Association of African American Race with Elevated Pulmonary Artery Diastolic Pressure: Data from the Heart and Soul Study

Kiran K. Khush, MD, Sanjiv J. Shah, MD, Bryan Ristow, MD, Teresa De Marco, MD, Mary A. Whooley, MD, and Nelson B. Schiller, MD *San Francisco, California*

Background: **Whether increased severity of heart failure in African Americans is a result of differences in cardiac physiology is uncertain. The end-diastolic pulmonary regurgitation (EDPR) gradient is associated with abnormal cardiac physiology. We hypothesized that African American race is associated with an elevated EDPR gradient that may partially predispose African Americans to heart failure.**

Methods: **The Heart and Soul Study prospectively assessed the EDPR gradient in 480 patients with coronary disease. We used multivariable linear regression to investigate the independent association of African American race with EDPR gradient.**

Results: **Compared with 393 non-African Americans, the 87 African Americans had similar indices of left ventricular systolic and diastolic function, left ventricular mass index, mitral regurgitation, peak tricuspid regurgitation gradient, and pulmonary velocity time integral. However, the EDPR gradient was significantly higher in African Americans (4.2 ± 3.3 mm Hg) than in Caucasians (3.1 ± 2.5 mm Hg) or other racial groups (3.5 ± 2.7 mm Hg) ($P = .008$). In a multivariable model, African American race was a significant predictor of elevated EDPR gradient (β coefficient 0.75, $P = .03$).**

Conclusion: **African American race is independently associated with an elevated EDPR gradient in patients with coronary artery disease.** (J Am Soc Echocardiogr 2007;20:1307-1313.)

Heart failure (HF) currently affects nearly 5 million people in the United States and is associated with substantial morbidity and mortality.[1,2] The African American community has been particularly affected by this epidemic because the incidence of HF among African Americans is higher than in non-African Americans.[3] Symptomatic HF occurs at an earlier age,[4] presents with more severe left ventricular (LV) dysfunction,[4] and progresses more rapidly in African American patients than it does in other groups.[5] As a result, the rates of HF hospitalization and mortality are higher in African Americans than in Caucasians in the United States today.[4,6,7] Research regarding the differences in HF pathophysiology, treatment, and outcomes across racial groups is needed to optimally target therapeutic responses. For example, it is unclear whether increased severity of HF in African Americans is a result of differences in demographic characteristics, comorbidities, or underlying cardiac pathophysiology, such as diastolic dysfunction. Identification of unique hemodynamic and echocardiographic features of HF in African Americans would help to target specific therapies for use in this group.

Previous studies have shown that the end-diastolic pulmonary regurgitation (EDPR) gradient provides an accurate estimate of pulmonary artery diastolic pressure,[8-10] and an EDPR gradient greater than 5.0 mm Hg is strongly correlated with cardiac dysfunction.[11] Specifically, an elevated EDPR gradient correlates with decreased functional status, elevated serum B-type natriuretic peptide, elevated LV mass index, LV systolic dysfunction, and LV diastolic dysfunction.[11] Furthermore, elevated EDPR gradients predict HF hospitalizations and all-cause mortality in patients with coronary artery disease (CAD).[12] We hypothesized that African American race is independently associated with an elevated EDPR gradient, supporting the argument that abnormal underlying cardiac physiology at least partially explains the predisposition of African Americans to HF. To test this hypothesis, we analyzed data from a prospective cohort study of patients with CAD.

From the Division of Cardiology (K.K.K., S.J.S., B.R., T.D.M., M.A.W., N.B.S.), Department of Medicine (K.K.K., S.J.S., B.R., T.D.M., M.A.W., N.B.S.), University of California; and Department of Veterans Affairs Medical Center (M.A.W., N.B.S.).

Reprint requests: Kiran K. Khush, MD, Division of Cardiology, Department of Medicine, University of California, 505 Parnassus Ave, Box 0124, San Francisco, CA 94143-0124(E-mail: *kkhush@medicine.ucsf.edu*).

