


Endothelial dysfunction and the risk of heart failure in a community-based study: the Multi-Ethnic Study of Atherosclerosis

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Abstract

Aims We aimed to investigate the association between endothelial dysfunction, assessed by brachial flow-mediated dilation (FMD), and the incidence of heart failure (HF) in the community-based Multi-Ethnic Study of Atherosclerosis.

Methods and results Brachial artery FMD was measured in a nested case-cohort sample including 3496 of 6814 Multi-Ethnic Study of Atherosclerosis participants without prevalent cardiovascular disease (mean age 61 years, 50% women). Multivariable probability-weighted Cox proportional hazards analysis was used to examine the association between FMD and incident HF. We also investigated the association between FMD and HF with reduced vs. preserved ejection fraction [HF_rEF (left ventricular ejection fraction <45%) vs. HF_pEF (left ventricular ejection fraction ≥45%)]. During follow-up (median 12 years), 149 participants developed incident HF (incidence rate 3.7 events per 1000 person years). There were 56 HF_rEF and 69 HF_pEF events (incidence rates 1.4 and 1.7 events per 1000 person years, respectively). In multivariable models adjusted for established HF risk factors (age, sex, race/ethnicity, body mass index, systolic blood pressure, antihypertensive treatment, heart rate, diabetes mellitus, history of myocardial infarction, current smoker, and former smoker status), individuals in the highest quartile of FMD (reflecting better endothelial function) had a lower HF risk compared with individuals in the lowest quartile [hazard ratio 0.53, 95% confidence interval (CI) 0.31–0.95]. Lower risk according to higher FMD was particularly evident for HF_rEF, but not for HF_pEF (hazard ratio per standard deviation increase 0.79, 95% CI 0.64–0.97 vs. 0.99, 95% CI 0.78–1.26, respectively). Results remained similar after adjustment for baseline natriuretic peptide levels. The addition of FMD to established HF risk factors generally rendered no or only modest improvement in C-statistics [C-statistics for model with established HF risk factors: 0.774, and with the addition of FMD: 0.776 (delta C 0.002, 95% confidence interval –0.002 to 0.006)].

Conclusions Endothelial dysfunction was independently associated with HF in this community cohort, suggesting a pathophysiological contribution of endothelial function to the development of HF, in particular HF_rEF. However, the value of FMD measurements for HF risk prediction seems limited.

Keywords Endothelial dysfunction; Epidemiology; Heart failure; HF_pEF; HF_rEF; Risk prediction

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Introduction

Heart failure (HF) is a major and growing public health problem in the USA that afflicts 5.7 million adults and accounts for >1 million hospital admissions every year.¹ Despite recent advancement in treatment options, the prognosis of HF patients is poor, and 1 year of mortality risk is almost 30%.² Thus, the early identification of individuals at risk for HF may provide important opportunities to prevent the development of HF. The underlying mechanisms leading to clinically overt HF are multifactorial and incompletely understood. For instance, approximately half of patients are hospitalized for HF with reduced ejection fraction (HFrEF) while the others have HF with preserved ejection fraction (HFpEF), indicating diverse underlying mechanisms.³

Our understating of the role of endothelial dysfunction in the development of cardiovascular disease such as myocardial infarction (MI) or stroke is increasing.⁴ Emerging evidence suggests that endothelial dysfunction is an important factor in the early stages of the atherosclerosis formation, but also in the later stages by destabilization of established plaques.⁵ Moreover, dysfunction of the peripheral vasculature may modulate cardiac loading conditions that also could influence the risk of HF.^{6,7} Although it has been established that patients with symptomatic HF have concomitant endothelial dysfunction,^{8–18} less is known regarding whether endothelial dysfunction predates incident HF.

In this study, we aimed to investigate the association between endothelial dysfunction, as assessed by brachial flow-mediated dilation (FMD),¹⁹ and the incidence of HF in a large multi-ethnic community-based cohort free from known clinical cardiovascular disease at baseline. We also focused on the contribution of impaired endothelial function for the development of subtypes of HF such as HFrEF vs. HFpEF or whether participants had an interim MI or not prior to the HF event.

Methods

Study population and data collection

The study design for the Multi-Ethnic Study of Atherosclerosis (MESA, [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00005487) identifier NCT00005487) has been published elsewhere.²⁰ In brief, MESA is a prospective cohort study initiated in July 2000 with the main goal to investigate the prevalence, correlates, and progression of subclinical cardiovascular disease in individuals without known cardiovascular disease.

