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Left Ventricular Amyloid Deposition in Patients With Heart Failure and Preserved Ejection Fraction

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Objectives This study sought to determine the frequency of left ventricular amyloid in heart failure with preserved ejection fraction (HFpEF).

Background Left ventricular amyloid deposition can cause diastolic dysfunction and HFpEF.

Methods Autopsy of left ventricular specimens from patients with antemortem diagnosis of HFpEF without clinically apparent amyloid (n = 109) and from control subjects (n = 131) were screened with sulfated Alcian blue and subsequent Congo red staining with microdissection for mass spectrometry–based proteomics to determine amyloid type. Fibrosis was assessed with quantitative whole-field digital microscopy.

Results The presence of wild-type transthyretin (wtTTR) amyloid was associated with age at death and male sex, but the age- and sex-adjusted prevalence of wtTTR amyloid was higher in HFpEF patients than in control subjects (odds ratio: 3.8, 95% confidence interval: 1.5 to 11.3; p = 0.03). Among HFpEF patients, moderate or severe interstitial wtTTR deposition, consistent with senile systemic amyloidosis as the primary etiology of HFpEF, was present in 5 (5%) patients (80% men), with mild interstitial and/or variable severity of intramural coronary vascular deposition in 13 (12%) patients. While, wtTTR deposition was often mild, adjusting for age and presence of HFpEF, wtTTR amyloid was associated with more fibrosis (p = 0.005) and lower age, sex, and body size–adjusted heart weight (p = 0.04).

Conclusions Given the age- and sex-independent association of HFpEF and wtTTR deposition and an emerging understanding of the pathophysiology of the amyloidoses, the current findings support further investigation of the role of wtTTR in the pathophysiology of HFpEF. (J Am Coll Cardiol HF 2014;2:113–22) © 2014 by the American College of Cardiology Foundation

Cardiac amyloid deposition can cause heart failure with preserved ejection fraction (HFpEF). While approximately 30 proteins have been linked to cardiac amyloidosis, monoclonal immunoglobulin from clonal plasma cells (AL amyloid) and transthyretin (TTR amyloid) are the most common forms.

Transthyretin is a hepatic-derived, homotetrameric transporter protein that exists in equilibrium with TTR monomers. A number of genetic variations in the TTR gene cause hereditary amyloidosis, affecting the nerves, heart, or both. Cardiac amyloidosis (senile systemic amyloidosis [SSA]) due to deposition of amyloid derived from wild-type TTR (wtTTR) in the myocardial interstitium and intramural coronary vessels is associated with left ventricular (LV) wall thickening, diastolic dysfunction, and HFpEF (1–4).

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Abbreviations and Acronyms

EF = ejection fraction
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
ICD = International Classification of Diseases
LV = left ventricle
SAB = sulfated Alcian blue
SSA = senile systemic amyloidosis
TTR = transthyretin
WFDM = whole-field digital microscopy
wtTTR = wild-type transthyretin

While marked amyloid deposition is present in clinically diagnosed SSA, emerging evidence suggests that cell damage in TTR amyloid is due to deposition of lower molecular weight non-amyloid TTR species that precede detectable TTR amyloid fibril deposition (5–10). Variant TTR is structurally less stable and more prone to amyloid fibril formation (7), but the factors leading to wtTTR amyloid deposition have yet to be fully elucidated. In vitro studies suggest that oxidative modification of wtTTR increases its amyloidogenicity (7). As aging is associated with increased oxidative stress, oxidative modification of wtTTR may account for the association of the SSA with age.

HFpEF accounts for one-half of HF patients, and its prevalence increases dramatically with age and female sex (11). Clinical suspicion of amyloid in HFpEF patients may be low, as they often have alternative explanations, such as chronic hypertension, for LV wall thickening and diastolic dysfunction.