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METHODS

Study Participants

This study represents a retrospective analysis of data obtained from the Heart and Soul Study–a prospective cohort study of psychosocial factors and health outcomes in patients with CAD. Details regarding the design and methods of this study have been published previously.[13] We used administrative databases to identify outpatients with documented CAD at two Department of Veterans Affairs Medical Centers (San Francisco and Palo Alto, Calif), one university medical center (University of California, San Francisco), and 9 public health clinics in the community health network of San Francisco, Calif. Criteria for enrollment were: (1) history of myocardial infarction; (2) angiographic evidence of at least 50% stenosis in one or more epicardial coronary arteries; (3) evidence of exercise-induced ischemia by treadmill electrocardiogram or stress nuclear perfusion imaging; or (4) history of coronary revascularization. Individuals were excluded if they were unable to walk one block or if they were planning to move out of the local area within 3 years. The institutional review board at each site approved our protocol, and all participants provided written informed consent.

Between September 2000 and December 2002, a total of 1024 patients were enrolled, including 549 (54%) with a history of myocardial infarction, 235 (23%) with a history of coronary revascularization but not myocardial infarction, and 238 (23%) with a diagnosis of CAD as documented by their physician. The EDPR gradient was measured in baseline echocardiographic studies in the 741 patients enrolled between July 2001 and December 2002.[11] All participants completed a day-long baseline study appointment that included a medical history interview, a physical examination, an exercise treadmill test with a baseline and stress echocardiogram, and a comprehensive health status questionnaire.

Echocardiographic Studies

All echocardiographic studies were performed in the standard left lateral recumbent and supine positions with a commercially available ultrasound system (Acuson Sequoia, Siemens Corp, Mountain View, Calif). From the standard parasternal short-axis view, a spectral Doppler pulmonary regurgitation waveform was obtained by color flow interrogation across the pulmonic valve. The velocity was measured on the R wave, near the termination of retrograde flow (Figure 1). The point of measurement corresponded with the first peak deflection of the QRS complex (usually at the R wave). In most cases, pulsed wave Doppler visualized an adequate waveform, but higher velocities occasionally mandated use of continuous wave Doppler.

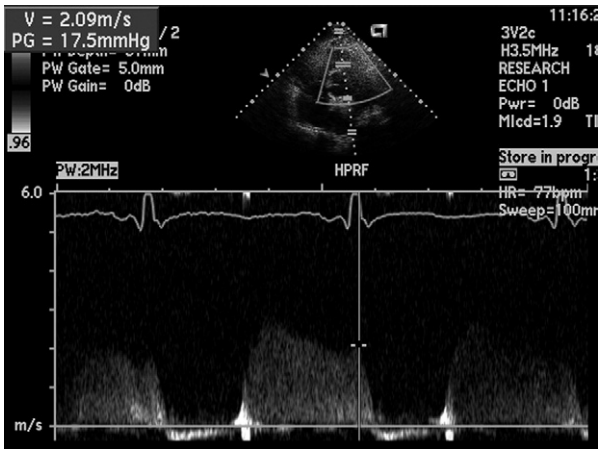

Figure 1 Measurement of end-diastolic pulmonary regurgitation (EDPR) velocity. On spectral Doppler signal from standard parasternal short-axis view, *vertical line* denotes termination of reverse flow across pulmonic valve at end diastole. *Horizontal dash* represents EDPR velocity. EDPR gradient is calculated by $4v^2$ where v equals EDPR velocity.

Before digital data collection, the sonographer screened at least 10 cardiac cycles with the patient breathing quietly at rest. Although the value of the EDPR gradient varied with respiration, the sonographer chose the highest EDPR velocity of the 10 cycles to minimize the significance of beat-to-beat variability. The modified Bernoulli equation ($\Delta P = 4v^2$) was then used to calculate EDPR pressure gradients from EDPR velocity.

Standard 2-dimensional apical 2- and 4-chamber views were obtained and were planimetered with a computerized digitization system to determine end-diastolic and end-systolic LV volumes by the biplane method of disks. We calculated LV ejection fraction (EF) as: (end-diastolic volume − end-systolic volume)/end-diastolic volume.[14] LV mass was calculated using the truncated-ellipse method.[15] LV volumes and mass were then indexed to the patient's body surface area. Right atrial pressure was estimated based on inferior vena cava diameter and collapsibility with respiration.[16]

