Original Investigation

Association of Elevated Plasma Endothelin-1 Levels With Pulmonary Hypertension, Mortality, and Heart Failure in African American Individuals
The Jackson Heart Study

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IMPORTANCE Despite pathophysiological links between endothelin-1 and pulmonary vascular remodeling, to our knowledge, the association between plasma endothelin-1 levels and pulmonary hypertension has not been studied in the general population. Also, whether endothelin-1 can predict future heart failure and mortality, outcomes that are associated with pulmonary hypertension, in a population cohort is unclear.

OBJECTIVE To determine whether elevated plasma endothelin-1 levels are associated with pulmonary hypertension, mortality, and heart failure.

DESIGN, SETTING, AND PARTICIPANTS Data from the Jackson Heart Study, a longitudinal, prospective observational cohort study of heart disease in African American individuals from Jackson, Mississippi, were analyzed. The community population sample was limited to participants with detectable tricuspid regurgitation on echocardiography. The study participants included self-identified African American individuals with plasma endothelin-1 levels and tricuspid regurgitation on echocardiogram (n = 3223) at the time of first examination (2000-2004). The analysis of the data began on April 14, 2014, and was completed on February 23, 2016.

EXPOSURE Log-transformed plasma endothelin-1 level.

MAIN OUTCOMES AND MEASURES Cross-sectional analysis: presence of pulmonary hypertension (defined as an elevated pulmonary artery systolic pressure >40 mm Hg on echocardiogram). Longitudinal outcomes were all-cause mortality (median follow-up, 7.75 years) and heart failure admissions (median follow-up, 5.32 years).

RESULTS Of the 3223 participants enrolled in the study, 1051 were men (32.6%). Mean (SD) endothelin-1 levels were 1.36 (0.64) pg/mL; 217 of 3223 cohort members (6.7%) had pulmonary hypertension. After adjusting for potential confounders, log-transformed endothelin-1 levels were associated with increased odds of pulmonary hypertension (adjusted odds ratio per log increment in endothelin-1, 1.66; 95% CI, 1.16-2.37). Log-transformed endothelin-1 levels were associated with mortality (adjusted hazard ratio per log increment in endothelin-1, 1.69; 95% CI, 1.27-2.25; median follow-up, 7.75 years) and heart failure (adjusted hazard ratio per log increment in endothelin-1, 1.57, 95% CI, 1.05-2.37; median follow-up, 5.32 years) in the study cohort. Phenotyping by pulmonary hypertension and endothelin-1 level showed mortality decreasing in order from subgroup with pulmonary hypertension and high endothelin-1 (high endothelin-1: ≥1.7 pg/mL; upper quartile); pulmonary hypertension and low endothelin-1 <1.7 pg/mL; lower 3 quartiles); no pulmonary hypertension and high endothelin-1; and no pulmonary hypertension and low endothelin-1 (log-rank $\chi^2 = 77.16$; $P < .01$).

CONCLUSIONS AND RELEVANCE Elevated plasma endothelin-1 levels, especially associated with an elevated pulmonary artery systolic pressure on echocardiogram, may identify an at-risk population that could be evaluated for targeted prevention and management strategies in future studies.

JAMA Cardiol. doi:10.1001/jamacardio.2016.0962
Published online June 8, 2016.

Supplemental content at jamacardiology.com

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Endothelin-1 (ET) is a peptide involved in vascular tone modulation with mitogenic and proinflammatory effects[1] that has been implicated in pathophysiological changes associated with both microvascular and macrovascular disease.[2-5] Overexpression of ET has been observed in individuals with elevated pulmonary artery pressures[6] such as in congestive heart failure [7-10] and idiopathic pulmonary arterial hypertension (PAH).[6,11] However, to our knowledge, the relationship between circulating ET levels and pulmonary artery pressures has not been studied in a community-based cohort. More importantly, whether ET can serve as a biomarker of poor vascular health and predict the future development of clinical heart failure (HF) requiring hospital admission or even mortality independent of baseline pulmonary artery pressures is unknown.

In this study, we sought to examine the association of plasma ET levels with pulmonary hypertension (PH) as indicated by an elevated pulmonary artery systolic pressure (PASP) on echocardiogram; mortality; and HF admissions in participants in the Jackson Heart Study (JHS). We hypothesized that elevated ET levels are associated with PH and would be associated with subsequent morbidity and mortality independent of PA pressures.

Key Points

Question Are plasma endothelin-1 levels associated with pulmonary hypertension, mortality, and heart failure hospitalizations?

Findings Plasma endothelin-1 levels were significantly associated with pulmonary hypertension in participants with detectable tricuspid regurgitation on echocardiography in the Jackson Heart Study, a prospective observational study of heart disease in African American individuals. Endothelin-1 levels were associated with subsequent heart failure admissions and mortality.

Meaning Elevated plasma endothelin-1 levels identify an at-risk population that could be evaluated for targeted prevention strategies in future studies.

