

Pedal Edema as an Indicator of Early Heart Failure in the Community

Prevalence and Associations With Cardiac Structure/Function and Natriuretic Peptides (MESA [Multiethnic Study of Atherosclerosis])

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Background—The prevalence of pedal edema (PE) and its associations with abnormal cardiac structure/function, natriuretic peptides, and incident heart failure (HF) is unknown, especially in community-dwelling adults without a history of cardiovascular disease.

Methods and Results—Out of 5004 MESA (Multiethnic Study of Atherosclerosis) participants who had cardiac magnetic resonance imaging, 4196 had complete data and were included in this analysis (3501 for the right ventricle analysis). Logistic regression and Cox proportional hazard analyses were used to assess the associations among self-reported PE, 2-pillow orthopnea, paroxysmal nocturnal dyspnea, left and right ventricular structure and function, natriuretic peptide levels, and incident HF. PE was present in 28% of the participants. PE was not associated with overt left or right ventricular systolic dysfunction (ejection fraction <50%). PE was associated with 2-pillow orthopnea (odds ratio 1.66; 95% confidence interval [CI], 1.30–2.12), paroxysmal nocturnal dyspnea (odds ratio 1.95; 95% CI, 1.55–2.44), and abnormal N-terminal pro-B-type natriuretic peptide levels (defined as >400 pg/mL; odds ratio 1.80; 95% CI, 1.21–2.68) in adjusted models. After a mean of 10.2 years of follow-up, 184/4196 (4.4%) participants had an adjudicated incident HF hospitalization. PE was associated with incident HF hospitalization in models adjusted for age, sex, and race (hazard ratio 1.44; 95% CI, 1.05–1.97). This association persisted after adding additional covariates, including comorbidities, baseline left ventricular ejection fraction, and antecedent myocardial infarction (hazard ratio 1.43; 95% CI, 1.02–1.99). The association of PE with incident HF was attenuated by further adjustment for N-terminal pro-B-type natriuretic peptide.

Conclusions—PE is prevalent in community-dwelling adults without clinically recognized cardiovascular disease and associated with future hospitalized HF. (*Circ Heart Fail.* 2016;9:e003415. DOI: 10.1161/CIRCHEARTFAILURE.116.003415.)

Key Words: cardiac structure and function ■ heart failure ■ natriuretic peptides ■ orthopnea ■ paroxysmal nocturnal dyspnea ■ pedal edema

Pedal edema (PE; foot and ankle swelling) is one of the cardinal signs of congestive heart failure (HF) but can also be because of other systemic or local conditions, including chronic kidney disease, liver disease, thyroid disorders, venous insufficiency, and venous thrombosis.¹ Often times, physicians are confronted with PE as an isolated complaint in a relatively asymptomatic patient. The finding of PE typically triggers investigations, such as an echocardiogram and B-type natriuretic peptide (BNP) testing, to rule out HF as the cause.² A normal BNP and normal biventricular systolic function are often considered helpful for excluding HF.³ However, it is now

clear that many patients have HF with a preserved ejection fraction (HFpEF) and that many patients with HFpEF have normal BNP levels.^{4–6}

See Clinical Perspective

Currently, there are no data on the prevalence of PE in the general population without clinically recognized cardiovascular disease (CVD). It is also unclear whether isolated PE is a benign process, a sign of early HF, or a harbinger of future clinically overt (hospitalized) HF. Given the difficulty in recognition (and underappreciation) of the clinical syndrome

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of HFpEF and the fact that epidemiological estimates of HF (including HFpEF) are based primarily on hospitalized HF, it is possible that PE—when combined with other symptoms of HF, abnormalities in cardiac structure/function, and BNP levels—could provide insight into the true prevalence of HF (particularly early HF) in the community.

We, therefore, examined PE in a multiethnic, community-based cohort free of overt CVD (the MESA [Multiethnic Study of Atherosclerosis]), with the following hypotheses: (1) PE is common in community-dwelling adults without known CVD, and (2) despite multiple possible causes of PE, it is frequently associated with indices of abnormal cardiac function, suggesting that early HF, particularly early HFpEF, is more common than previously appreciated. Here we report the association between self-reported PE, symptoms of HF, biventricular structure and function, N-terminal proBNP (NT-proBNP) levels, and incident hospitalized HF in MESA.