Classification of diastolic dysfunction was based on mitral flow ratios of peak velocities at early rapid filling (E) and late filling as a result of atrial contraction (A) and systolic or diastolic dominant pulmonary venous flow as modified from previous studies.[17,18] A normal diastolic pattern was defined by an E/A ratio between 0.75 and 1.5 and systolic dominant pulmonary venous flow. An impaired relaxation pattern was characterized by E/A less than or equal to 0.75 with systolic dominant pulmonary venous flow. A pseudonormal pattern was defined as E/A between 0.75 and 1.5 and diastolic dominant

pulmonary venous flow. A restrictive pattern, finally, was defined by E/A greater than 1.5 and diastolic dominant pulmonary venous flow.[19]

Other Measurements

Age, sex, medical history, smoking status, and race were determined by patient questionnaire. We measured weight and height, and calculated body mass index (kg/m^2). Participants were instructed to bring their medication bottles to the study appointment, and study personnel recorded all current medications. Supine blood pressure was measured after a 5-minute rest, and pulse pressure was calculated as systolic minus diastolic blood pressure. Laboratory measurements, including serum creatinine, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol, N-terminal-pro-B-type natriuretic peptide, and C-reactive protein were measured from serum or plasma after an overnight fast.

Clinical End Points

We conducted annual telephone follow-up interviews with participants (or their proxy) to ask about death or hospitalization for "heart trouble." For any reported event, medical records, electrocardiograms, death certificates, and coroner's reports were retrieved and reviewed by two independent and blinded adjudicators. If the adjudicators agreed on the outcome classification, their classification was binding. In the event of disagreement, the adjudicators conferred, reconsidered their classification, and requested consultation from a third blinded adjudicator. The end point definition for HF hospitalization has been described in detail previously.[12]

Statistical Analysis

Participants were classified as Caucasian, African American, or other based on their self-reported race on the enrollment questionnaire. The "other" category included Hispanic, Latino, or Latin American; Asian or Pacific Islander; and "another group not listed." Differences in baseline characteristics among these 3 groups were determined using analysis of variance (or nonparametric equivalent) for continuous variables and χ^2 tests for dichotomous variables. To examine the independent association of African American race with elevated EDPR gradient, we used a multivariable linear regression model with African American race as the independent variable and EDPR gradient as the dependent variable. We adjusted for variables thought to be associated with an elevated EDPR gradient or African American race (age, sex, history of hypertension, history of HF, blood pressure, serum creatinine, LV EF, LV mass index, and New York Heart Association [NYHA] class), and for variables that were found to be significantly different between the groups based on univariate analysis at P less than .10 (body surface area, A-wave velocity, E/A ratio, use of calcium-channel blockers, diabetes, smoking, HDL, triglycerides, and diuretic use).

The purpose of this study was to examine the association between African American race and EDPR. This study was not powered to determine whether elevated EDPR mediates the association between black race and HF. However, in an effort to explore whether EDPR mediates the association between African American race and HF, we used logistic regression with race as the independent variable and HF as the dependent variable. We first examined whether African American race was predictive of HF in age-adjusted analyses, and then examined this association after adjustment for EDPR. All analyses were performed using Stata software (Stata, Version 9, StataCorp Inc, College Station, Tex).

RESULTS

The EDPR gradient was measurable in 481 of the 741 participants (65%). One of these participants was excluded because of lack of data on race, leaving 480 total patients for the analysis. Of the 480 study participants, 275 were Caucasian (57%), 87 were African American (18%), and 118 were neither Caucasian nor African American (other) (25%). African American patients were younger than patients in the other groups, more likely to smoke, and more likely than Caucasians to have hypertension, diabetes, and obstructive lung disease. African American race was associated with higher serum creatinine levels, higher HDL levels, and lower triglyceride levels. Baseline use of antihypertensive medications and statins was similar between the two groups, but diuretic use was more common among African Americans than the other two groups (Table 1).

When comparing echocardiographic measurements between African American, Caucasian, and "other" groups, we found no significant differences in LV EF, mass index, and volumes (Table 2). A composite assessment of diastolic function revealed no significant differences among the groups, although there was a trend toward increased diastolic dysfunction in African Americans ($P = .10$). Importantly, there was no significant difference between pulmonary velocity time integral (a surrogate marker of right ventricular stroke volume), tricuspid regurgitation gradient (an indirect measurement of pulmonary artery systolic pressure), estimated right atrial pressure, or right atrial end-systolic volume index across racial groups. The African American patients, however, had a significantly higher EDPR gradient (4.2 ± 3.3 mm Hg) than the other two