Methods

We conducted cross-sectional and longitudinal analyses using data from the JHS. The conduct of the JHS was approved by the University of Mississippi Medical Center Institutional Review Board. The participants gave written informed consent to participate in the research study. This analysis of the JHS data was approved by the Providence Veterans Affairs Medical Center Institutional Review Board. See eMethods in the Supplement for complete details.

Population

The JHS is a longitudinal, population-based cohort study of cardiovascular disease that recruited noninstitutionalized adult participants (N = 5301) residing in Jackson, Mississippi, who self-identified as African American.[12] Participants answered predefined questionnaires and underwent phlebotomy including plasma ET measurement, echocardiography, and spirometry at the time of first examination between 2000 and 2004. The cohort used for this study included participants who had measureable tricuspid regurgitation (TR) jet velocity on echocardiography (allowing for estimation of the PASP, as described in the Echocardiography Parameters section) and plasma ET levels (n = 3223) at their first study visit. One hundred and one participants were excluded from analyses owing to absence of plasma ET level measurement. The characteristics of the 1977 excluded participants with measured plasma ET levels but no TR jet (excluded from the primary analysis owing to inability to estimate a PASP in the absence of a TR jet) compared with the 3223 included study participants are detailed in eTable 1 in the Supplement. Participants with no TR jet had comparable plasma ET levels and similar longitudinal outcomes.

Exposure

The main exposure was plasma ET level at the baseline study visit. Endothelin-1 was measured in picograms per milliliter by QuantiGlo Human ET-1 Immunoassay (R&D Systems Inc).

Outcome

The main outcome for the cross-sectional analysis was presence of PH, defined as a PASP greater than 40 mm Hg on baseline echocardiography. For the longitudinal analysis, the main outcome was all-cause mortality, with time to death calculated from the time of the index echocardiographic examination; the mortality cutoff date was December 31, 2010. We also conducted a longitudinal analysis in which the main outcome was adjudicated episodes of probable or definite decompensated HF requiring hospital admission,[13] with event adjudication beginning on January 1, 2005, and time to HF calculated from that date (cutoff date, December 31, 2010). Adjudication was based on abstracted data on history, physical examination, diagnostic tests, biochemical analysis, and medication use as per procedures for event adjudication used in the Atherosclerosis Risk in Communities Study.[13]

Clinical Covariates

Definitions for clinical covariates, such as diabetes, used in this study are in the eMethods in the Supplement. The list of covariates for each analysis are detailed in the Statistical Analysis section.

Echocardiography Parameters

Detailed echocardiography procedures are available online.[14] The echocardiography data used for this study included: PASP (calculated by addition of 5 mm Hg right atrial pressure to the transtricuspid gradient[15,16]); pulmonary artery acceleration time in milliseconds; left atrial diameter index in millimeters per meters squared; the unitless ratio of mitral valve peak E wave velocity (in meters per second) to mitral valve peak A wave velocity (in meters per second); and semiquantitative left ventricular ejection fraction to the nearest 5%. Left ventricular hypertrophy was defined as a left ventricular mass index greater than 51 g/(height in meters/100)$^{2.7}$. Valvular disease was qualitatively graded.

Statistical Analysis

Endothelin-1 levels were log-transformed to approximate normality (log-ET). Regression analysis was performed to assess the association between log-ET and baseline clinical characteristics. A cutoff for an elevated ET level was also established as a level in the upper quartile (≥1.7 pg/mL) of the study cohort, an approach that has been used previously[17]; this group of participants was designated high ET. The remainder of the cohort, with an ET level less than 1.7 pg/mL, was categorized as low ET. Differences in baseline characteristics between the high ET and low ET groups were compared using the Mann-Whitney *U* test for continuous variables and χ^2 analysis for categorical variables.

The association between log-ET and presence of PH was assessed using logistic regression. The model was then adjusted for age, sex, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), pulse pressure (mm Hg), hypertension, diabetes, coronary heart disease, severe mitral/aortic valvular heart disease, history of chronic lung disease, spirometry profile (normal, obstruction, and restriction), and a left ventricular ejection fraction less than 50%, a model adapted from Choudhary et al.[18] This PH model (without log-ET) has an area under the receiver operating characteristic curve for correctly classifying participants with an elevated PASP greater than 40 mm Hg in this study population of 0.805. Sensitivity analyses were repeated using high ET as the main exposure in lieu of log-ET. Linear regression analyses were also conducted using log-transformed PASP (to approximate normality for PASP distribution) as the outcome. Integrated discrimination improvement was assessed following the addition of log-ET to the PH model. Exploratory analyses were performed with addition of left atrial diameter index to the PH model.