Methods

Study Population and Data Collection

A detail study design for MESA has been published elsewhere.⁷ In brief, MESA is a prospective cohort study begun in July 2000 to investigate the prevalence, correlates, and progression of subclinical CVD in individuals without known CVD at baseline. The cohort includes 6814 women and men aged 45 to 84 years recruited from 6 US communities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; northern Manhattan, NY; and St. Paul, MN). MESA participants were 38% white (n=2624), 28% black (n=1895), 22% Hispanic (n=1492), and 12% Chinese (n=803). Individuals with a history of physician-diagnosed myocardial infarction, angina, HF, stroke or transient ischemic attack, or who had undergone an invasive procedure for CVD (coronary artery bypass graft, angioplasty, valve replacement, pacemaker placement, or other vascular surgeries) were excluded. This study was approved by the Institutional Review Boards of each study site, and written informed consent was obtained from all participants.

Demographics, medical history, anthropometric and laboratory data for this study were obtained at the first MESA examination (July 2000 to August 2002). Current smoking was defined as having smoked a cigarette in the last 30 days. Diabetes mellitus was defined as fasting glucose ≥ 126 mg/100 mL or the use of hypoglycemic medications. Use of antihypertensive and other medications was based on the review of prescribed medication containers. Resting blood pressure (BP) was measured 3 \times in seated position, and the average of the second and third readings was recorded. Hypertension was defined as a systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg, or use of medication prescribed for hypertension. Body mass index was calculated as weight (kg)/height (m²). Total and high-density lipoprotein cholesterol were measured from blood samples obtained after a 12-hour fast. Low-density lipoprotein cholesterol was estimated by the Friedewald equation.⁸

MESA Questionnaire Variables

During the baseline MESA examination, a questionnaire was administered to participants. Participants answered yes, no, and don't know to questions such as, "do you experience swelling of your feet or ankles," "how many pillows do you sleep on at night," and "do you sometimes wake up at night with trouble breathing." Participants who responded yes having feet or ankle swelling were labeled as having PE. Participants who sleep on >2 pillows were labeled as having orthopnea, and those who wake up at night with trouble breathing were labeled as having paroxysmal nocturnal dyspnea (PND). Participants who responded don't know were excluded from the present analysis (n=15).

Cardiac Magnetic Resonance Imaging

Consenting participants underwent a cardiac magnetic resonance imaging (MRI) scan a median of 16 days after the baseline evaluation; 95% was completed within 11 weeks after the baseline examination. Participation in the MRI examination was voluntary unless participants have contraindications such as metal implants. All imaging was done with a 4-element phased-array surface coil positioned anteriorly and posteriorly, electrocardiographic gating, and brachial artery BP monitoring.⁹ Imaging consisted of fast gradient echo cine images of the left ventricle with time resolution <50 ms. Functional parameters and mass were determined by volumetric imaging. Imaging data were read using MASS software (version 4.2; Medis, Leiden, the Netherlands) at a single reading center by trained readers blinded to risk factor information. Papillary muscles were included in the LV volumes and excluded from LV mass. LV end-diastolic volume and LV end-systolic volume were calculated using Simpson's rule (the summation of areas on each separate slice multiplied by the sum of slice thickness and image gap). LV mass was determined by the sum of the myocardial area (the difference between endocardial and epicardial contour) times slice thickness plus image gap in the end-diastolic phase multiplied by the specific gravity of myocardium (1.05 g/mL). Left ventricular ejection fraction (LVEF) was calculated as LV stroke volume/LV end-diastolic volume $\times 100$. The interobserver variability in estimating LV parameters was LVEF (5.1%; 95% confidence interval [CI], 3.6–6.7), and intraobserver variability in estimating LV parameters was left ventricular mass (6.3 gm; 95% CI, 5.17–7.38); LVEF (3.9%, 95% CI, 3.06–4.72). LV systolic dysfunction (LVSD) was defined as LVEF <50%. Five thousand and four out of 6814 MESA participants had cardiac MRI during the baseline examination.