Table 1 Baseline characteristics of study participants

Characteristic	African American	Caucasian	Other	*P* value
	N = 87	N = 275	N = 118	
Age, y	62 ± 12	66 ± 11	65 ± 12	.004
Male, No. (%)	59 (68)	219 (80)	90 (76)	.075
Medical history, No. (%)				
• Hypertension	66 (76)	170 (62)	90 (77)	.003
• Heart failure	18 (21)	37 (14)	16 (14)	.23
• Diabetes	24 (28)	46 (17)	37 (31)	.003
• Myocardial infarction	42 (49)	141 (51)	58 (49)	.91
• Current smoker	33 (38)	44 (16)	14 (12)	<.0001
• COPD	23 (26)	41 (15)	12 (10)	.006
• Stroke	13 (15)	34 (12)	20 (17)	.47
NYHA symptoms, No. (%)				
• Class I	29 (33)	119 (43)	48 (41)	
• Class II	34 (39)	111 (40)	48 (41)	.20*
• Class III-IV	27 (28)	45 (16)	22 (18)	
Measurements				
• BMI, kg/m^2	28 ± 6	28 ± 5	27 ± 5	.32
• SBP, mm Hg	137 ± 22	132 ± 21v	135 ± 24	.27
• DBP, mm Hg	78 ± 12	75 ± 10	77 ± 12	.12
• MAP, mm Hg	98 ± 14	94 ± 12	96 ± 14	.13
• Pulse pressure, mm Hg	58 ± 18	57 ± 16	58 ± 18	.76
Renal function				
• Serum creatinine, mg/dL	1.30 ± 1.1	1.1 ± 0.4	1.2 ± 0.7	.03
• Measured creatinine clearance, mL/min	83 ± 33	81 ± 29	81 ± 30	.85
Laboratory studies				
• Total cholesterol, mg/dL	170 ± 36	179 ± 41	181 ± 43	.15
• LDL cholesterol, mg/dL	101 ± 32	104 ± 32	108 ± 34	.33
• HDL cholesterol, mg/dL	49 ± 14	45 ± 15	44 ± 12	.036
• Triglycerides, mg/dL	105 ± 66	146 ± 125	142 ± 101	.009
• CRP, mg/dL	4.8 ± 6.5	4.0 ± 6.2	4.0 ± 9.6	.68
• NT-pro-BNP, pg/mL	616 ± 1735	444 ± 951	346 ± 855	.23
Medications, No. (%)				
• ACEI or ARB	44 (51)	139 (51)	63 (53)	.87
• Beta blocker	50 (57)	150 (55)	69 (59)	.74
• Calcium channel blocker	27 (31)	54 (20)	27 (23)	.085
• Statin	46 (53)	173 (63)	75 (64)	.21
• Diuretic	34 (39)	60 (22)	35 (30)	.005

ACEI, Angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptor blocker; *BMI*, body mass index; *COPD*, chronic obstructive pulmonary disease; *CRP*, C-reactive protein; *DBP*, diastolic blood pressure; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *MAP*, mean arterial pressure; *NT-proBNP*, N-terminal pro-B-type natriuretic peptide; *NYHA*, New York Heart Association; *SBP*, systolic blood pressure.Plus-minus values are mean ± SD.
*Across 3 groups of NYHA class.

groups (Caucasian 3.1 ± 2.5 mm Hg, other 3.5 ± 2.7 mm Hg, $P = .008$).

After adjustment for variables thought to be associated with an elevated EDPR gradient or African American race (age; sex; history of hypertension, HF, or chronic obstructive pulmonary disease; blood pressure; serum creatinine; LV EF; LV mass index; and NYHA class) and variables that were found to be significantly different among the groups based on univariate analysis at *P* less than .10 (A-wave velocity, E/A ratio, use of calcium-channel blockers, diabetes, smoking, HDL, triglycerides, and diuretic use), African American race remained a significant predictor of an elevated EDPR gradient (β coefficient 0.75, $P = .025$). Table 3 shows the independent predictors of an elevated EDPR gradient based on our multivariable analysis.

Results of our exploratory analyses were consistent with the hypothesis that an elevated EDPR gradient may partially explain the association of African American race with HF. African Americans had a trend toward increased hospitalization for HF (age-adjusted odds ratio 2.1, 95% confidence interval 1.0-4.4; $P = .06$), but further adjustment for EDPR attenuated this association (hazard ratio 1.6, 95% confidence interval 0.7-3.5; $P = .3$).