For the longitudinal analyses, Cox proportional hazards modeling was used. The hazard ratio (HR) for all-cause mortality associated with log-ET was determined in a univariate analysis, followed by adjustment for a model of mortality adapted from Gu et al[19] and controlling for age, sex, BMI, physical activity, smoking status, high cholesterol, diabetes, history of HF, history of coronary heart disease, hypertension, estimated glomerular filtration rate, and history of stroke. The median (range) follow-up time for the mortality analysis was 7.75 (0-9.94) years. Presence of left atrial diameter index, PH, or the log-transformed PASP value was added as a variable to the mortality models to assess whether the association of ET with mortality was independent of these variables. Sensitivity analyses were conducted using high ET and also quartiles of ET as the main exposure(s) in lieu of log-ET. Kaplan-Meier survival curves for the high ET and low ET groups were plotted. To account for age-dependent mortality risk, we also conducted mortality analyses using an age-based time scale.[20] Exploratory analyses were conducted phenotyping the population into 4 subgroups based on presence or absence of PH and high or low ET levels. Survival curves were drawn and compared for the 4 groups using the log-rank test.

Next, the association of ET levels with adjudicated decompensated HF events requiring hospital admission was assessed. Cox proportional hazards modeling was used to determine the HR for HF events associated with log-ET in a univariate analysis, followed by a fully adjusted model of HF (Atherosclerosis Risk in Communities model) from Agarwal et al,[21] adjusting for age, sex, coronary heart disease, diabetes, systolic blood pressure, blood pressure medication use, heart rate, smoking status, and BMI. Additional analyses adjusting for the Atherosclerosis Risk in Communities model parameters and for left atrial diameter index, presence of pulmonary hypertension, or log-transformed PASP were also performed. Participants who died before a HF event were censored. To confirm that censoring participants who died (competing event) did not significantly alter the hazards of HF admission (main event), we repeated our analyses, estimating the subhazard ratios using the competing risks regression model, according to the method of Fine and Gray.[22] The median (range) follow-up for HF events was 5.32 (0-6) years.

Mortality and HF admission analyses were also performed in the excluded participants without measureable tricuspid regurgitation but with plasma ET levels to assess internal validity.

Interaction testing was performed to assess possible effect modification on the association of ET and outcomes. Interaction terms were developed for the following variables: age categories[23]; sex; BMI categories[24]; hypertension[25]; diabetes[24]; coronary heart disease[26]; smoking categories[27]; spirometry profiles[28]; left ventricular ejection fraction (normal or reduced)[29]; left ventricular hypertrophy[1]; left atrial diameter index[30]; estimated glomerular filtration rate[25]; and, for the mortality and HF outcomes, PH. Details of the analysis plan are included in the eMethods in the Supplement. Exploratory subgroup analyses were performed on those variables with significant multiplicative interaction testing at a significance level of less than 0.05.

Missing data for clinical covariates were handled using multiple imputation (see eMethods in the Supplement).

All analysis was performed using Stata/SE, version 11.2 software (StataCorp LP). A 2-sided *P* value of less than .05 was considered significant.

Results

Baseline Characteristics

Table 1 shows the baseline characteristics of the study cohort. The mean (SD) age of the study population was 56.6 (12.6) years, and 1051 study participants were men (32.6%). Hypertension, obesity, and diabetes were prevalent in the cohort, and most participants were taking antihypertensive medication. However, most participants never smoked, and decreased left ventricular ejection fraction and severe valvular heart disease were uncommon in this community-based population. The median value (range) of plasma ET was 1.3 (1.0-1.6) pg/mL in the study cohort. The eFigure in the Supplement shows a cumulative frequency plot of ET levels. Log-ET levels were significantly associated with pulmonary artery systolic pressure and with multiple clinical characteristics including age, blood pressure parameters, heart disease, smoking status, and spirometry profile and with evidence of left heart remodeling on echocardiography (Table 1).

Table 1. Baseline Characteristics of the Study Cohort and Results of Regression Analysis With Log-transformed Plasma ET