In total, 6814 participants aged 45 to 84 years were recruited from six US communities (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan, New York; and St

Paul, Minnesota). Thirty-eight per cent of participants were White, 28% Black, 22% Hispanic, and 12% of Chinese origin. The first examination (July 2000 to August 2002) was used as the baseline in the present study. Participants were excluded from the FMD examination if they had uncontrolled hypertension ($n = 158$), blood pressures in the left and right arms that differed by ≥ 15 mmHg, a history of Raynaud phenomenon ($n = 55$), a congenital abnormality of the arm or hand ($n = 12$), or a radical mastectomy on either side ($n = 100$), resulting in 6489 participants who underwent the brachial FMD examination.⁴ The actual reading of FMD results in MESA was only carried out in a subset of MESA ($n = 3496$).⁴

The investigation conforms with the principles outlined in the Declaration of Helsinki. The institutional review boards of each study site approved the study, and all participants provided written informed consent. Requests to access the dataset from qualified researchers trained in human subject confidentiality and protection protocols may be sent to the coordinating centre (<https://www.mesa-nhlbi.org>) or the NIH BioLincc data repository (<https://biolincc.nhlbi.nih.gov/studies/mesa>).

Resting blood pressure was measured three times in the seated position, and the average of the second and third readings was recorded. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of medication prescribed for hypertension. Body mass index was calculated as weight (kg)/height (m^2). Diabetes mellitus was defined as fasting glucose ≥ 126 mg/dL or the use of hypoglycaemic medications. Use of medications was based on review of prescribed medication containers. Current smoking was defined as having smoked a cigarette in the last 30 days. N-terminal of pro B-type natriuretic peptide (NT-proBNP) was measured by an Elecsys immunoassay (Roche Diagnostics Corporation, Indianapolis, Indiana). Plasma LDL cholesterol and HDL cholesterol were measured using the Roche Hitachi 911 analyser (Roche Diagnostics) and high-sensitivity C-reactive protein (hsCRP) was measured using a particle-enhanced immunonephelometric assay on the BNII nephelometer (Dade-Behring, Inc.). The resting heart rate was measured by baseline electrocardiogram. Assessment of coronary artery calcification (CAC) was performed by computed tomography scanning as previously described.²¹ Interim MI was defined as MI (by expert adjudication process as previously described)⁴ that occurred during follow-up but before the diagnosis of HF.

Brachial flow-mediated dilation measurement

Participants were examined in the supine position after 15 min of rest and after at least a 6 h fast. An automated sphygmomanometer (Dinamap device) was used to monitor blood pressure and pulse in the left arm at 5 min intervals

throughout the examination. A standard blood pressure cuff was positioned around the right arm, 2 inches below the antecubital fossa, and the artery was imaged 5 to 9 cm above the antecubital fossa. A linear-array multifrequency transducer operating at 9 MHz (GE Logiq 700 Device) was used to acquire images of the right brachial artery. After baseline images were obtained, the cuff was inflated to 50 mmHg above the participant's systolic blood pressure for 5 min. Digitized images of the right brachial artery were captured continuously for 30 s before cuff inflation and for 2 min beginning immediately before cuff deflation to document the vasodilator response.

Brachial ultrasound videotapes were analysed at the Wake Forest University Cardiology Image Processing Laboratory with the use of a previously validated semiautomated system.²² The readings of these digitized images generated the baseline and maximum diameters of the brachial artery from which % FMD was computed, as follows: % FMD = [(the maximum diameter minus the baseline diameter)/baseline diameter] * 100%.

Measurements from 40 MESA participants were used to evaluate reproducibility. Intra-reader reproducibility for FMD was 0.93. Repeated examinations from 19 participants were performed on two separate days 1 week apart. The intra-class correlation coefficient for baseline FMD was 0.54, and per cent technical error of measurement was 28.4%.⁴

Outcome definitions

Incident HF was defined as definite or probable HF and was an adjudicated event requiring symptoms such as shortness of breath or oedema, a physician diagnosis of HF, and documented medical treatment for HF. Definite HF required one or more criteria, such as pulmonary oedema or congestion by chest X-ray, ventricular dilation or poor left ventricular function by echocardiography or ventriculography, or evidence of left ventricular diastolic dysfunction. Participants with an evaluation of left ventricular ejection fraction (LVEF) by echocardiography at the time of HF diagnosis were categorized as either HFpEF (LVEF \geq 45%) or HFrEF (LVEF <45%) as has been previously described.^{23,24} HF events without data on echocardiography were excluded when evaluating the association between FMD and these subtypes of HF. In order to gain additional mechanistic insights, we also categorized HF events by whether they had an interim MI or not prior to the HF event (HF with vs. without prior MI).