The cardiac MRI protocol and interpretation of right ventricular (RV) parameters have previously been described.^{10–12} The endocardial and epicardial borders of the RV were traced manually on the short-axis cine images at the end-systolic and end-diastolic phases. Full visualization of the correct placement of RV contours relied on evaluation of cine images to determine the demarcation between the right atrium and the RV. Contours were modified at basal slices of the heart by careful identification of the tricuspid valve so as to exclude the right atrium and to avoid overestimation of the volumes. The outflow tract was included in the RV volume. Papillary muscles and trabeculae were included in the RV volumes. RV end-diastolic volume (RVEDV) and RV end-systolic volume were calculated with the Simpson rule by summation of areas on each slice multiplied by the sum of slice thickness and image gap. RV mass was determined at the end-diastole phase as the difference between end-diastolic epicardial and endocardial volumes multiplied by the specific gravity of myocardium (1.05 g/mL). Right ventricular stroke volume was calculated by subtracting RV end-systolic volume from RVEDV; RV ejection fraction (RVEF) was calculated by dividing right ventricular stroke volume by RVEDV. The intrareader intraclass correlation coefficient from random, blinded rereads of 229 scans for RVEDV and RVEF were 0.99 and 0.89 respectively. The inter-reader intraclass correlation coefficients from random, blinded rereads of 240 scans for RVEDV and RVEF were 0.96 and 0.80, respectively. RV systolic dysfunction (RVSD) was defined as RVEF <50%.^{13,14} Four thousand two hundred and four out of the 5004 MESA participants who had baseline cardiac MRI had RV structure and function were assessed.

NT-ProBNP Assay

NT-proBNP levels were measured from serum collected during the baseline MESA examination and stored at -70°C . The serum samples were thawed prior to testing (maximum of 3 freeze-thaw cycles). NT-proBNP levels were measured using the Elecsys 2010 system (Roche Diagnostic, Indianapolis IN) at a core laboratory (Veteran's Affairs San Diego Healthcare System, La Jolla, CA). Prior studies have shown that measurement of NT-proBNP using this assay does not change after 5 freeze-thaw cycles.^{15,16} Intra-assay and interassay coefficient of variation at various concentrations of NT-proBNP have been previously reported.¹⁶ The analytic measurement range for NT-proBNP was 5 to 35 000 pg/dL. Abnormal NT-proBNP levels was defined as >400 pg/dL. Four thousand one

hundred and ninety-six out of the 5004 participants who had cardiac MRI had NT-proBNP levels measured.

Ascertainment of Outcomes

Outcomes in MESA are adjudicated by a committee, which includes a cardiologist, a cardiovascular physician-epidemiologist, and a neurologist. Reviewers/adjudicators classified incident hospitalized HF as definite, probable, or absent. Definite or probable HF required HF symptoms, such as shortness of breath or edema; probable HF required HF diagnosed by a physician and patient receiving medical treatment for HF. Definite HF required one or more other criteria, such as pulmonary edema/congestion by chest X-ray; dilated ventricle or poor LV function by echocardiography or ventriculography; or echocardiography evidence of left ventricular diastolic dysfunction. Individuals with adjudicated definite or probable HF were used in our analysis. All-cause mortality (death) was also adjudicated by committee.

Statistical Analysis

Demographic characteristics of participants who responded yes to ankle and feet swelling (PE) and those who reported no (no PE) are reported as mean±SD for continuous variables and as counts and percentages for categorical variables. *T* tests were used for continuous variables, and chi-squared tests were used for categorical variables for the comparison of baseline variables between those with versus without PE. Nonparametric tests were used for non-normally distributed continuous variables. Logistic regression analysis was used to assess the association between PE and orthopnea, PND, LVSD, RVSD, and abnormal NT-proBNP on univariable and multivariable analyses. Covariates for the multivariable model were chosen based on clinical relevance and included the following potential confounders: age, sex, race/ethnicity, body mass index, systolic BP, diabetes mellitus, cigarette smoking status, and serum creatinine levels. A relatively small number of participants had LVSD and RVSD (Table 1); therefore, as a sensitivity analysis, the association between PE and RVEF and LVEF was also assessed using the general linear model.

Cumulative hazard curves of participants with versus without incident hospitalized HF were generated and evaluated using the log-rank test. Cox proportional hazard analyses were used to assess the association between PE and incident HF adjusting for covariates (chosen based on clinical or pathophysiological relevance) in 3 models: model 1 adjusted for age, sex, and race/ethnicity; model 2 adjusted for model 1 covariates plus systolic BP, body mass index, BP medication use, diabetes mellitus, cigarette smoking status, baseline LVEF, high-density lipoprotein, low-density lipoprotein cholesterol, serum creatinine levels, urinary albumin levels, and antecedent MI, which occurred during the follow-up; and model 3 adjusted for model 2 covariates plus NT-proBNP levels. We also assessed the effects of mortality as a competing risk in our analyses using the subdistribution proportional hazard models proposed by Fine and Gray.¹⁷ All statistical analyses were performed using SAS software (version 9.2, SAS Institute, Cary, NC).