Characteristic	All (N = 3223)	R^2[a]	*P* Value[a]
Age, mean (SD), y	56.6 (12.6)	.03[b]	<.001[b]
Men, No. (%)	1051 (32.6)	.004[b]	<.001[b]
BMI, mean (SD)	31.4 (7.0)	.001	.07
AHA physical activity category, No. (%)			
Poor amount of physical activity reported	1606 (49.9)	.002	.05
Intermediate amount of physical activity reported	1018 (31.6)	NA	NA
Ideal amount of physical activity reported	597 (18.5)	NA	NA
Hemodynamics, mean (SD)			
Mean heart rate, bpm	63 (10)	<.001	.46
Mean systolic blood pressure, mm Hg	126 (18)	.02[b]	<.001[b]
Mean diastolic blood pressure, mm Hg	78 (10)	.002[b]	.01[b]
Mean pulse pressure, mm Hg	48 (16)	.02[b]	<.001[b]
Medical conditions, No. (%)			
Hypertension	1968 (61.1)	.01[b]	<.001[b]
Diabetes	626 (19.4)	<.001	.21
High cholesterol	803 (31.4)	.002[b]	.04[b]
Coronary heart disease	326 (10.1)	.005[b]	<.001[b]
Severe mitral/aortic valvular disease	7 (0.22)	.002[b]	.01[b]
Heart failure	86 (2.84)	.007[b]	<.001[b]
Stroke	141 (4.37)	.001	.08
Atrial fibrillation	15 (0.47)	.009[b]	<.001[b]
Chronic lung disease	225 (7.0)	.001	.21
Medications, No. (%)			
Antihypertensives	1636 (62.2)	.02[b]	<.001[b]
β-blockers	332 (12.6)	.004[b]	.001[b]
Calcium channel blockers	605 (23.0)	.008[b]	<.001[b]
Diuretics	1037 (39.4)	.01[b]	<.001[b]
Smoking history, No. (%)			
Never smoked	2172 (68.0)	.02[b]	<.001[b]
Former smoker	635 (19.9)	NA	NA
Current smoker	388 (12.1)	NA	NA
Spirometry profile, No. (%)			
Normal	2173 (71.0)	.01[b]	<.001[b]
Obstruction	275 (9.0)	NA	NA
Restriction	612 (20.0)	NA	NA
Echocardiography characteristics			
Mean estimated pulmonary arterial systolic pressure, mean (SD), mm Hg	28 (7)	.02[b]	<.001[b]
Pulmonary hypertension, No. (%), estimated pulmonary artery systolic pressure >40 mm Hg	217 (6.7)	.01[b]	<.001[b]
Mean pulmonary artery acceleration time, mean (SD), msec	126.9 (32.8)	.006[b]	<.001[b]
Mean left atrial diameter index, mean (SD), mm/m^2	18.0 (2.5)	.006[b]	<.001[b]
Ratio of mitral valve peak E wave velocity (m/s)/mitral valve peak A wave velocity, mean (SD), m/s	1.11 (0.37)	<.001	.83
Mean left ventricular ejection fraction, mean (SD), %	62 (8)	.003[b]	.001[b]
LVEF <50%, No. (%)	87 (2.7)	.01[b]	<.001[b]
LV Hypertrophy, %, LV mass index >51 g/height in meters/100$^{2.7}$	180 (8.0)	.02[b]	<.001[b]
Laboratory values, mean (SD)			
Mean aldosterone, ng/dL	5.6 (5.9)	.004[b]	<.001[b]
Mean serum creatinine calibrated to Cleveland clinic equivalent, mg/dL	1.0 (0.6)	.02[b]	<.001[b]
Mean eGFR based on MDRD formula, ml/min/1.73m^2	84.9 (18.3)	.01[b]	<.001[b]
Plasma ET, mean (SD), pg/mL	1.36 (0.64)	NA	NA

Abbreviations: AHA, American Heart Association; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); bpm, beats per minute; eGFR, estimated glomerular filtration rate; ET, endothelin-1; LV, left ventricular; LVEF, left ventricular ejection fraction; MDRD, Modification of Diet in Renal Disease; NA, not applicable.

SI conversion factors: To convert aldosterone to picomoles per liter, multiply by 27.74; to convert creatinine to micromoles per liter, multiply by 88.4.

[a] For regression analysis of variable with log-transformed ET.

[b] Statistically significant.

Table 2. Association of Log-Transformed Plasma ET (Log-ET) Levels and High Plasma ET Level (≥1.7 pg/mL) With Presence of Pulmonary Hypertension (Estimated PASP> 40 mm Hg) and Log-transformed PASP

Variable	Odds Ratio (95% CI) for Pulmonary Hypertension	Coefficient, Log PASP
Log-ET, univariate	2.66[a] (1.92-3.70)	0.087[a] (0.066-0.108)
Log-ET, adjusted model[b]	1.66[a] (1.16-2.37)	0.039[a] (0.020-0.059)
High ET, univariate	2.25[a] (1.70-3.00)	0.072[a] (0.051-0.092)
High ET, adjusted model[b]	1.66[a] (1.22-2.26)	0.035[a] (0.016-0.054)

Abbreviations: ET, endothelin-1; PASP, pulmonary artery systolic pressure.

[a] Significant.

[b] Adjusted for age, sex, body mass index, pulse pressure (mm Hg), hypertension, diabetes, coronary heart disease, severe mitral/aortic valvular disease, chronic lung disease (history of), spirometry profile (normal, obstruction, restriction), and left ventricular ejection fraction <50%.