Statistical methods

In the primary analyses, the association between FMD (modelled as a continuous variable and expressed per standard deviation on log scale) and the incidence of HF was

investigated using weighted Cox proportional hazards regression analyses to account for sampling structure for the nested case-cohort study. We also quantified the hazard for HF across quartiles of FMD using the first quartile as referent. Proportional hazards assumptions were confirmed by Schoenfeld's tests.

The following multivariable models were used: Model A was adjusted for age, sex, and race/ethnicity (Chinese American, African American, Hispanic vs. Caucasian). Model B was adjusted for the covariates in Model A and the risk factors in an HF prediction model derived from a community-based cohort, the Atherosclerosis Risk in Communities Study,²⁵ including body mass index, systolic blood pressure, antihypertensive treatment, heart rate, diabetes mellitus, history of MI, current smoker, and former smoker status. In Model C, NT-proBNP (log transformed) was added to Model B. In secondary analyses, we also performed additional adjustment for estimated glomerular filtration rate, statin use, total cholesterol, HDL cholesterol, hsCRP, CAC (modelled as a continuous variable), fasting glucose, diastolic blood pressure, and alcohol use.

As sensitivity analyses, we performed additional analyses where we modelled age as a time scale of survival analysis, accounted interim MI as a time-updated covariate, and investigated the influence of competing risk using Fine and Gray analyses and where we only included participants with an ankle/brachial index >0.9. We also investigated whether there was any effect modification by age, sex, and race/ethnicity using interaction terms between the effect modifier and FMD in multivariable Cox Model B. To obtain reliable estimates in this analysis, FMD was modelled as a linear term.

In order to provide a better understanding of potential pathophysiological contributions of endothelial dysfunction to the development of HF, the associations between FMD and different subtypes of HF (HFrEF vs. HFpEF and HF with vs. without prior MI) were also investigated.

Differences in Harrell's C-statistics after the addition of FMD to the Atherosclerosis Risk in Communities Study HF risk score were estimated in order to evaluate improvement in model discrimination.

Results

Baseline characteristics of the whole study cohort and by quartiles of FMD are shown in *Table 1*. With higher levels of FMD (reflecting a better endothelial function), participants were younger, more likely to be female, had lower blood pressure, and a lower prevalence of diabetes. A histogram of the distribution of FMD is shown in Supporting Information, *Figure S1*. FMD was weakly inversely correlated with baseline NT-proBNP (correlation coefficient -0.04 , $P = 0.02$).

Table 1 Baseline characteristics by flow-mediated dilation quartiles and in participants with vs. without heart failure during follow-up