DISCUSSION

In a retrospective analysis of a well-characterized cohort of 480 patients with established CAD and a measurable EDPR gradient, we found that African American race was associated with an elevated

Table 2 Echocardiographic characteristics of study participants

Characteristic	African American	Caucasian	Other	*P* value
	N = 87	N = 273	N = 118	
LV parameters				
• LV ejection fraction, %	61 ± 10	62 ± 9	62 ± 9.	.79
• LV mass index, g/m^2	98 ± 29	93 ± 24	96 ± 27	.28
• LV ESVI, mL/m^2	23 ± 16	22 ± 16	21 ± 16	.67
• LV EDVI, mL/m^2	54 ± 21	52 ± 18	50 ± 21	.50
Diastolic parameters				
• LA volume index, mL/m^2	34 ± 11	32 ± 10	31 ± 10	.13
• IVRT, ms	123 ± 24	122 ± 26	126 ± 26	.42
• E-wave velocity, m/s	0.80 ± 0.22	0.76 ± 0.22	0.76 ± 0.20	.16
• A-wave velocity, m/s	0.76 ± 0.27	0.75 ± 0.23	0.82 ± 0.24	.03
• E/A ratio	1.2 ± 0.47	1.1 ± 0.5	1.0 ± 0.36	.024
• Mitral deceleration time, ms	227 ± 58	236 ± 57	243 ± 59	.15
Diastolic function, No. (%)				
• Normal	46 (63)	152 (62)	74 (69)	
• Impaired relaxation	14 (19)	62 (25)	28 (26)	.1*
• Pseudonormal or restrictive	13 (18)	32 (13)	6 (6)	
Right atrial pressure, mm Hg	5.4 ± 1.7	5.6 ± 2.1	5.2 ± 0.9	.071
Right atrial end-systolic volume index, mL/m^2	25 ± 9	24 ± 10	23 ± 8	.28
Pulmonary VTI, m	0.20 ± 0.04	0.20 ± 0.04	0.21 ± 0.04	.55
Mitral regurgitation, moderate or worse, No. (%)	22 (25)	55 (20)	20 (17)	.34
Tricuspid regurgitation gradient, mm Hg	28 ± 9	26 ± 10	26 ± 9	.36
End-diastolic pulmonic regurgitation gradient, mm Hg	4.2 ± 3.3	3.1 ± 2.5	3.5 ± 2.7	.008

A, Late filling as a result of atrial contraction; *E*, early rapid atrial filling; *EDVI*, end-diastolic volume index; *ESVI*, end-systolic volume index; *IVRT*, isovolumic relaxation time; *LA*, left atrial; *LV*, left ventricular; *VTI*, velocity time integral.Plus-minus values are means ± SD.
*Across all 4 groups of diastolic function.

Table 3 Independent predictors of elevated end-diastolic pulmonary regurgitation gradient

Predictor	β-coefficient	*P* value
Age*	0.21	.095
LV mass index†	0.17	.003
LV ejection fraction‡	0.49	.001
Diabetes	0.66	.0298
African American race	0.75	.025

LV, Left ventricular.Adjusted for variables thought to be associated with an elevated end-diastolic pulmonary regurgitation gradient or African American race (age; sex; history of hypertension, heart failure, or chronic obstructive pulmonary disease; blood pressure; serum creatinine; LV ejection fraction; LV mass index; and New York Heart Association class) and variables significantly different among the groups based on univariate analysis at *P* less than .10 (late filling as a result of atrial contraction wave [A] velocity, early rapid filling/A ratio, use of calcium-channel blockers, diabetes, smoking, high-density lipoprotein, triglycerides, and diuretic use).
*Per decade.
†Per 10 g/m^2 increase.
‡Per 10% decrease.