Results

Out of the 5004 MESA participants who had cardiac MRI during the baseline examination, 4196 participants responded yes/no to the questionnaire and were, therefore, included in this analysis. Table I in the [Data Supplement](#) shows the demographics and CVD risk factor profile of the present study cohort compared with the total MESA cohort. Total MESA participants (N=6814) were older and more likely to be female, to be smoker (former/current), and to have diabetes mellitus compared with the present study cohort (N=4196).

Only 3501 out of the 4196 had data on RV structure and function. One thousand one hundred and eighty-six of 4196 (28.2%) participants admitted to having PE. One hundred and twenty-nine

Table 1. Participant Characteristics, Stratified by Presence or Absence of Pedal Edema (N=4196)

Variables	No Pedal Edema (N=3010); Mean±SD or %age	Pedal Edema (N=1186); Mean±SD or %age	P Value
Age, y	61.1±10.2	63.5±10.1	<0.001
Female, %	43.6	69.7	<0.001
Race/ethnicity, %			
White	40.5	36.7	<0.0001
Chinese	17.4	6.8	
Black	19.9	30.4	
Hispanic	22.2	26.0	
Body mass index, kg/m ²	26.9±4.5	29.7±5.4	<0.001
Blood pressure, mm Hg			
Systolic	123.8±20.5	130.1±30.1	<0.001
Diastolic	71.9±10.1	71.2±10.8	0.86
Blood pressure meds, %	26.3	43.5	<0.001
Any CCB	9.8	17.4	
Any diuretics	8.5	21.6	
Any ACEI	9.7	15.6	
Any β-blocker	7.6	12.4	
Cigarette smoking, %			
Never	52.1	52.2	0.41
Former	35.2	36.6	
Current	12.7	11.2	
Cholesterol, mg/dL			
Total	194.4±34.9	194.2±37.2	0.86
LDL	117.7±31.0	115.1±32.2	0.002
HDL	50.4±14.8	52.4±15.0	0.01
Triglycerides	133.0±88.2	134.5±84.9	0.60
Diabetes mellitus	10.7	14.9	0.002
Serum creatinine, mg/dL	0.96±0.23	0.96±0.52	0.88
Sleep on >2 pillows	6.4	13.8	<0.001
Wake up at night with trouble breathing	8.1	15.3	<0.001
Estimated GFR, mL/min per 1.73 m ²	81.1±16.4	79.8±20.4	0.11
Urinary albumin, mg/dL, Median (Q1–Q3)	0.60 (0.3–1.2)	0.7 (0.3–1.5)	0.002
LVEF, %	68.7±7.5	69.8±7.4	0.18
ASLVD (<50%)	66 (2.1)	15 (1.3)	
LV mass index, g/m ²	78.7±16.5	77.5±16.6	0.35
LV end diastolic vol, mL/m ²	68.9±13.8	67.2±13.2	0.08
RVEF,* %	70.2±6.5	71.2±6.5	0.115
RVSD (<50%)	0.2	0.5	
RV mass index,* g/m ²	11.5±1.9	11.1±1.9	0.13

(Continued)

Table 1. Continued

Variables	No Pedal Edema (N=3010); Mean±SD or %age	Pedal Edema (N=1186); Mean±SD or %age	P Value
RV end diastolic vol,* mL/m ²	67.7±12.7	64.8±12.4	0.003
NT-proBNP, pg/mL, Median (Q1–Q3)			
Abnormal NT-proBNP	48.2 (20.8–95.0)	71.9 (33.5–153.7)	<0.0001
> 400 pg/mL	62.3	5.1	

ACEI indicates angiotensin-converting enzyme inhibitor; ASLVD, asymptomatic left ventricular systolic dysfunction; CCB, calcium channel blocker; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricle; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Q1–Q3, first–third quartiles; RV, right ventricular; RVEF, right ventricular ejection fraction; and RVSD, right ventricular systolic dysfunction.