Characteristics		Quartile 1	Quartile 2	Quartile 3	Quartile 4	No HF	HF
Number of participants	3496	874	874	874	874	3347	149
Age (SD) (years)	61 (10)	65 (10)	63 (10)	60 (9)	57 (9)	61 (10)	68 (9)
Male (%)	1735 (50%)	490 (56%)	456 (52%)	441 (50%)	348 (40%)	1650 (49%)	85 (57%)
Caucasian (%)	1168 (33%)	249 (28%)	285 (33%)	287 (33%)	347 (40%)	1105 (33%)	63 (42%)
Chinese American (%)	634 (18%)	120 (14%)	159 (18%)	175 (20%)	180 (21%)	619 (18%)	15 (10%)
African American (%)	791 (23%)	298 (34%)	199 (23%)	160 (18%)	134 (15%)	752 (22%)	39 (26%)
Hispanic (%)	903 (26%)	207 (24%)	231 (26%)	252 (29%)	213 (24%)	871 (26%)	32 (21%)
BMI (SD) (kg/m ²)	28 (5)	28 (5)	28 (5)	28 (5)	28 (6)	28 (5)	29 (6)
Systolic BP (SD) (mmHg)	125 (20)	130 (21)	127 (20)	123 (18)	120 (19)	125 (20)	134 (21)
Diastolic BP (SD) (mmHg)	72 (10)	73 (10)	72 (10)	72 (10)	70 (10)	72 (10)	72 (11)
HTN medications (%)	1231 (35%)	399 (46%)	303 (35%)	293 (34%)	236 (27%)	1139 (34%)	92 (62%)
Heart rate (SD) (per minute)	63 (9)	62 (10)	63 (10)	63 (9)	64 (9)	63 (9)	65 (11)
Diabetes (%)	411 (12%)	133 (15%)	112 (13%)	93 (11%)	73 (8%)	372 (11%)	39 (26%)
Glucose (SD) (mmol/L)	97 (29)	100 (33)	97 (28)	95 (23)	94 (30)	96 (28)	108 (41)
Current smoker (%)	519 (15%)	139 (16%)	131 (15%)	127 (15%)	122 (14%)	491 (15%)	28 (19%)
Former smoker (%)	1234 (35%)	335 (38%)	310 (35%)	310 (35%)	279 (32%)	1177 (35%)	57 (38%)
Current drinker (%)	1920 (55%)	463 (53%)	476 (55%)	481 (55%)	500 (57%)	1849 (55%)	71 (48%)
Former drinker (%)	768 (22%)	219 (25%)	185 (21%)	184 (21%)	180 (21%)	721 (22%)	47 (32%)
NT-proBNP (IQI) (pg/mL)	50 (22, 103)	53 (25, 118)	54 (22, 109)	47 (21, 95)	48 (21, 94)	48 (21, 98)	133 (77, 276)
Total cholesterol (mg/dL)	194 (35)	192 (35)	193 (35)	194 (36)	197 (34)	194 (35)	189 (36)
HDL cholesterol (mg/dL)	51 (15)	50 (14)	51 (15)	50 (15)	51 (15)	51 (15)	50 (14)
eGFR (mL/min/1.73 m ²)	80 (16)	77 (17)	79 (16)	81 (16)	83 (15)	80 (16)	76 (18)
hsCRP (mg/L)	1.7 (0.8, 4.0)	1.8 (0.8, 3.9)	1.7 (0.8, 4.0)	1.6 (0.8, 3.7)	1.8 (0.7, 4.3)	1.7 (0.8, 4.0)	2.7 (1.1, 4.9)
Lipid-lowering medications (%)	543 (16%)	146 (17%)	135 (15%)	143 (16%)	119 (14%)	513 (15%)	30 (20%)
FMD (IQI) (%)	3.9 (2.3, 6.0)	1.4 (0.9, 1.9)	3.0 (2.6, 3.5)	4.7 (4.3, 5.3)	7.7 (6.7, 9.1)	3.9 (2.3, 6.0)	2.9 (1.7, 4.5)

BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; FMD, flow-mediated dilation; HF, heart failure; hsCRP, high-sensitivity C-reactive protein; HTN, hypertension; IQI, interquartile interval; NT-proBNP, N-terminal of pro B-type natriuretic peptide; SD, standard deviation.

During a median of 12 years of follow-up, 149 participants developed HF (incidence rate 3.7 events per 1000 person years) (Figure 1, Supporting Information, Figure S2). There were 56 HFrEF cases (incidence rates 1.4 events per 1000 person years), 69 HFpEF cases (incidence rates 1.7 events per 1000 person years, Supporting Information, Figures S3 and S4), and 24 unclassifiable cases. When categorized by ischaemic aetiology, 41 events were HF with prior MI (incidence

rates 1.0 events per 1000 person years), and 108 were HF without prior MI (incidence rates 2.7 events per 1000 person years, Supporting Information, Figures S5 and S6). The follow-up and number of events in the different quartiles of FMD are shown in Supporting Information, Table S1.

As seen in Table 2, individuals in the highest quartile of FMD had a lower risk of incident HF compared with individuals in the lowest quartile in multivariable models adjusted

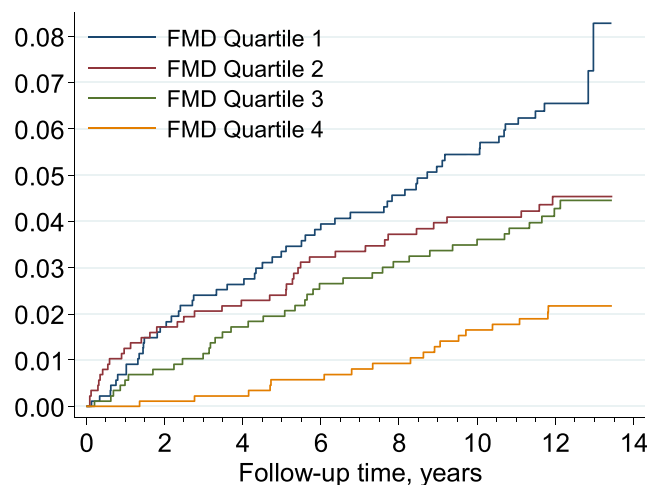
Figure 1 Accumulated incidence of heart failure by flow-mediated dilation (FMD) quartiles.