EDPR gradient, independent of LV systolic and diastolic function, LV mass index, blood pressure, and other important covariates (Figure 2). An elevated EDPR gradient has previously been shown to be a marker of cardiac dysfunction, and correlates with decreased functional status.[11] Thus, elevated pulmonary artery diastolic pressure (a surrogate for LV filling pressure) may, in part, explain why African Americans with HF have a worse prognosis compared with patients of other racial groups.[7,20,21]

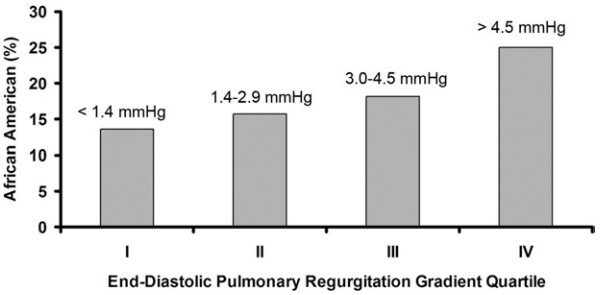

Figure 2 Proportion of African American patients by end-diastolic pulmonary regurgitation gradient quartile.

The Studies of Left Ventricular Dysfunction were among the first to suggest differential HF outcomes as a function of race.[22] A post hoc analysis of the primary trial results demonstrated that mortality from HF was higher in African Americans than in Caucasians, with a 1.8-fold increase for African American men and a striking 2.4-fold increase for African American women. Subsequent studies have shown that African Americans have a more rapid progression of HF than Caucasians,[5] are more likely to have NYHA functional class III symptoms,[5] and have higher rates of HF hospitalizations.[4,7,23]

Differences in health care outcomes among racial/ethnic populations are becoming increasingly apparent, and remain poorly characterized. Although there are many identified causes of health care

disparities, including differences in socioeconomic status, educational attainment, and access to care,[24] further research is needed to identify other causes of differential health outcomes.

Research efforts have identified potential biological differences that may account for the worse HF outcomes in African Americans. Studies have shown that African American patients may have a less active renin-angiotensin system than Caucasians[25] and may have lower nitric oxide bioavailability.[26,27] These findings were initially supported by a retrospective analysis of the Vasodilator Heart Failure Trial, which suggested that African American patients have a unique, clinically significant response to the combination of isosorbide dinitrate (a nitric oxide donor) and hydralazine (which may prevent nitric oxide degradation).[28,29] More recently, the prospective African-American Heart Failure Trial demonstrated a 33% relative reduction in HF hospitalizations and a 43% reduction in mortality among African American patients with HF treated with combination isosorbide dinitrate and hydralazine.[30] Moreover, recent studies have identified genetic differences that may contribute to the variation in HF presentation and outcomes seen in different racial groups.[31]

Despite the differences in HF outcomes noted between African American and Caucasian populations, there is a paucity of echocardiographic and/or hemodynamic data that supports these clinical observations. Indeed, as we report in our study population, there were no significant differences in measures of LV systolic function, LV mass, or pulmonary artery systolic pressure (as estimated by the tricuspid regurgitation gradient) between the racial groups. There was, however, a trend ($P = .1$) toward increased diastolic dysfunction in the African American patients in our study cohort. Our finding of an elevated EDPR gradient, a surrogate marker for LV end-diastolic pressure, thereby represents a novel echocardiographic marker of impaired cardiac function in the African American population.

There are several important clinical variables that may cause an elevation in pulmonary artery pressures in this population. For example, chronic obstructive pulmonary disease and other forms of chronic lung disease,[32] renal insufficiency with chronic volume overload,[33] and long-standing systemic hypertension with LV hypertrophy[34] may all eventually lead to the development of pulmonary hypertension. However, we found that the association between African American race and elevated EDPR gradient persisted after controlling for these potential covariates.

Several limitations must be considered when interpreting these results. First, only patients with prospectively measured EDPR gradients were included in our analysis. In all, 35% of these patients did not have interpretable EDPR gradients, because of poor pulmonary regurgitation flow signals, irregular heart rate, and other technical limitations. Second, the study population was predominantly elderly men, and all participants had known CAD. Thus, the implications of an elevated EDPR gradient in women, younger individuals, or in patients without CAD cannot be determined. Finally, the current investigation was limited to cardiac imaging at a single point in time. Extended observation of this population, with repeated echocardiography at predetermined intervals, would be helpful to determine changes in EDPR gradients over time, and to determine the correlation of these changes with cardiovascular events.

In summary, we found that African American race is associated with an elevated EDPR gradient in patients with CAD. Further research regarding the cause of elevated LV filling pressures in African Americans may contribute to the development of specific, tailored HF therapies for this population.

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