Table 3. Cox Proportional Hazards Analysis of Mortality by Log-Transformed Plasma ET Level (Log-ET) and High Plasma ET Level (≥1.7 pg/mL)

Variable	Hazard Ratio (95% CI)	*P* Value
Log-ET, univariate	2.70[a] (2.08-3.52)	<.001
Log-ET, adjusted for mortality model[b]	1.69[a] (1.27-2.25)	<.001
Log-ET, adjusted for mortality model[b] and left atrial diameter index	1.61[a] (1.21-2.14)	.001
Log-ET, adjusted for mortality model[b] and presence of PH	1.61[a] (1.21-2.14)	.001
Log-ET, adjusted for mortality model[b] and log PASP	1.61[a] (1.21-2.14)	.001
High ET, univariate analysis	2.12[a] (1.67-2.68)	<.001
High ET, adjusted for mortality model[b]	1.42[a] (1.11-1.81)	.006
High ET, adjusted for mortality model[b] and left atrial diameter index	1.38[a] (1.08-1.76)	.01
High ET, adjusted for mortality model[b] and presence of PH	1.37[a] (1.07-1.75)	.01
High ET, adjusted for mortality model[b] and log PASP	1.37[a] (1.07-1.76)	.01

Abbreviations: ET, endothelin-1; PASP, pulmonary artery systolic pressure; PH, pulmonary hypertension.

[a] Significant.

[b] Adjusted for age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), physical activity category (none, intermediate, and ideal), smoking status (never, former, and current), total cholesterol category (<200 mg/dL vs ≥200 mg/dL [to convert to millimoles per liter, multiply by 0.0259]), diabetes (fasting plasma glucose ≥126 mg/dL [to convert to millimoles per liter, multiply by 0.0555], hemoglobin A_{1C} ≥6.5% [to convert to proportion of total hemoglobin, multiply by 0.01], or use of diabetes medications), history of heart failure, history of coronary heart disease, hypertension (blood pressure ≥140/90 mm Hg or use of antihypertensive), estimated glomerular filtration rate, and history of stroke.

eTable 2 in the Supplement includes a comparison of the baseline characteristics of participants with high ET (upper quartile, ≥1.7 pg/mL) vs low ET levels (<1.7 pg/mL). Participants in the high ET group were significantly older, with higher systolic blood pressure and pulse pressure, and were more likely to have hypertension and to have coronary heart disease and valvular heart disease than participants in the low ET group. Participants in the high ET group were also more likely to be current smokers and to have abnormal lung function profiles. While left ventricular ejection fraction was not significantly different in the high ET and low ET groups, 4.7% of participants in the high ET group had an ejection fraction of less than 50% compared with 2.1% of participants in the low ET group (Pearson $\chi^2 = 14.61$; $P < .001$).

Association of Plasma ET Levels With Pulmonary Hypertension

Log-transformed ET was significantly associated with the presence of PH. Following adjustment for the PH model, the adjusted odds ratio (OR) for PH per log increment of ET was 1.66 (95% CI, 1.16-2.37; $P = .005$) (**Table 2**). Integrated discrimination improvement was 0.0067 (SE, 0.0022; $P = .002$) following addition of log-ET to the PH model. Furthermore, log-ET was also significantly associated with log-transformed PASPs in a continuous fashion (regression coefficient, 0.087; 95% CI, 0.066-0.108; $P < .001$; Table 2), an association that persisted after adjustment for the model of PH.

In sensitivity analyses dichotomizing ET levels, PH prevalence was 11.2% in the high ET group compared with 5.3% in the low ET group (Pearson $\chi^2 = 32.80$; $P < .001$). The mean (SD) estimated PASP was 30 (8) mm Hg in the high ET group compared with 27 (7) mm Hg in the low ET group ($P < .001$). Pulmonary artery acceleration time was significantly lower in the high ET group compared with the low ET group. After adjustment for the PH model, the adjusted odds of having PH were significantly higher in the high ET group compared with the low ET group (adjusted OR, 1.66; 95% CI, 1.22-2.26). High ET was also significantly associated with log-transformed PASP (Table 2).

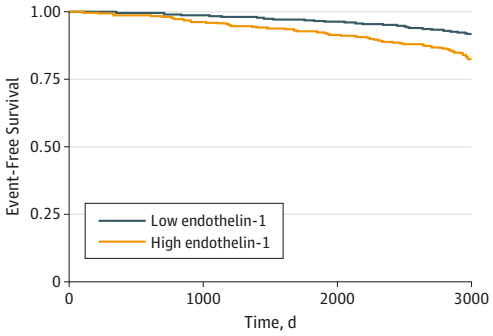
In exploratory analyses, ET levels remained significantly associated with PH following addition of left atrial diameter index to the PH model. For example, the adjusted OR for PH per log increment of ET was 1.53 (95% CI, 1.07-2.18) and for high ET was 1.59 (95% CI, 1.16-2.16) following additional adjustment for left atrial diameter index.

Elevated Plasma ET and All-Cause Mortality

During the available follow-up period, 289 deaths occurred. After risk adjustment, log-ET was significantly associated with mortality (adjusted HR, 1.69; 95% CI, 1.27-2.25). Further adjustments for log-transformed PASP (HR, 1.61; 95% CI, 1.21-2.14), presence of PH (HR, 1.61; 95% CI, 1.21-2.14), or left atrial diameter index (HR, 1.61; 95% CI, 1.21-2.14) did not significantly change the results (**Table 3**).