Table 2 The association between endothelial function (flow-mediated dilation) and the incidence of heart failure subgroups (heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, heart failure with a prior myocardial infarction, and heart failure without a prior myocardial infarction): multivariable Cox regression

FMD	Model A HR (95% CI)	Model B HR (95% CI)	Model C HR (95% CI)	Model D HR (95% CI)	Model E HR (95% CI)	
Heart failure	Per SD on log scale Q1 Q2 Q3 Q4 Per SD on log scale Q1 Q2 Q3 Q4	0.90 (0.78, 1.05) 1 (referent) 0.78 (0.50, 1.21) 0.92 (0.57, 1.48) 0.54 (0.30, 0.96) 0.77 (0.62, 0.94) 1 (referent) 0.49 (0.24, 1.03) 0.59 (0.27, 1.25) 0.30 (0.11, 0.81) 1.01 (0.80, 1.28)	0.90 (0.78, 1.05) 1 (referent) 0.82 (0.52, 1.28) 0.93 (0.58, 1.50) 0.53 (0.30, 0.95) 0.79 (0.64, 0.97) 1 (referent) 0.53 (0.25, 1.12) 0.63 (0.29, 1.35) 0.32 (0.12, 0.87) 0.99 (0.78, 1.26)	0.83 (0.69, 1.00) 1 (referent) 1.01 (0.59, 1.71) 0.73 (0.41, 1.30) 0.56 (0.30, 1.08) 0.70 (0.54, 0.90) 1 (referent) 0.51 (0.20, 1.33) 0.43 (0.15, 1.20) 0.35 (0.13, 0.96) 0.90 (0.67, 1.20)	0.90 (0.77, 1.05) 1 (referent) 0.83 (0.52, 1.32) 0.98 (0.60, 1.59) 0.53 (0.30, 0.95) 0.78 (0.63, 0.97) 1 (referent) 0.53 (0.25, 1.14) 0.64 (0.29, 1.43) 0.31 (0.12, 0.84) 1.01 (0.78, 1.29)	0.91 (0.78, 1.06) 1 (referent) 0.85 (0.54, 1.34) 0.94 (0.59, 1.52) 0.53 (0.30, 0.96) 0.79 (0.64, 0.98) 1 (referent) 0.54 (0.26, 1.15) 0.64 (0.30, 1.38) 0.32 (0.12, 0.88) 1.00 (0.79, 1.26)
HFrEF	Per SD on log scale Q1 Q2 Q3 Q4	1.03 (0.54, 1.99) 1.28 (0.64, 2.55) 0.77 (0.34, 1.74) 0.72 (0.59, 0.87) 1 (referent)	1.08 (0.56, 2.09) 1.26 (0.62, 2.53) 0.73 (0.33, 1.64) 0.69 (0.58, 0.84) 1 (referent)	1.28 (0.61, 2.70) 1.01 (0.44, 2.30) 0.72 (0.28, 1.83) 0.68 (0.55, 0.84) 1 (referent)	1.07 (0.54, 2.14) 1.39 (0.68, 2.82) 0.73 (0.32, 1.65) 0.69 (0.57, 0.85) 1 (referent)	1.13 (0.58, 2.21) 1.27 (0.63, 2.55) 0.73 (0.32, 1.64) 0.70 (0.57, 0.86) 1 (referent)
Heart failure with a prior myocardial infarction	Q1 Q2 Q3 Q4	0.69 (0.33, 1.44) 0.48 (0.20, 1.13) 0.10 (0.02, 0.44) 1.00 (0.82, 1.21)	0.73 (0.35, 1.55) 0.43 (0.17, 1.06) 0.10 (0.02, 0.43) 1.01 (0.83, 1.23)	0.90 (0.37, 2.16) 0.36 (0.13, 0.98) 0.12 (0.03, 0.55) 0.90 (0.70, 1.16)	0.78 (0.36, 1.69) 0.47 (0.19, 1.21) 0.10 (0.02, 0.45) 1.01 (0.83, 1.24)	0.80 (0.37, 1.71) 0.45 (0.18, 1.13) 0.10 (0.02, 0.44) 1.02 (0.84, 1.23)
Heart failure without a prior myocardial infarction	Q1 Q2 Q3 Q4	1 (referent) 0.82 (0.47, 1.41) 1.18 (0.67, 2.08) 0.81 (0.42, 1.54)	1 (referent) 0.86 (0.50, 1.50) 1.23 (0.70, 2.16) 0.81 (0.43, 1.55)	1 (referent) 1.05 (0.55, 2.02) 0.95 (0.47, 1.91) 0.84 (0.40, 1.74)	1 (referent) 0.87 (0.49, 1.53) 1.31 (0.74, 2.31) 0.81 (0.42, 1.54)	1 (referent) 0.88 (0.51, 1.54) 1.24 (0.71, 2.17) 0.81 (0.43, 1.55)