*Right ventricular (RV) measures available in 3501 out of 4196 participants.

of 4196 (3.1%) participants had abnormal NT-proBNP levels, and 60/1186 (5.1%) participants who admitted to having PE also had abnormal NT-proBNP. The Venn diagram shows the distribution PND±2-pillow orthopnea and an abnormal NT-proBNP among MESA participants who reported having PE (298/1186; Figure 1). Eighteen of 256 (7.0%) participants with PND±2-pillow orthopnea had abnormal NT-proBNP levels. Participants with PE were older, more likely to be females, and had worse cardiovascular risk factor distribution compared with those who denied having PE (Table 1). Participants with PE had similar LV/RV structure and functional parameters compared with those with no PE, except for RVEDV index, which was significantly higher in those with no PE.

In our logistic regression models, PE was not associated with abnormal LVSD/RVSD in both univariate and multivariable models. However, participants with PE were more likely to sleep on at least 2 pillows and wake up at night with trouble breathing (PND) in our multivariable logistic regression models (hazard ratio [95% CI], 1.66 [1.30–2.12] and 1.95 [1.55–2.44], respectively). PE was also significantly associated with abnormal NT-proBNP levels in univariate and multivariable models (hazard ratio [95% CI], 2.27 [1.60–3.20] and 1.80 [1.21–2.68], respectively; Table 2). PE was also not significantly associated with LVEF (continuous variable) and RVEF (continuous variable) in both the univariate (data not shown) and multivariable general linear models ($\beta \pm SE$, -0.092 ± 0.26 ; $P=0.72$ and -0.162 ± 0.25 ; $P=0.51$, respectively).

After 10 years of follow-up, 184/4196 (4.5%) of the participants had an adjudicated hospitalized HF (No PE =4.0% versus PE=5.4%). PE was a predictor of incident HF in univariate analysis (Table 3 and Figure 2). PE was an independent predictor of future adjudicated HF in our multivariable Cox models (Table 3). The association of PE with incident HF was attenuated when NT-proBNP levels (continuous and categorical) were added to the multivariable Cox model. Our subdistribution proportional hazard models assessing mortality as a competing risk of HF yielded similar estimates and CIs as in Table 3. Two-pillow orthopnea and PND were not

associated with incident CHF in univariate and multivariable models (data not shown) and, therefore, were not treated as confounders of the association between PE and incident hospitalized HF. However, forcing 2-pillow orthopnea or PND into our multivariable Cox models did not change our point estimates or 95% confidence intervals.

Discussion

The goal of this study was to assess the prevalence of PE in community-dwelling adults without clinically recognized CVD, the associations of PE with other symptoms of HF and abnormalities in indices of cardiac structure/function, and the association of PE and incident hospitalized HF. Our data showed that PE is prevalent (28%) in community-dwelling adults and is not associated with overt LVSD or RVSD, but is associated with abnormal levels of NT-proBNP and incident hospitalized HF. Thus, PE in asymptomatic community-dwelling adults may be a sign of early HF (particularly early HFpEF) and also may be a harbinger of future hospitalized HF. To our knowledge, this is the first study that has (1) provided the prevalence of PE in community-dwelling adults with no history of CVD and (2) shown an association between PE and incident hospitalized HF.

MESA is a population-based study that by design recruited adults with no prior clinical history (or clinical recognition) of CVD, including HF. However, based on the present analysis, greater than one fourth of the participants admitted to having PE. Even though participants with PE were not more likely to have overt LVSD or RVSD compared with those with no PE, they were twice as likely to sleep on ≥ 2 pillows (orthopnea) and wake up at night with trouble breathing (PND) and were more likely to have abnormal NT-proBNP levels. Diastolic function was not assessed during the MESA baseline examination, and therefore, it is unknown if PE is also associated with impaired LV relaxation, reduced LV compliance, or both. However, the associations observed in the participants with PE in MESA, such as orthopnea and PND, are suggestive of early signs and symptoms of HF. It is possible that targeting

