in the pathogenesis of AF.

Endothelial cells regulate oxidative stress, vascular permeability, platelet aggregation, thrombosis, and vascular tone by controlling the release of several vasoactive substances, including NO.[11] The dysfunctional endothelium results in the down-regulation of NO and the up-regulation of adhesion molecules that promote increased levels of inflammation and oxidative stress. Recent evidence suggests that increased oxidant generation by endothelial NADPH oxidase promotes the uncoupling of NO synthase and subsequent generation of reactive oxygen species and oxidative injury that leads to the electrophysiological

remodeling observed in AF.[8] Additionally, exogenous NO has been shown to reduce spontaneous electrical activity in cardiomyocytes isolated from the pulmonary vein, implicating NO as a regulator of AF arrhythmiogenesis.[9] Endothelial dysfunction also is associated increased levels of inflammation that result in atrial ectopy in discharging cells near the pulmonary veins.[12, 13] Therefore, it is plausible that persons with endothelial dysfunction, as evidenced by abnormal FMD, are more likely to have dysfunctional regulation of the aforementioned processes that increase their risk for AF. FMD potentially is able to identify persons with abnormal vascular biological profiles that precede this arrhythmia. However, further studies are needed to validate our findings before screening programs that use FMD are introduced.

Alternatively, a number of shared risk factors for AF, such as increasing age, diabetes, hypertension, and smoking have been associated with endothelial dysfunction.[14-18] Potentially, these conditions increase the level of vascular endothelial dysfunction and predispose individuals to AF. However, our results remained significant after adjustment for these risk factors, suggesting that the association between endothelial dysfunction and AF is not completely explained by shared risk factors.

Brachial FMD has been shown to independently predict incident CVD events among persons who are free of CVD at baseline.[5] Abnormal FMD values possibly identify individuals with subclinical atherosclerosis who are at-risk for CVD. Additionally, as evidenced by our results, FMD potentially is able to identify at-risk persons for AF. However, further research is needed to examine the predictive ability of FMD for AF among at-risk populations.

Our results should be interpreted in the context of certain limitations. Paroxysmal cases of AF possibly were missed due to the time-dependent nature of the condition. Incident AF cases were ascertained from hospitalization discharge records and inpatient Medicare claims data using International Classification of Disease codes which possibly resulted in misclassification. However, this method has been reported to have adequate positive predictive value for AF case identification.[19-21] Brachial FMD measurements were obtained during the initial MESA visit and the association of FMD with AF may vary with repeat FMD measurements. The clinical significance of the FMD values (e.g., increase per 1-SD, median) used in this study is unknown and those used were designed to demonstrate exploratory associations (e.g., lower FMD values are associated with increased AF risk). Future studies are needed to define clinically relevant values. Non-significant interactions were observed by age, sex, and race/ethnicity but the current analysis potentially was underpowered to detect such differences. Furthermore, our results are limited regarding generalizability to other populations due to the older age of participants with FMD values lower than the median value for study participants.

In conclusion, we have shown that brachial FMD values are inversely associated with incident AF in MESA. Our results suggest that endothelial dysfunction precedes the development of AF and may play an important role in the pathogenesis of this common arrhythmia. Further research is needed to confirm our findings and also to explore the clinical utility of FMD to identify those who are at-risk for developing AF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Nonstandard Abbreviations and Acronyms

AF	Atrial fibrillation
CVD	Cardiovascular disease
FMD	Flow-mediated dilation
hs-CRP	High-sensitivity C-reactive protein
MESA	Multi-Ethnic Study of Atherosclerosis
NO	Nitric oxide

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SIGNIFICANCE

Endothelial dysfunction has been reported in patients with atrial fibrillation. However, the temporal association between impaired endothelial function and atrial fibrillation has not been examined. In this analysis from the Multi-Ethnic Study of Atherosclerosis, we have shown that impaired brachial artery flow-mediated dilation, an indirect marker of endothelial dysfunction, precedes the development of atrial fibrillation. These findings support the hypothesis that alterations in vascular biology predispose to the arrhythmiogenesis of atrial fibrillation.