CI, confidence interval; FMD, flow-mediated dilation; HR, hazard ratio; HFpEF, heart failure with preserved ejection fraction (≥45%); HFrEF, heart failure with reduced ejection fraction (<45%); Q, quartile; SD, standard deviation.

Data are Cox proportional hazard ratios (95% confidence intervals). Bold indicate statistical significance ($P < 0.05$). Model A: age, sex, and race, Model B: Model A + predictors in the Atherosclerosis Risk in Communities Study heart failure score (body mass index, systolic blood pressure, sex, antihypertensive treatment, heart rate, diabetes, history of myocardial infarction, current smoker, and former smoker status), Model C: Model B + N-terminal of pro B-type natriuretic peptide, Model D: Model B + total and HDL cholesterol, lipid-lowering medication, estimated glomerular filtration rate, high-sensitivity C-reactive protein, fasting glucose, diastolic blood pressure, and alcohol, and Model E: Model B + coronary artery calcification.

for age, sex, and race/ethnicity or additional HF risk factors (Models A and B, respectively). Lower risk according to higher FMD was particularly evident for HFrEF and HF with prior MI, while no association was seen between FMD and HFpEF or HF without prior MI. Results remained similar after further adjustment for baseline NT-proBNP, albeit no longer statistically significant for overall HF (Table 2). As seen in Table 2, additional multivariable adjustment for total and HDL cholesterol, lipid-lowering medication, estimated glomerular filtration rate, hsCRP, fasting glucose, diastolic blood pressure, and alcohol use did not influence associations to a major extent (Model D), nor did additional adjustment for baseline CAC (Model E). Moreover, results were essentially unchanged when modelling age as a time scale of survival analysis, when accounting interim MI as a time-updated covariate, when taking the competing risk of death into account, or in sensitivity analyses including participants with an ankle/brachial index >0.9 (data not shown).

As seen in Table 3, we observed a significant interaction by race/ethnicity (P for interaction = 0.003). Specifically, there was reduced HF risk according to higher FMD in Caucasians (hazard ratio per standard deviation increment in FMD 0.72, 95% confidence interval 0.59–0.90) but a non-significant increase in HF risk (hazard ratio 1.18, 95% confidence interval 0.92–1.51) in African Americans. The risk estimate in Chinese was of similar magnitude as for the Caucasians (but with wider confidence intervals), while for Hispanics there

appeared to be no association between FMD and future HF. There was no effect modification of age or sex (data not shown).

The addition of FMD to established HF risk factors without or with NT-proBNP (Models B and C, respectively) generally rendered no or only modest improvement in C-statistics (Table 4). The only exception was the prediction of HF with prior MI where the addition of FMD rendered a substantial and statistically significant improvement in C-statistics beyond established risk factors, but not when NT-proBNP was included in the model (Table 3).

Discussion

Principal findings

In the present multi-ethnic cohort, endothelial dysfunction, as assessed by FMD, was primarily associated with HFrEF and HF with prior MI, but not with HFpEF or HF without a prior MI. Furthermore, our analyses suggest that there may be an interaction with race/ethnicity. Our data confirm and extend our understanding of the importance of endothelial dysfunction as an early risk factor predisposing to future HF events.