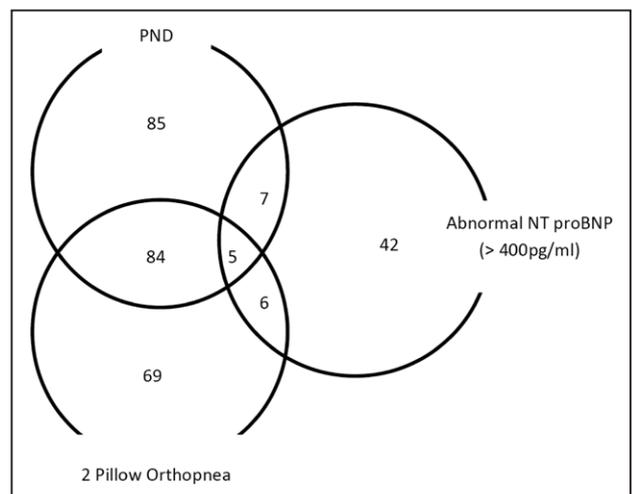


Figure 1. Distribution of paroxysmal nocturnal dyspnea (PND) ±2 pillow orthopnea and abnormal N-terminal pro-B-type natriuretic peptide (NT-proBNP; >400 pg/mL) among MESA (Multiethnic Study of Atherosclerosis) participants with pedal edema (N=298).

Table 2. Logistic Regression Models Showing the Association of Self-Reported Pedal Edema and Left/Right Ventricular Systolic Dysfunction (EF<50%) and Abnormal NT-ProBNP (>400 pg/mL) in MESA

	Univariate Odds Ratio (95% CI)	P Value	Multivariable* Odds Ratio (95% CI)	P Value
LVSD (LVEF <50%)	0.61 (0.35–1.08)	0.87	0.83 (0.45–1.54)	0.57
RVSD (RVEF <50%)†	0.70 (0.42–1.19)	0.19	0.67 (0.38–1.19)	0.82
Abnormal NT-proBNP (>400 pg/mL)	2.27 (1.60–3.20)	<0.001	1.80 (1.21–2.68)	0.004
Sleep on >2 pillows	2.36 (1.90–2.94)	<0.001	1.66 (1.30–2.12)	<0.001
Wake up at night with trouble breathing	2.06 (1.67–2.53)	<0.001	1.95 (1.55–2.44)	<0.001

BMI indicates body mass index; BP, blood pressure; CI, confidence interval; EF, ejection fraction; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MESA, Multiethnic Study of Atherosclerosis; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RVEF, right ventricular ejection fraction; and RVSD, right ventricular systolic dysfunction.

*Adjusted for age, sex, race/ethnicity, BMI, systolic BP, diabetes mellitus, cigarette smoking status, and serum creatinine levels.

†Only 3501 out of 4196 had RVEF available.

individuals in early stages of HF may reduce the prevalence of overt, hospitalized HF in the community. Based on our results, systematic programs for the early detection of community-dwelling individuals at risk or with early signs and symptoms of HF are likely needed, and screening based on simple measures such as PE, orthopnea, and PND with subsequent natriuretic peptide testing could be tested with the goal of reducing incident hospitalizations for HF.

HF is a leading cause of morbidity and mortality in the world today, despite decades of research and multiple therapeutic options for chronic HF with reduced EF.^{18,19} Current data suggest that although the prevalence of HF with reduced EF seems to have plateaued or on the decline, the prevalence of HFpEF is rising.^{20,21} Unfortunately, nearly all therapeutic HFpEF trials have produced null results.^{22,23} Historically, HFpEF clinical trials have included patients with relatively preserved LVEF and a clinical history of overt HF, defined as either a prior hospitalization of HF or elevated natriuretic peptides.²³ Such patients may already have advanced stages of HFpEF and, therefore, may be difficult to either reverse or control with therapy. Prevention may be a better approach to reducing and controlling HFpEF and should target community-based adults with early stages of the HFpEF syndrome.

In response to increased myocardial stress because of volume/pressure overload states, the BNP gene is activated in cardiomyocytes, resulting in the production of an intracellular precursor propeptide (proBNP₁₀₀).³ Further processing of this propeptide results in the release of the biologically inert