When ET levels were dichotomized, 113 deaths occurred in 775 participants in the high ET group (14.6%) compared with 176 deaths in 2448 participants in the low ET group (7.2%). Kaplan-Meier survival curves for the high ET vs low ET group are displayed in **Figure 1**. After mortality risk adjustment, high ET was significantly associated with mortality (HR, 1.42; 95% CI, 1.11-1.81). The association between high ET and all-cause mortality remained significant even after PH (HR, 1.37; 95% CI, 1.07-1.75) or left atrial diameter index (HR, 1.38; 95% CI, 1.08-1.76) was included in the adjusted model. Sensitivity analyses using quartiles of ET as the main exposure showed generally consistent results (eTable 3 in the Supplement). Mortality models using an age-based time scale showed similar results to analyses using study follow-up time (eTable 4 in the Supplement).

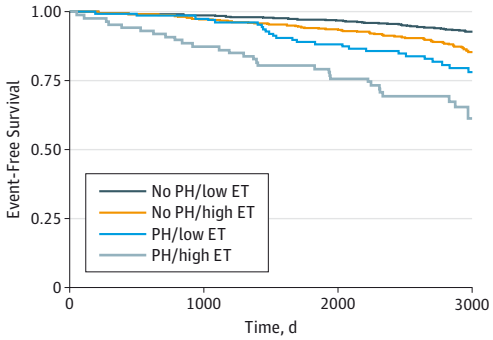
Figure 1. Kaplan-Meier Survival Curves for High (Plasma Level >75th Percentile) Endothelin-1 and Low (Plasma Level ≤75th Percentile) Endothelin-1 Groups



No. at risk				
Low endothelin-1	2423	2347	2191	653
High endothelin-1	768	727	669	173

Survival was significantly worse in the high endothelin-1 group compared with the low endothelin-1 group ($P < .001$).

Figure 2. Kaplan-Meier Survival Curves for Subgroups of the Study Population Based on Presence or Absence of Pulmonary Hypertension (PH) and High or Low Endothelin-1 (ET) Level



No. at risk				
No PH/low ET	2295	2222	2082	606
No PH/high ET	681	651	605	159
PH/low ET	128	125	109	47
PH/high ET	87	76	64	14

Survival was significantly different across these subgroups ($P < .01$ by log-rank), with the worst survival seen in the subgroup with PH and high ET.

In exploratory analysis phenotyping the population into 4 subgroups based on presence or absence of PH and based on ET level (high vs low ET), Kaplan-Meier survival curves (**Figure 2**) demonstrated that the worst survival was in the subgroup with PH and high ET, followed by the subgroups with PH and low ET; no PH and high ET; and no PH and low ET (log-rank $\chi^2 = 77.16$; $P < .001$). Relative to the subgroup with no PH and low ET levels, the group with PH and high ET level had 6 times the relative hazard of death (eTable 5 in the Supplement, $P < .001$). After adjustment for age, sex, and BMI, there remained a significantly increased risk of mortality in each of these 3 subgroups relative to the subgroup with no PH and low ET levels (eTable 6 in the Supplement).

Elevated Plasma ET and HF Events

During the follow-up period for HF hospitalizations, 148 patients were admitted with decompensated HF. After risk adjustment, log-ET was significantly associated with HF events (HR, 1.57; 95% CI, 1.05-2.37). However, log-ET was not significantly associated with HF events when the model was further adjusted for left atrial diameter index (HR, 1.35; 95% CI, 0.91-2.05; $P = .13$), PH (HR, 1.35; 95% CI, 0.90-2.02; $P = .15$), or log-transformed PASP (HR 1.37; 95% CI, 0.91-2.05; $P = .13$) (eTable 6 in the Supplement). Similar results were obtained when death was treated as a competing risk (eTable 7 in the Supplement).

Plasma ET Levels and Outcomes in Participants Without Measureable Tricuspid Regurgitation

In the follow-up, there were 202 deaths and 82 hospitalizations for HF in participants excluded from the primary analyses owing to lack of a measureable TR jet. Plasma ET levels were significantly associated with mortality and HF admission events in participants without a TR jet (see eTables 8 and 9 in the Supplement). Hazard ratios for mortality and HF admission were comparable with those seen in the study population with measureable TR.

Effect Modification of the Association of Plasma ET Levels and Outcomes

The results of interaction testing for each of the outcomes are detailed in eTable 10 in the Supplement. For PH, there was no significant interaction between log-ET levels and hypertension, diabetes, left ventricular ejection fraction category (≥50% or <50%), left ventricular hypertrophy category (present or absent), left atrial diameter index, or estimated glomerular filtration rate. However, age categories, coronary heart disease, BMI category, smoking history category, and spirometry profile category significantly modified the association between log-ET and PH. Exploratory subgroup analysis (eTable 11 in the Supplement) showed that log-ET was significantly associated with PH only when a history of coronary heart disease was present (adjusted OR for PH for log-ET, 6.00; 95% CI, 2.13-16.88) but not when coronary heart disease history was absent, and log-ET was associated with PH in never-smokers (OR, 1.93; 95% CI 1.22-3.06) but not in current or former smokers. Similarly, log-ET was significantly associated with PH in the subgroups with airflow obstruction (OR, 2.31; 95% CI, 1.03-5.19) or restriction (OR, 5.24; 95% CI, 2.28-12.03), but not in the subgroup of participants with normal lung function.