Table 3 The association between endothelial function (flow-mediated dilation) and the incidence of heart failure modified by race and ethnicity: multivariable Cox regression

Heart failure	Caucasian	Chinese American	African American	Hispanic
HR (95% CI) FMD per SD on log scale	0.72 (0.59, 0.90)	0.78 (0.41, 1.50)	1.18 ^a (0.92, 1.51)	1.00 (0.68, 1.46)
Number of events/participants	63/1168	15/634	39/791	32/903

CI, confidence interval; FMD, flow-mediated dilation; HR, hazard ratio; SD, standard deviation.

Data are Cox proportional hazard ratios (95% confidence intervals). Bold indicate statistical significance ($P < 0.05$). Model adjusted for age, sex, and race and predictors in the Atherosclerosis Risk in Communities Study heart failure score (body mass index, systolic blood pressure, sex, antihypertensive treatment, heart rate, diabetes, history of myocardial infarction, current smoker, and former smoker status).

^aStatistically different from Caucasian.

Table 4 Improvements in model discrimination by the addition of flow-mediated dilation to heart failure risk factors

FMD	Model B	Model B + FMD	Delta C	Model C	Model C + FMD	Delta C
Heart failure	0.774	0.776	0.002 (−0.002, 0.006)	0.841	0.840	−0.001 (−0.005, 0.004)
HFrEF	0.796	0.805	0.009 (−0.004, 0.022)	0.885	0.892	0.005 (−0.006, 0.016)
HFpEF	0.807	0.807	−0.000 (−0.001, 0.000)	0.837	0.836	−0.001 (−0.004, 0.002)
Heart failure with a prior myocardial infarction	0.786	0.808	0.023 (0.001, 0.044)	0.824	0.838	0.014 (−0.003, 0.032)
Heart failure without a prior myocardial infarction	0.791	0.791	0.000 (−0.000, 0.001)	0.858	0.857	−0.002 (−0.005, 0.002)

FMD, flow-mediated dilation; HFpEF, heart failure with preserved ejection fraction ($\geq 45\%$); HFrEF, heart failure with reduced ejection fraction ($< 45\%$).

Data are C-statistics. Bold indicate statistical significance ($P < 0.05$). Model B: age, sex, and race + Atherosclerosis Risk in Communities Study heart failure risk score, Model C: age, sex, and race + Atherosclerosis Risk in Communities Study heart failure risk score + N-terminal of pro B-type natriuretic peptide.

Comparison with the literature

During the last decades, several studies have reported that patients with symptomatic HF have coinciding endothelial dysfunction.^{8–11} Some of these previous studies demonstrated that endothelial dysfunction is particularly evident in patients with prevalent HFpEF,^{12,14–18} while another showed that this also holds true for prevalent HFrEF patients.¹³ In the community-based setting, FMD has been shown to be a powerful predictor for atherosclerotic diseases such as MI and stroke,^{4,26} but we are not aware of any previous study reporting the association between FMD and the incidence of HF or the different subtypes of HF. Importantly, our data do not support the previously proposed hypothesis that endothelial dysfunction is of particular importance for the development of HFpEF.^{12,14–18}

Potential mechanisms

Endothelial dysfunction and HF share many common risk factors, such as hypertension, obesity, dyslipidaemia, inflammation, impaired glucose metabolism, impaired kidney function, and smoking. Adjustment for these risk factors did not influence the associations between FMD and HF incidence to a major extent, indicating that they are not important confounders or mediators for the present associations. There was, however, a weak cross-sectional association between FMD and NT-proBNP at baseline, which implies that FMD to some degree also reflects subclinical left ventricular dysfunction. Still, FMD was associated with both HFrEF and HF with prior MI even after adjusting for baseline NT-proBNP, which indicates that confounding or mediation by asymptomatic left ventricular dysfunction at baseline is not the sole explanations of our findings.

