Albuminuria Is Independently Associated With Cardiac Remodeling, Abnormal Right and Left Ventricular Function, and Worse Outcomes in Heart Failure With Preserved Ejection Fraction

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ABSTRACT

OBJECTIVES The purpose of this study was to determine the relationship between albuminuria and cardiac structure/function in heart failure with preserved ejection fraction (HFpEF).

BACKGROUND Albuminuria, a marker of endothelial dysfunction, has been associated with adverse cardiovascular outcomes in HFpEF. However, the relationship between albuminuria and cardiac structure/function in HFpEF has not been well studied.

METHODS We measured urinary albumin-to-creatinine ratio (UACR) and performed comprehensive echocardiography, including tissue Doppler imaging and right ventricular (RV) evaluation, in a prospective study of 144 patients with HFpEF. Multivariable-adjusted linear regression was used to determine the association between UACR and echocardiographic parameters. Cox proportional hazards analyses were used to determine the association between UACR and outcomes.

RESULTS The mean age was 66 ± 11 years, 62% were female, and 42% were African American. Higher UACR was associated with greater left ventricular mass, lower preload-recruitable stroke work, and lower global longitudinal strain. Higher UACR was also significantly associated with RV remodeling (for each doubling of UACR, RV wall thickness was 0.9 mm higher [95% confidence interval: 0.05 to 0.14 mm; $p = 0.001$, adjusted $p = 0.01$]) and worse RV systolic function (for each doubling of UACR, RV fractional area change was 0.56% lower [95% confidence interval: 0.14 to 0.98%; $p = 0.01$, adjusted $p = 0.03$]. The association between UACR and RV parameters persisted after the exclusion of patients with macroalbuminuria (UACR >300 mg/g). Increased UACR was also independently associated with worse outcomes.

CONCLUSIONS In HFpEF, increased UACR is a prognostic marker and is associated with increased RV and left ventricular remodeling and longitudinal systolic dysfunction. (Classification of Heart Failure With Preserved Ejection Fraction; NCT01030991) (J Am Coll Cardiol HF 2014;2:586–96) © 2014 by the American College of Cardiology Foundation.

Albuminuria is associated with cardiovascular morbidity and mortality in diabetics, hypertensives, and the general population (1-5). In patients with heart failure (HF), there is increased prevalence of albuminuria, and a higher urine albumin-to-creatinine ratio (UACR) is associated with greater overall cardiovascular mortality and more frequent hospitalization for HF (6-8). However, studies have largely been focused on HF with reduced ejection fraction (HFrEF). In HF with preserved EF (HFpEF), a positive urine dipstick for albuminuria has been found to be associated with worse outcomes (9), and

urinary albumin excretion preferentially predicts progression to HFpEF (compared with HFrEF) (10).

Although albuminuria is known to be associated with increased left ventricular (LV) mass (11), the more specific structural or functional changes in the heart that underlie these phenomena remain unclear. Albuminuria is theoretically related to multiple pathophysiological processes, including systemic inflammation and endothelial dysfunction (12). Some evidence suggests that systemic inflammation and endothelial dysfunction play a role in HFpEF (13,14) and that these abnormalities in HFpEF extend beyond the LV to other cardiovascular structures (15,16).

For these reasons, we sought to better understand the relationship between elevated UACR and abnormal cardiac structure/function in HFpEF. We hypothesized that increased UACR is associated with multiple measures of cardiac remodeling and dysfunction (including abnormal right ventricular [RV] structure/function) and is predictive of adverse outcomes in HFpEF. Therefore, we prospectively studied the association between UACR, cardiac structure/ function, and outcomes in a well-characterized HFpEF cohort.

METHODS

STUDY POPULATION. Between March 2008 and May 2011, consecutive patients were prospectively enrolled from the outpatient clinic of the Northwestern University HFpEF Program as part of a systematic observational study of HFpEF (NCT01030991). All patients were enrolled in the study in the outpatient setting after a hospitalization for HF. Patients were initially identified by an automated daily query of the inpatient electronic medical record at Northwestern Memorial Hospital using the following search criteria: 1) diagnosis of HF or the words "heart failure" in the hospital notes; or 2) B-type natriuretic peptide (BNP) >100 pg/ml; or 3) administration of 2 or more doses of intravenous diuretic agents.

Patients were offered post-discharge follow-up in a specialized HFpEF outpatient program if they met the following 3 inclusion criteria: age ≥21 years, LV ejection fraction (EF) ≥50%, and presence of HF as defined by Framingham criteria (17). The HF diagnosis was confirmed in the post-hospitalization outpatient HFpEF clinic. Consistent with previously published criteria (18,19), all patients were found to have at least 1 of the following 3 diagnostic hallmarks of HFpEF: grade 2 or worse LV diastolic dysfunction

on echocardiography; elevated pulmonary capillary wedge pressure or LV end-diastolic pressure on invasive hemodynamic testing; or elevated BNP (>100 pg/ml). Patients were excluded if they had greater than moderate valvular disease, prior cardiac transplantation, prior LV EF <40%, LV end-diastolic volume >97 ml/m², or constrictive pericarditis. All study patients were seen in the outpatient HFpEF program within 1 month of hospital discharge. All study participants gave written informed consent, and the institutional review board at Northwestern University approved the study.

CLINICAL CHARACTERISTICS. We collected the following data for all study participants: demographics, race/ethnicity, New York Heart Association (NYHA) functional class, comorbidities, medications, vital signs, body mass index, and laboratory data, including serum sodium, blood urea nitrogen, creatinine, hemoglobin, and BNP. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation. Chronic kidney disease (CKD) was defined as eGFR <60 ml/min/1.73 m². Diabetes mellitus (DM) was defined by the presence of physician-documented history of diabetes or the use of oral hypoglycemic agents or insulin for the treatment of hyperglycemia. Coronary artery disease (CAD) was defined as presence of physician-documented history of CAD, known coronary stenosis >50%, history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, or abnormal stress test results consistent with myocardial ischemia. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, physician-documented history of hypertension, or current use of antihypertensive medications. Hyperlipidemia was defined as physician-documented history of hyperlipidemia or current use of lipid-lowering medications. Obesity was defined as body mass index >30 kg/m². Anemia was defined as hemoglobin <11.6 g/dl for women or <13 g/dl for men; hemoglobin cutoff values were chosen based on lower limits of normal as reported by the laboratory at our institution (Northwestern Memorial Hospital).

URINE ALBUMIN-TO-CREATININE RATIO. Urinary albumin excretion was measured on spot urine specimens by immunoturbidimetry using goat anti-human albumin antiserum with a coefficient of variation <10%. Urinary creatinine was measured

ABBREVIATIONS AND ACRONYMS

AUC = area under the curve

BNP = B-type natriuretic peptide

CKD = chronic kidney disease

DM = diabetes mellitus

EF = ejection fraction

eGFR = estimated glomerular filtration rate

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

IDI = integrated discrimination improvement

IQR = interquartile range

LV = left ventricular

NYHA = New York Heart Association

PASP = pulmonary artery systolic pressure

PRSW = preload-recruitable stroke work

RAP = right atrial pressure

RV = right ventricular

RVFAC = right ventricular fractional area change

TAPSE = tricuspid annular plane systolic excursion

UACR = urine albumin-to-creatinine ratio