Development of novel compounds that may attenuate TTR amyloid cardiac deposition has heightened interest in the significance of TTR amyloid as a cause of HF (12–14). While autopsy rates in older HF patients are low (15), autopsy specimens provide the optimal opportunity to assess the prevalence of unsuspected amyloid deposition in HFpEF, as endomyocardial biopsy is infrequent in older HFpEF patients (16) and fat aspirate has limited sensitivity for detection of wtTTR amyloid (17–19).

Accordingly, we sought to determine the frequency, extent, and type of cardiac amyloid deposition in patients with an antemortem diagnosis of HFpEF (but not of amyloid) who subsequently underwent autopsy, as compared with age-appropriate control autopsy subjects.

Methods

The study was approved by Mayo Clinic Institutional Review Board and the Mayo Biospecimens Committee. Only autopsy specimens with consent for use of specimens for research purposes were used.

Identification of HFpEF cases with autopsy. HFpEF subjects were identified using cohorts previously assimilated from administrative datasets. Consecutive patients admitted to Mayo Clinic hospitals in Rochester, Minnesota, between January 1, 1986, and December 31, 2001, with a discharge diagnosis of HF confirmed by both the International Classification of Diseases-, Ninth Revision-, Clinical Modification (ICD-9-CM) code 428 and the diagnosis related-group code 127 for HF (n = 6,440), were identified as previously described (20,21).

This patient list was crossed to the MTR (Mayo Tissue Registry) (15,22) to identify patients who had undergone autopsy (n = 441, 6.8%) (23). Characteristics, including EF distribution, of patients with and without autopsy were similar except for a slightly higher rate of hypertension and coronary disease in patients with autopsy (Online Table 1). Many autopsies were restricted in extent (neurologic only). Thus, of the 441 patients with autopsy, 331 had EF measured at HF diagnosis and of these, 75 had EF >40% at HF diagnosis.

To supplement this cohort, additional patients hospitalized with HF (ICD-9-CM code 428) at Mayo hospitals from 2003 to 2010 were identified and crossed with the MTR, yielding 25 additional cases with EF >40% at HF diagnosis and cardiac autopsy. Additionally, outpatients with HF (ICD-9-CM code 428) diagnosed between March 1980 and July 2009 who were residents of Olmsted County, Minnesota, and who had HF confirmed by medical record review (Framingham criteria) (24) were crossed with the MTR, yielding an additional 12 cases with EF >40% at HF diagnosis and autopsy, for a total of 112 cases with antemortem diagnosis of HFpEF and cardiac specimens from autopsy.

Medical records of these subjects were reviewed and any mention of definitive or probable cardiac amyloid in the clinical notes or reference to echocardiographic features of amyloid or cardiac biopsy findings suggestive of amyloid was considered antemortem suspicion. Three HFpEF cases had antemortem diagnosis of amyloidosis. Importantly, in all 3 patients, the amyloid was light chain type. Thus, exclusion of these patients does not affect estimates of the prevalence of wtTTR amyloid in HFpEF. As antemortem suspicion of cardiac amyloidosis could influence the decision to perform an autopsy, these 3 patients were excluded, leaving 109 patients with HFpEF and no clinical suspicion of cardiac amyloidosis prior to death and autopsy.

Identification of control subjects. After reviewing the distribution of age at death and sex of the HFpEF autopsy cases, a minimum of 20 subjects per age at death decade, ≥40 years of age without antemortem HF diagnosis and who died of noncardiovascular causes and had undergone autopsy between January 3, 1971, and October 12, 2010, were identified from the MTR database (n = 131) to serve as age- and sex-appropriate control subjects. Though not formally age-matched in a 1:1 ratio (where equal numbers of control and HFpEF patients of the same age would be studied, due to the small number of HFpEF patients in some age groups), appropriate numbers of control subjects were selected to allow statistical assessment of age dependence of findings. Medical record review was performed to define clinical characteristics and exclude antemortem diagnosis of amyloid in control subjects.

Autopsy data and tissue processing. Finalized autopsy reports were reviewed and included assessment of absolute