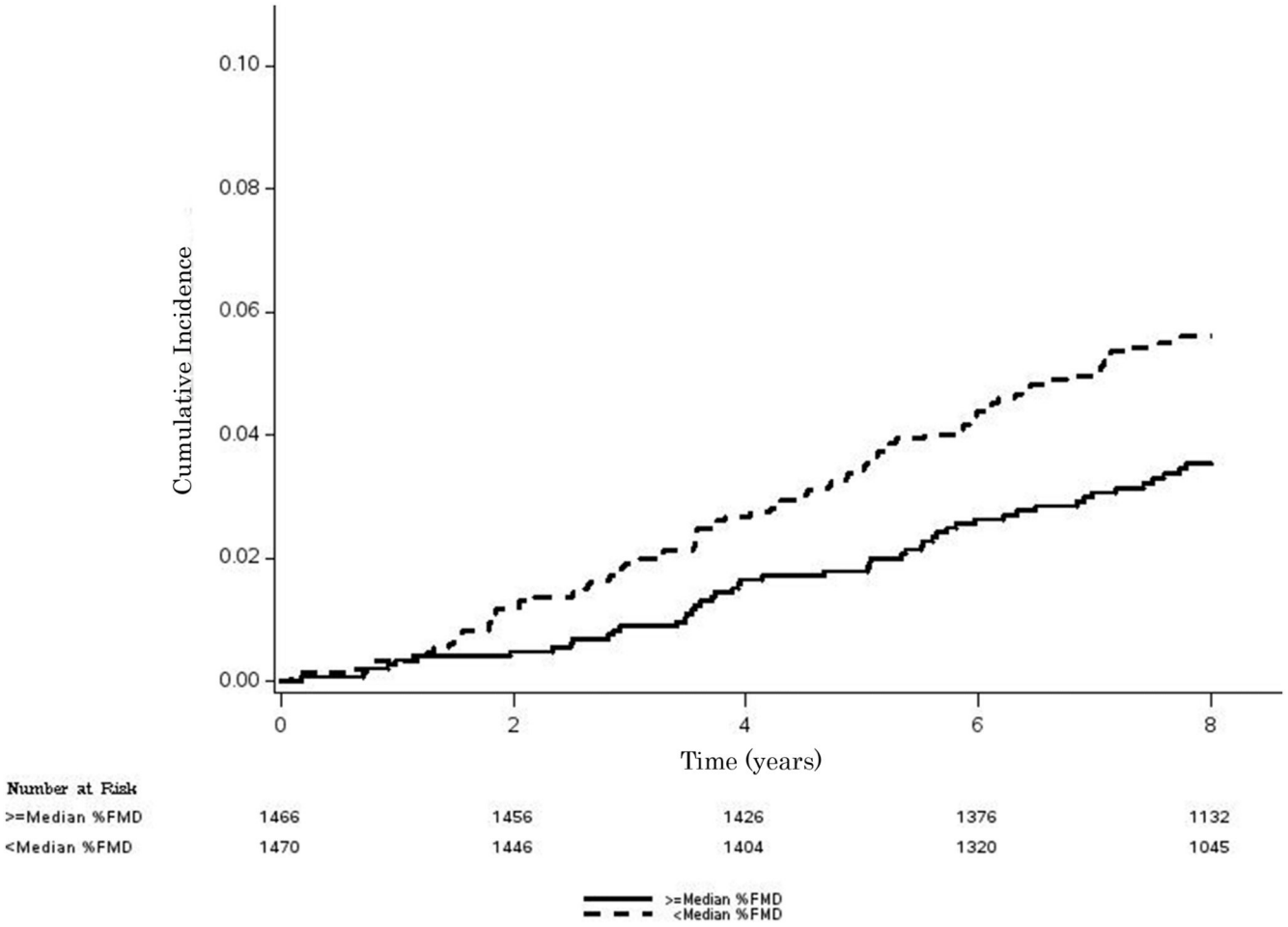

Figure 1. Cumulative Incidence of AF by Median %FMD*

*Median %FMD values for male and female participants were 3.6% and 4.2%, respectively. Kaplan-Meier estimates were significantly different (log-rank p=0.0043).

