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EDITORIAL COMMENT

# Hepatocyte Growth Factor and Cardiac Amyloidosis*

Frederick L. Ruberg, MD, Omar K. Siddiqi, MD

Once the subject of case reports and rare disease clinical-pathological conferences, it seems that cardiac amyloidosis is now everywhere. Awareness of this restrictive cardiomyopathy caused by the interstitial deposition of misfolded protein fragments has been fueled by revolutionary advances in diagnostic testing and innovative therapies. Although AL (misfolded immunoglobulin light-chain) amyloidosis remains a rare disease affecting 10,000 to 15,000 patients in the United States (1), ATTR amyloidosis (misfolded transthyretin or prealbumin) resulting from an inherited variation (referred to as hATTR or ATTRv) or from genetically normal (wild-type) TTR protein (referred to as ATTRwt) may affect 100,000 people or more (2). Previously untreatable, therapies for AL cardiac amyloidosis can extend survival in most patients for many years and for some for well over a decade (3). Similarly, ATTR amyloidosis, once treatable only by organ transplantation until a few years ago, now is primarily managed by highly effective pharmaceutical therapies that stabilize the TTR protein or silence its production (2), resulting in symptomatic improvement and increased survival.

Diagnosis of cardiac amyloidosis still requires that the astute clinician exercise a high degree of suspicion to recognize "red flag" features of symptoms and laboratory or echocardiographic derangements (4). Next, appropriate testing must be ordered and correctly interpreted. Recent multisocietal consensus recommendations have been developed that standardize both test acquisition and interpretation, as well as frame diagnostic testing within appropriate clinical contexts (5,6). Although the capacity to diagnose ATTR amyloidosis noninvasively through imaging has undoubtedly contributed to its increased recognition (7), there remains considerable heterogeneity in adherence to guideline recommendations, resulting in test misuse and inaccurate diagnoses. A highly discriminative blood biomarker test would represent a significant advancement in the approach to cardiac amyloidosis diagnosis by serving as a gatekeeper whereby follow-on imaging testing could be triggered or avoided.

Circulating biomarkers are attractive as screening tests for cardiac amyloidosis because they lack the inherent subjectivity of imaging and are easy to acquire and easy to interpret. Free light-chain concentration in AL amyloidosis identifies systemic disease but does not specify organ involvement. Cardiac-specific biomarkers including natriuretic peptides (B-type natriuretic peptide [BNP] and N-terminal pro-B type natriuretic peptide [NTpro-BNP]) and troponins (troponin I and T) are useful for prognostication in both AL (8,9) and ATTR (10), but are not specific diagnostically. In ATTR, there is evidence that prealbumin (or TTR) concentration may also prove prognostic (11) and appears to be a means to follow response to ATTR-specific therapy (12), but its role as a diagnostic screening test for cardiac amyloidosis remains unproven. At present, only retinol binding protein 4 appears useful as a specific biomarker screening test for hATTR amyloidosis, but one that functions best when incorporated into a prediction model that requires other diagnostic test results

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From the Section of Cardiovascular Medicine, Department of Medicine, Amyloidosis Center, Boston University School of Medicine, Boston Medical Center, Boston, Massachusetts, USA. Dr. Ruberg is supported by the National Institutes of Health R01 HL139671; and has received research grants from Pfizer and Eidos Therapeutics. Dr. Siddiqi has reported that he has no relationships relevant to the contents of this paper to disclose. The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: CardioOncology* author instructions page.

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(electrocardiogram and echocardiography) (13). No biomarker appears to confer both reliable diagnostic and prognostic information.

In this context, one can consider the report by Zhang et al. (14) in this issue of *JACC: CardioOncology* as a potential major advancement if validated in larger studies. Hepatocyte growth factor (HGF) was first described as a mitogen for hepatic cells but is expressed in mesenchymal cell derivatives (including cardiomyocytes) as, among other actions, a pro-angiogenic cytokine. Increased circulating concentrations of HGF, attributed to response to injury, have been associated with mortality in heart failure (15), whereas transfection of HGF into myocytes in animal models of post-infarction cardiomyopathy improved left ventricular (LV) remodeling (16). Zhang et al. (14) postulated that in the context of amyloid fibril deposition, HGF would be upregulated and measurable in the circulation, as has been reported in smaller studies (17), thus potentially representing a specific marker for cardiac amyloidosis.