For both the mortality and the HF hospitalization outcomes, there were significant interactions between log-ET and age, BMI category, smoking history, and spirometry profile, but not for diabetes, hypertension, coronary heart disease, left ventricular ejection fraction, left atrial diameter index, left ventricular hypertrophy, or estimated glomerular filtration rate. Subgroup analysis for variables with significant interactions is detailed in eTable 11 in the Supplement. Of note, log-ET levels were significantly associated with mortality in never-smokers but not in current and former smokers; and log-ET levels were significantly associated with mortality in the setting of airflow obstruction but not in those with normal spirometry or restriction on spirometry.

Discussion

In this study, we demonstrated that in a community-based population sample of African American individuals, plasma ET levels were associated with the presence of elevated PASP, with mortality, and with HF admissions. Given the increased prevalence of risk factors, such as diabetes[31] and systemic hypertension,[32] in the community of African American adults in the United States, African American individuals have higher rates than white individuals of cardiovascular events, such as HF.[33] Presence of an elevated PASP, consistent with PH, is also prevalent in the African American community[18] and is associated with subsequent HF admissions.[16] Further understanding of the association between ET (a relevant vasoactive mediator), PH, and HF in this at-risk population is therefore important. The association of ET levels with elevated PASP and HF admissions are novel findings not previously demonstrated in any community-based cohort to the best of our knowledge and therefore may be of general relevance. We further demonstrate that having both an elevated PASP and high ET level is associated with highest mortality risk. Therefore, these noninvasive tests can potentially be used to refine risk stratification in populations at risk for HF.

Endothelin-1 may cause elevations in the PASP by causing increased vasoconstriction and adverse vascular remodeling in pulmonary circulation.[6,34-37] Furthermore, it is associated with increased arterial stiffness,[38] systemic hypertension, and adverse left ventricular remodeling and thereby can conceivably result in left atrial hypertension. Elevated ET levels are in fact observed in the setting of clinical HF.[39,40] Several pathophysiological mechanisms may therefore underlie the association we observed between ET and elevated PASP including those that affect left heart function and cause left atrial hypertension. Indeed, left ventricular hypertrophy was more prevalent and left atrial diameter was greater in the high ET than the low ET group. However, we found that the association of ET with PASP remained independent of numerous comorbidities and left heart remodeling. We therefore speculate that PH related to elevated ET may in part be owing to direct effects of circulating ET on the pulmonary vasculature. Endothelin-1 levels were strongly associated with PH in the setting of coronary heart disease and abnormal lung function, suggesting potential relevance to the pathophysiology of PH in these settings. The strong association of ET with PH in the subgroup of participants with restriction on spirometry is particularly intriguing and merits further study to elucidate potential profibrogenic or other pathophysiologic mechanisms.

The role of ET in PH may be especially important in the African American population, which has a high prevalence of cardiovascular comorbidities and is at increased risk of adverse cardiovascular outcomes.[41] African American individuals with systemic hypertension have been shown to have higher circulating levels of ET[42] and an ET precursor[43] than white individuals with hypertension. Higher circulating levels of an ET precursor are associated with greater evidence of end-organ effects of systemic hypertension in African American individuals.[44] African American individuals with hypertension experience greater vasodilator responses to endothelin-A receptor blockade than white individuals.[45] The relationship between ET and elevated PASPs further highlights the role of ET in cardiovascular disease in the African American population.

In our study, having an ET level in the upper 25th percentile of the population was associated with a 2-fold increased risk of mortality. Elevated ET levels have been shown to be an adverse prognostic marker after myocardial infarction[17] and in the setting of asymptomatic atherosclerosis[46] and congestive HF.[47-49] A study conducted in a cohort of healthy Japanese adults showed that ET levels were higher in participants who died than in survivors[50]; in that study, participants in the highest quartile of ET level (ET level ≥5.9 pg/mL) had a higher adjusted hazard of all-cause mortality than participants in the lower quartile of ET levels (ET≤3.8 pg/mL).[50] To our knowledge, this is the first demonstration of a similar independent association between ET levels and mortality in an African American population. Whether and how associations between ET and mortality may be modified by race/ethnicity can only be determined in other, more ethnically diverse cohorts.