AF=atrial fibrillation; FMD=flow-mediated dilation.

Table 1

Baseline Characteristics (N=2,936)*

Variable	<Median %FMD (n=1,470)	≥Median %FMD (n=1,466)	P-value†
Age, mean (SD), years	64 (10)	58 (9.1)	<0.0001
Male Sex (%)	738 (50)	722 (49)	0.61
Race/ethnicity			
White (%)	440 (30)	561 (38)	
Black (%)	396 (27)	205 (14)	
Chinese-American (%)	263 (18)	326 (22)	
Hispanic (%)	371 (25)	374 (26)	<0.0001
High school or less (%)	569 (39)	496 (34)	0.0060
Income <$20,000 (%)	407 (28)	351 (24)	0.020
Body mass index, mean (SD) kg/m^2	28 (5.1)	28 (5.4)	0.44
Current or former smoker (%)	697 (47)	679 (46)	0.55
Diabetes (%)	229 (16)	146 (10)	<0.0001
Systolic blood pressure, mean (SD), mm Hg	128 (20)	121 (19)	<0.0001
Total cholesterol, mean (SD), mg/dL	193 (36)	196 (34)	0.048
HDL-cholesterol, mean (SD), mg/dL	51 (14)	50 (14)	0.014
Antihypertensive medications (%)	570 (39)	427 (29)	<0.0001
Statins (%)	222 (15)	185 (13)	0.052
Aspirin (%)	357 (24)	311 (21)	0.047
Lipid-lowering medications (%)	245 (17)	205 (14)	0.044
hs-CRP, mean (SD), mg/L	3.5 (5.3)	3.4 (5.7)	0.13
Left ventricular hypertrophy (%)	70 (4.8)	34 (2.3)	0.0003

AF=atrial fibrillation; FMD=flow-mediated dilation; HDL=high-density lipoprotein; hs-CRP=high-sensitivity C-reactive protein; SD=standard deviation.

*Median %FMD values for male and female participants were 3.6% and 4.2%, respectively.

†Statistical significance was tested for categorical variables using the chi-square method and for continuous variables the Wilcoxon-rank sum method was used.

Table 2

Association of FMD with AF by Age, Sex, and Race/Ethnicity*†

	Events/No. at risk	Model 1‡ HR (95%CI)	P-value	Model 2§ HR (95%CI)	P-value	P-interaction‖
All	137/2,936	0.82 (0.69, 0.98)	0.029	0.84 (0.70, 0.99)	0.048	-
Age						
≤65 years	47/1,898	0.68 (0.52, 0.89)	0.0048	0.73 (0.56, 0.95)	0.022	0.55
>65 years	90/1,038	0.79 (0.63, 0.99)	0.037	0.81 (0.64, 1.01)	0.065	
Race						
White	70/1,001	0.88 (0.70, 1.1)	0.27	0.86 (0.68, 1.1)	0.22	0.97
Non-White	67/1,935	0.77 (0.59, 1.0)	0.054	0.83 (0.64, 1.1)	0.19	
Sex						
Male	85/1,460	0.87 (0.69, 1.1)	0.26	0.89 (0.70, 1.1)	0.33	0.31
Female	52/1,476	0.77 (0.59, 0.99)	0.048	0.77 (0.59, 1.01)	0.062	

AF=atrial fibrillation; CI=confidence interval; FMD=flow-mediated dilation; HDL=high-density lipoprotein; hs-CRP=high-sensitivity C-reactive protein; HR=hazard ratio; SD=standard deviation.

*HR presented are for %FMD per 1-SD increase (SD=2.8%).

†Subgroups were adjusted according to Models 1 and 2 excluding the covariate of interest.

‡Adjusted for age, sex, race/ethnicity, income, and education.

§Adjusted for Model 1 covariates plus smoking status, systolic blood pressure, diabetes, body mass index, total cholesterol, HDL-cholesterol, aspirin, antihypertensive and lipid-lowering medications, hs-CRP, and left ventricular hypertrophy.

‖Interactions tested using Model 2.