SEE PAGE 56

In this retrospective, single-center cohort study, plasma biomarkers including natriuretic peptides, troponins, HGF, galectin-3, and interleukin-6 were measured in 102 patients with systemic amyloidosis and 86 controls. The systemic amyloidosis cohort was further categorized as cardiac amyloidosis (n = 72 of whom 55% had endomyocardial biopsy) and amyloidosis without cardiac involvement (n = 30). Noncardiac biopsy assessment of cardiac involvement required an extra-cardiac biopsy showing amyloid in conjunction with either increased wall thickness based on echocardiography, low-voltage electrocardiogram pattern or characteristic late gadolinium enhancement noted based on cardiac magnetic resonance. The looseness of this definition comprises a relative weakness of the study and would tend to equilibrate the two amyloid subgroups, reducing the capacity to identify differences. The amyloid patient group was mixed with respect to type but predominantly consisted of light-chain disease in 67% of the total cohort, while 60% of the cardiac amyloidosis subgroup had AL amyloidosis. It is notable that 88% of the patients with amyloidosis were Caucasian, suggesting that the conclusions of this study may not be generalizable to the population with pV142I hereditary ATTR amyloidosis (an allele noted in 3.4% of African Americans). The control groups were composed of patients with normal LV systolic function but with hypertrophy (by mass index and relative wall thickness; n = 44) and heart failure with reduced left ventricular ejection fraction (LVEF) (LVEF ≤30% and class 3 to 4 heart failure; n = 42). Baseline plasma markers were then tested for association with a composite clinical outcome endpoint of all-cause mortality, cardiac transplantation, or left ventricular assist device implantation over a median observation of 2.6 years (interquartile range: 1.9 to 3.1 years). A total of 30 events occurred, nearly entirely mortality (n = 27).

The authors found that HGF concentrations were higher in cardiac amyloidosis as compared with all other groups, and that this association persisted after adjustment for baseline differences in age (cardiac amyloidosis patients were older), septal thickness, and LVEF. Using receiver operator characteristic analysis, an HGF of >205 pg/ml conferred an 86% sensitivity (95% confidence interval [CI]: 78% to 94%), 84% specificity (95% CI: 76% to 92%), and area under the curve (AUC) of 0.88 (95% CI: 0.83 to 0.94) for the differentiation of cardiac amyloidosis from the 2 non-amyloid control groups. HGF did not differ between cardiac amyloidosis owing to AL or ATTR. In respect to predictive capacity, a baseline HGF at a threshold of 320 pg/ml was associated with the composite outcomes similar to that of baseline NT-proBNP and troponin T using the Mayo 2004 classification thresholds. The addition of HGF to NT-proBNP and troponin T significantly improved the predictive model for outcomes. Galectin-3, although lower in cardiac amyloidosis as compared with the 2 non-amyloid control groups, proved a poorer discriminator as compared with HGF.

As a means to identify cardiac involvement in the systemic amyloidosis group, measurement of the established biomarkers NT-proBNP and troponin-T discriminated cardiac from non-cardiac amyloidosis as predicted. HGF also similarly discriminated cardiac involvement (AUC: 0.69; 95% CI: 0.55 to 0.83), but proved inferior to either NT-proBNP (AUC: 0.89; 95% CI: 0.80 to 0.97) and troponin-T (AUC: 0.83; 95% CI: 0.73 to 0.93). As a means to identify outcomes, the authors performed a sensitivity analysis to evaluate the capacity of HGF to improve established prediction models using NT-proBNP and troponin T among the patients with amyloidosis. Significant improvement in the predictive model was observed for AL but not ATTR, perhaps related to lack of adequate power. Interestingly, lower eGFR did not associate with worse outcomes, likely owing to the smaller component of patients with ATTR.

There are a number of important limitations to this study that merit discussion. First, and foremost, this is a relatively small single-center study with results that should be seen as hypothesis-generating, requiring validation in larger cohorts (as the authors

are intending). Second, because this was clearly a dataset comprised through retrospective review and subject to variation in clinical practice (different troponin and BNP assays, for example), there was a considerable amount of missing data. To address this shortcoming, the authors repeated analyses with multiple imputation datasets demonstrating consistent results. Third, AL and ATTR are diseases with distinct courses and treatments. It is difficult to interpret these survival results without treatment response information, and, furthermore, because clinical courses are different, outcomes for these 2 amyloid types cannot be equitably compared. Fourth, various HGF thresholds are presented (205 pg/ml to differentiate cardiac amyloidosis from other causes of heart failure, 320 pg/ml to identify cardiac involvement in systemic amyloidosis, 676 pg/ml to best discriminate outcomes) creating confusion as to what to use clinically. As larger datasets become available, a single value or range affording clinical utility may become evident. Fifth, while the left ventricular hypertrophy control group is well selected, heart failure with reduced ejection fraction as characterized here is really not a phenotypic match for cardiac amyloidosis. Finally, the rationale for selecting HGF as a marker in cardiac amyloidosis, although briefly touched upon by the authors, is unclear with only speculative mechanisms. Although well beyond the scope of this study, pathophysiological evidence of HGF relevance to cardiac amyloidosis from cellular or animal-based studies would support these findings. Will HGF prove to be that elusive biomarker that might specifically identify cardiac amyloidosis and confer information regarding prognosis? We eagerly await the answer.

**ADDRESS FOR CORRESPONDENCE:** Dr. Frederick L. Ruberg, Section of Cardiovascular Medicine, Boston Medical Center, 72 East Concord Street, Boston, Massachusetts 02118. E-mail: frruberg@bu.edu. Twitter: @BUMedicine, @omarsiddiqi, @frederickruberg, @BU_Amyloidosis.

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