amino-terminal fragment (NT-proBNP). Thus, high levels of NT-proBNP signals an increase in myocardial wall stress, an abnormality associated with HF syndromes.²⁴ However, an invasive exercise hemodynamic study by Borlaug et al²⁵ showed that patients with early HFpEF have low/normal natriuretic peptide levels and normal filling pressures at rest but increased filling pressures diagnostic of HF during exercise. High or abnormal NT-proBNP levels at rest may, therefore, represent a more advanced stage of HFpEF than the very early stage studied by Borlaug et al.²⁵ However, the invasive nature of the approach used by Borlaug et al to screen/diagnose early HFpEF makes it impractical for deployment on a wide scale as a screening tool compared with PE. In the present study, NT-proBNP levels were drawn at rest, and participants with PE were twice as likely to have high/abnormal NT-proBNP compared with those without PE. The addition of NT-proBNP to our full model also attenuated the association between PE and incident HF. Thus, in community-dwelling adults without history of CVD, PE may indicate high/abnormal NT-proBNP and may signal an increase in myocardial wall stress, a pathological process central to the development of clinical HF. Even though the vast majority of MESA participants with PE had normal NT-proBNP levels, the median values were 50% higher than in participants without PE, and given the association with orthopnea and PND (with no overt LVSD), many of these participants likely had unrecognized early HFpEF. This finding underscores the possibility that the prevalence of (early) HF is likely higher than previously

Table 3. Cox Proportional Hazard Models Showing the Association Between Self-Reported Pedal Edema and Incident Congestive Heart Failure

	No. of Events	Unadjusted Hazard Ratio (95% CI)	Model 1,* Hazard Ratio (95% CI)	Model 2,† Hazard Ratio (95% CI)	Model 3,‡ Hazard Ratio (95% CI)
Pedal edema	184/4196	1.39 (1.03–1.88)	1.44 (1.05–1.97)	1.43 (1.02–1.99)	1.27 (0.94–1.79)
		P=0.032	P=0.022	P=0.038	P=0.166

BMI indicates body mass index; BP, blood pressure; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Model 1, adjusted for age, sex, and race/ethnicity.

†Model 2, model 1+systolic BP, BP meds, diabetes mellitus, BMI, cigarette smoking status, baseline LVEF, LDL and HDL cholesterol, serum creatinine and urinary albumin level, and antecedent myocardial infarction, which occurred during the follow up.

‡Model 3, model 2+NT-proBNP levels.

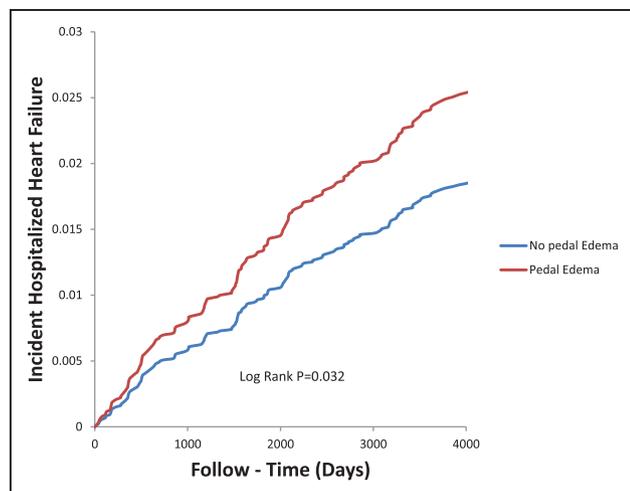


Figure 2. Cumulative hazard curves of participants with and without pedal edema and incident hospitalized heart failure over the follow-up period.

recognized in the general population and that early HF, particularly HFpEF, is common.

Our study found lower RV mass index (did not reach statistical significance) and RVEDV index in participants with PE compared with those without PE during the baseline MESA examination. Although this finding is unadjusted (Table 1), it is contrary to the accumulating data that RV dysfunction is common in patients with HFpEF.^{26–28} However, it should be noted that our study population consists of participants with no clinical diagnosis or established HFpEF,⁷ and therefore, those with PE may represent early undiagnosed HFpEF, while most of these studies^{27,28} used patients with diagnosed and more advanced stage of HFpEF.^{26,27} In addition, most of these advanced-stage HFpEF patients had other significant comorbidities, such as atrial fibrillation, significant tricuspid regurgitation, RV pacemaker insertions, and pulmonary hypertension,^{26–28} to name a few, all of which were absent in our cohort and are possible causes of RV dysfunction. MESA also did not assess pulmonary hemodynamics, and so it is unclear whether the difference in RV parameters observed could be attributed to differences in pulmonary pressures in those with and without PE. In the highly selected but clinically important retrospective and invasive study by Borlaug et al²⁶ on early HFpEF, RV parameters and PE were not reported in participants. Thus, the RV dysfunction observed in prior HFpEF studies^{25–27} may either be a marker of clinically advanced stages of HFpEF or may be because of other comorbidities prevalent in clinically advanced HFpEF patients. Our study findings also suggest that PE may predate RV dysfunction in early HFpEF.