In our study, high ET levels were associated with increased hazard of mortality in participants with and without PH. We also noted that ET levels were significantly associated with mortality in participants without tricuspid regurgitation on echocardiogram, and the association with mortality was consistent between the study group with tricuspid regurgitation and the group without tricuspid regurgitation, suggesting a robust association. The potential pathophysiologic effects of ET may extend beyond influences on the pulmonary circulation, as suggested by the residual mortality risk associated with higher ET levels in participants without evidence of PH. However, there was no effect modification of diabetes, hypertension, or left heart remodeling on the association between ET and mortality, while subgroup analysis showed that ET was significantly associated with mortality in never-smokers and in those with airflow obstruction, suggesting hypotheses for further study of ET effects in particular patient groups. Expansion of our understanding of the pleiotrophic effects of ET on organ systems and within particular disease states as well as of environmental influences on ET effects through basic and translational research would aid in our interpretation of these epidemiologic findings.

Presence of an elevated PASP is associated with HF in the African American population.[16] Endothelin-1 levels have been demonstrated to be significantly elevated in the setting of established congestive HF.[39,40] We extend those prior observations to show that ET levels are associated with subsequent HF hospitalizations in the African American population, with the risk of HF admissions increased by 1.57-fold with each log increase in ET levels after adjustment for a validated HF risk prediction model.[21] However, ET levels were not significantly associated with HF after adjustment for left atrial diameter index, PH, or PASP. Therefore, elevations of PASP and/or left atrial pressure may represent an intermediate pathophysiologic mechanism between ET elevation and development of decompensated HF.

Studies of endothelin receptor antagonists (ERAs) have led to conflicting results. Endothelin receptor antagonists were associated with adverse effects and lack of clinical efficacy in CHF.[51,52] Although ERAs have been shown to be beneficial in idiopathic and associated PAH,[11,53] benefits in nongroup 1 PAH and in subgroups of group 1 PAH, such as portopulmonary hypertension, remain uncertain.[54] In studying a cohort from the community setting, with a lower prevalence of advanced disease states, we may have identified a risk marker for a subpopulation in which preventive interventions focused on the ET pathway may be more efficacious. However, this can only be determined through carefully designed future clinical studies.

There are a number of limitations to our study. The analysis of ET levels and PASP was cross-sectional; therefore, we cannot determine whether elevations in ET preceded or caused development of PH or vice versa. Because ET levels and tricuspid regurgitation gradient were one-time measurements, we could not determine whether ET elevations are sustained or transient or whether PASP fluctuates with changes in ET levels. For the same reason, we could not track changes in these measurements over time and assess how such changes might relate with outcomes. Given the observational nature of the study, observed associations may be a result of incomplete confounding adjustment, despite using robust regression models. We did not have any data on the use of ERAs in study participants; use of these medications can elevate plasma ET levels.[3,10] However, because ERAs are indicated for treatment of idiopathic and associated PAH, use of these medications by study participants would likely have been rare. The cutoff value for the upper quartile of ET in our study (≥1.7 pg/mL) was lower than that observed in a Japanese study (≥5.9 pg/mL).[50] This may relate to differences in ET assays used; however, further studies are needed to confirm relevant cutoffs for ET levels. Heart failure hospitalization assessment did not begin immediately after participants completed their baseline study visit but began on January 1, 2005,[16] so interval HF events may have been missed, biasing our findings toward the null hypothesis. Despite this limitation, we were able to find a significant association between log-ET levels and HF events. Because PH and ET are correlated, it is possible that the loss of significance of the association between log-ET and HF after adjustment for PH is related to collinearity and/or that PH is part of the mechanistic pathway between ET and HF.

Conclusions

In summary, this study demonstrates an association between circulating plasma ET levels and PH by echocardiogram in African American participants in the JHS. Plasma ET levels were associated with future mortality, independent of PH or PASP, and with HF admissions. In exploratory analysis, having both PH and elevated plasma ET levels was associated with the highest hazard for mortality. Elevated plasma endothelin levels, especially associated with an elevated pulmonary artery systolic pressure on echocardiogram, identify an at-risk population that could be evaluated for targeted prevention and management strategies in future studies.

ARTICLE INFORMATION

Published Online: June 8, 2016. doi:10.1001/jamacardio.2016.0962.

Author Contributions: Dr Choudhary had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Jankowich, Choudhary.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: All authors.
Administrative, technical, or material support: Jankowich.
Study supervision: Wu.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Choudhary reports an investigator-initiated grant support from Novartis.

Funding/Support: The Jackson Heart Study is supported by contracts HHSN268201300046C, HHSN268201300047C, HHSN268201300048C, HHSN268201300049C, and HHSN268201300050C from the National Heart, Lung, and Blood Institute and the National Institute on Minority Health and Health Disparities, with additional support from the National Institute on Biomedical Imaging and Bioengineering. This material is based on work supported by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development: Biomedical Laboratory Research, and Development Service (MERIT Review Award to Dr Choudhary, IBX000711A).

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank the participants and data collection staff of the Jackson Heart Study.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or of the United States government.

Previous Presentations: Some of the findings in this manuscript were previously presented at the American Thoracic Society International Conference; May 19, 2015; Denver, Colorado.

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