The exact underlying pathophysiological mechanism for the association between FMD and HF incidence remains elusive. Even though it is not possible to draw firm conclusions regarding causality based on our observational data, there are several possible explanations for the present associations. The endothelium is responsible for a number of physiological functions that have been suggested to be important underlying factors in HF pathogenesis, including regulation of vascular tone, control of blood fluidity and coagulation, and regulation of inflammatory processes.⁸ Moreover, coronary endothelial dysfunction may lead to myocardial hypertrophy, stiffening, and interstitial fibrosis, and this crosstalk between the coronary endothelium and the cardiomyocytes may directly lead to impairments in cardiac function but possibly also to an increased susceptibility for widespread myocardial damage following an ischaemic event.²⁷

Regarding the more evident results for HFrEF over HFpEF and for HF with prior MI over HF without prior MI in our

study, impaired brachial artery FMD has been suggested to primarily reflect endothelial dysfunction in larger arteries but also an increased atherosclerotic burden.^{5,19,28} On the other hand, cardiac microvascular disease, a condition that is poorly reflected by FMD, has been shown to be an important underlying pathophysiological mechanism for HFpEF and HF without a previous MI.^{12,14,29} Thus, it may be reasonable that individuals with suboptimal FMD have an increased risk for atherosclerosis and MI, which in turn leads to HFrEF or HF with prior MI. Still, atherosclerosis may not be the only underlying mechanism as adjustment for baseline CAC did not influence the associations to a major extent. Studies evaluating the role of endothelial dysfunction in the micro-circulation for the development of HF are warranted.³⁰

Clinical implications

Whether FMD may be a useful tool for the prediction of atherosclerotic cardiovascular disease, such as MI or stroke, in the general population is under debate.^{4,31} In the present study, the addition of FMD to a model with established HF risk factors only improved the prediction of HF with prior MI, but not the other types of HF. Importantly, no improvement in risk prediction by FMD was seen if NT-proBNP was included in the base model. Particularly, because FMD is somewhat cumbersome to measure and not available in general clinical practice, our data do not suggest a broad application of estimating endothelial function by FMD in order to improve the prediction of HF in clinical practice, particularly if data on NT-proBNP are available.

Several types of treatment regimens, such as increased physical activity,³² dietary interventions,³³ weight loss,³⁴ or pharmacological treatment with statins³⁵ or antihypertensive agents,³⁶ have been shown to improve endothelial function. Of interest, many of these are simultaneously shown to reduce the risk of HF.³⁷ Nonetheless, future studies would be needed to assess whether targeting endothelial function can be an effective preventive approach for HF.

Strengths and limitations

Several limitations need to be acknowledged. First, the characterization of HFrEF and HFpEF was based on chart review, and the echocardiographic images obtained were not analysed centrally at a core facility. Second, around 15% of the HF events could not be classified as either of HF subtypes due to lack of ejection fraction data. Third, interaction analyses suggest that ethnicity may be an effect modifier of the associations between FMD and HF. However, as the number of HF events was modest in the different race/ethnicity strata, particularly for the subtypes of HF, these results should be interpreted with caution. Previous

reports from MESA suggest that although there may be differences in HF incidence by race/ethnicity,³⁸ there were no major differences in the importance of individual HF risk factors.³⁹ Additional studies are warranted to firmly establish the potential effect modification by race/ethnicity on the FMD–HF association. Our approach of subdividing HF events by whether participants had a preceding MI or not may be prone to misclassification as it is likely that some participants had MI that remain undiagnosed. The lack of 24 h blood pressure measurements may have underestimated the impact of blood pressure levels on these associations. As there was no data available on prevalent valvular disease or drug use, and as only one participant had prevalent atrial fibrillation at baseline, it was not possible for us to add these potential confounders in our multivariable modelling. Finally, this study was observational, and causality of relationships seen cannot be determined.

On the other hand, there were several strengths in the study such as the large study sample with measurements of FMD, a representative measure of endothelial function, and established HF risk factors, as well as the availability of longitudinal data on incident subtypes of HF.

Conclusions

Our community-based data suggest that endothelial dysfunction, as assessed by brachial FMD, is predominantly associated with the development of subtypes of HF such as HFrEF and HF with prior MI. Although our data do not support a role for FMD measurements for HF risk prediction in clinical practice, our results could have implications on our understanding of the pathophysiological contributions of endothelial function to the development of HF.

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Conflict of interest

There were no conflicts of interest for any of the authors.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Follow-up and number of HF events in quartiles of FMD.

Figure S1. Distribution of FMD.

Figure S2. Accumulated incidence of the different types of heart failure.

Figure S3. Accumulated incidence of HFrEF by FMD quartiles.

Figure S4. Accumulated incidence of HFpEF by FMD quartiles.

Figure S5. Accumulated incidence of HF with a prior MI by FMD quartiles.

Figure S6. Accumulated incidence of HF without a prior MI by FMD quartiles.

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