Our study had several limitations, notably the lack of objective data on PE. There may be recall bias in the self-reported PE, which may affect our results and conclusions. Data for validation of self-reported PE is not available in MESA. We are also not aware of any data on the reliability of self-reported PE. However, any discrepancy in self-reported versus objective PE would have likely attenuated

the associations observed in our study. Our study is also an observational study, and although we adjusted for covariates, our results may be affected by residual confounding. The baseline MESA examination cardiac MRI did not evaluate for diastolic function or myocardial fibrosis, both of which could have added additional pathophysiologic insight into the association between PE and HF, particularly HFpEF. However, it should be noted that HFpEF is now known to be associated with multiple cardiac and extra-cardiac pathophysiologic abnormalities beyond diastolic dysfunction and myocardial fibrosis. The current analysis also did not account for change in medications use, especially diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β -blockers during the follow-up period. About 10% of participants were taking calcium channel blockers, a group of drugs associated with PE, during the baseline MESA examination. Sensitivity analyses eliminating participants on calcium channel blockers produced similar estimates and conclusions. We did not stratify our analysis by type of HF (HF with reduced EF and HFpEF) because of the relatively small number of MESA participants with available data on LVEF at time of clinical HF diagnosis.

Conclusions

PE is present in nearly one third of community-dwelling adults without clinically recognized CVD. The presence of PE is not associated with overt LVSD or RVSD but is associated with other symptoms of HF, abnormal NT-proBNP levels, and incident hospitalized HF. These findings suggest that early HF, particularly early HFpEF, may be under-recognized in the general population and may present an important opportunity for the prevention and progression of HF and HF-related morbidity/mortality.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Heart failure (HF) is a major cause of morbidity and mortality in the developed world. Prevention and early identification in asymptomatic community-dwelling adults may help reduce the prevalence of HF. Pedal edema (PE) is one of the cardinal signs of HF. However, the prevalence, associations, and prognosis of PE in asymptomatic community-dwelling adults without history of cardiovascular disease is unknown. We used data from participants of the ongoing MESA cohort (Multi-ethnic Study of Atherosclerosis) to show that PE is (1) prevalent ($\approx 28\%$); (2) associated with other signs and symptoms of congestive HF, such as orthopnea and paroxysmal nocturnal dyspnea; (3) associated with abnormal N-terminal pro-B-type natriuretic peptide levels; and (4) associated with future hospitalized HF in community-dwelling adults without history of cardiovascular disease. PE was not associated with reduced right or left ventricular systolic function in this cohort. Thus, despite the heterogeneous causes of HF, a preventive approach targeting PE as a symptom may help identify those with early HF or at risk for future hospitalized HF. These findings also suggest that early HF, particularly early HF with preserved ejection fraction, may be under-recognized in the general population and may present an important opportunity for the prevention and progression of HF and HF-related morbidity/mortality.

Pedal Edema as an Indicator of Early Heart Failure in the Community: Prevalence and Associations With Cardiac Structure/Function and Natriuretic Peptides (MESA [Multiethnic Study of Atherosclerosis])

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SUPPLEMENTAL MATERIAL

Supplemental Table 1: Demographic and CVD risk factor characteristics of the total MESA cohort (N=6814) and the participants in this study (N=4196)

	MESA Cohort(N=6814)	Study Cohort(N=4196)	P value
Age(yrs.)	62.3 ±10.2	61.8 ±10.2	0.02
Female (%)	52.5	51.0	0.01
Body mass index	28.4 ±5.5	27.7± 4.9	0.21
Race/Ethnicity (%)			0.001
White	38.0	39.4	
Chinese	12.0	14.4	
African American	28.0	22.9	
Hispanic	22.0	23.3	
Cigarette Smoking (%)			0.01
Never	50.2	52.1	
Former	36.6	35.6	
Current	13.2	12.6	
Blood Pressure			0.32
Systolic	126.8 ±12.6	125.6± 21.4	
Diastolic	72.0± 10.3	71.7± 10.3	
Cholesterol			0.11
Total	194.0± 35.7	194.3 ±35.6	
LDL	117.1± 31.4	117.0± 31.4	
HDL	50.8± 14.8	50.9 ±14.8	
Triglycerides	132.0± 88.8	133.0± 87.2	
Diabetes Mellitus (%)	12.9	11.9	0.04