*National Institute for Health Research Cardiovascular Biomedical Research Unit
Royal Brompton Hospital
Sydney Street
London, SW3 6NP
United Kingdom
E-mail: s.babu-narayan@rbht.nhs.uk OR
s.babu-narayan@imperial.ac.uk

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CMR-Verified Regression of Cardiac AL Amyloid After Chemotherapy

Systemic light-chain (AL) amyloidosis is characterized by interstitial deposition of aggregated misfolded monoclonal immunoglobulin light chains in the form of amyloid fibrils. Cardiac involvement is the main driver of prognosis. Brain natriuretic peptides and echocardiography are currently the reference standards for assessing cardiac responses, but neither directly quantifies the amyloid burden. Cardiac magnetic resonance (CMR) is a sensitive tool for characterizing myocardial amyloid deposits: late gadolinium enhancement (LGE) shows a continuum of cardiac infiltration, from subendocardial LGE to transmural as the disease progresses (1). Native myocardial T1 and extracellular volume (ECV) measurements have been shown to track clinical disease in cardiac amyloidosis and improve diagnostic accuracy and patient stratification (2).

The aim of this study was to evaluate cardiac AL amyloidosis serially using CMR and ECV measurement. The study group comprised 31 consecutive patients diagnosed with cardiac AL amyloidosis (21 males [68%], age 61 ± 9 years) who underwent serial CMR evaluation with T1 mapping as well as comprehensive clinical assessment (electrocardiogram, echocardiogram, CMR, serum amyloid P [SAP] scintigraphy, and N-terminal pro-B-type natriuretic peptide [NT-proBNP] measurements) before and after chemotherapy in our center between 2011 and 2015. The clonal hematologic response was evaluated according to international consensus criteria (3). All subjects underwent CMR at 1.5-T (Avanto or Aera, Siemens Healthcare, Erlangen, Germany). T1 mapping was acquired using modified look-locker inversion recovery or the shortened modified look-locker inversion recovery sequence. Conventional 2-dimensional LGE was acquired with magnitude inversion recovery or phase-sensitive inversion recovery. ECV was measured as previously described (1). Regression in the cardiac amyloid burden was defined as a decrease in ECV by 2 SD. Changes in the visceral amyloid burden were assessed using serial SAP scintigraphy (4).

At baseline, the overall prevalence of LGE was 87%, with an average ECV of 54 ± 11%. The pattern of LGE was transmural in 29% and subendocardial in 58%; 4 patients (13%) had no LGE. The overall hematologic response rate was 61% and comprised complete response in 36%, very good partial response in 29%, and partial response or no response in 39% (3). Reduction in ECV attaining the CMR criteria for regression of amyloid occurred in 13 patients. The prevalence of regression was higher in patients with complete response/very good partial response (92%) versus patients in partial response/no response ($p < 0.01$) (**Figure 1**). The mass changed concordantly in 7 of the 13 patients (54%) whose amyloid regressed; the LGE pattern changed in 5 (38%). More than 30% reduction in NT-proBNP levels was present in 69% of patients with amyloid regression. Overall, regression of amyloid was associated with improvements in NT-proBNP, left ventricular mass, left atrial area, and diastolic function parameters. Regression of cardiac

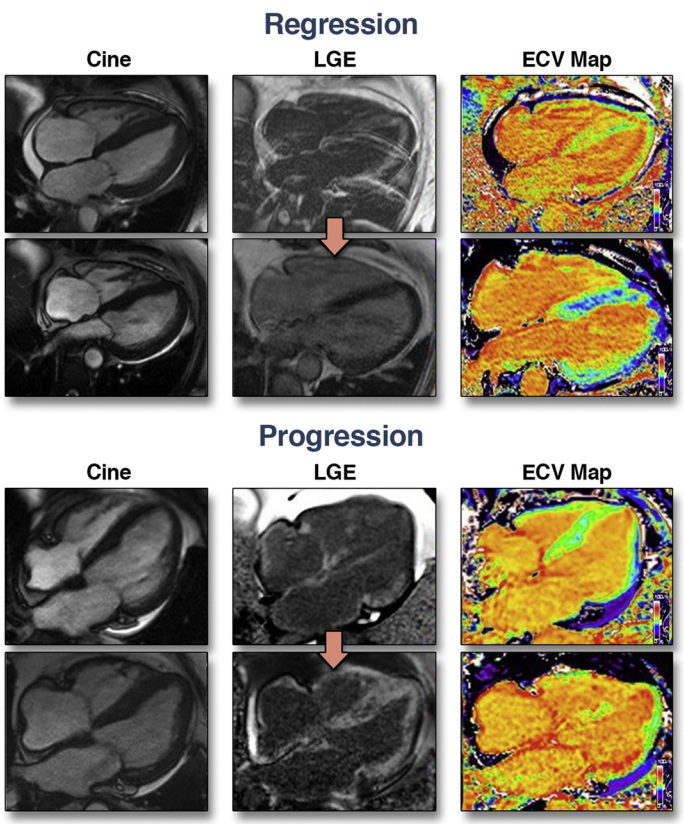
amyloid by CMR correlated with regression of extracardiac amyloid by SAP scintigraphy. By contrast, among patients whose ECV did not diminish, there were deteriorations in left ventricular and right ventricular systolic function and maximal wall thickness.

Cardiac organ response has historically been sought using echocardiography, but improvements are seldom evident, engendering the belief that cardiac amyloid may only stabilize following successful chemotherapy. These serial CMR studies demonstrate that regression of cardiac amyloid following a substantial response to chemotherapy is a relatively common phenomenon, occurring in 42% of patients in our cohort. Although reduction in native T1 and ECV could in part be related to reduction in myocardial edema, the magnitude of reduction in native T1, ECV, reversal of LGE pattern, and correlation with regression in other organs by SAP scintigraphy provide compelling evidence of cardiac amyloid regression. Tracking changes in the cardiac amyloid burden has the potential to redefine cardiac response to treatment, enabling the stratification of patients with lower risk of progression and better prognosis and in whom the need to intensify chemotherapy may not be required. Furthermore, the development of immunotherapies to promote regression of amyloid is well advanced and the ability to measure amyloid regression could be of great value as an endpoint.

Important limitations of this study include retrospective analysis of a small patient cohort with different time intervals between scans. There is a survival bias in that we quote only subjects with paired scans. Finally, 2 different T1 mapping techniques were used.

Ana Martinez-Naharro, MD
Amna Abdel-Gadir, MBBS
Thomas A. Treibel, MBBS
Giulia Zumbo, MD
Daniel S. Knight, MBBS
Stefania Rosmini, MD
Thirusha Lane, RN, PhD
Shameem Mahmood, MD
Sajitha Sachchithanantham, MD
Carol J. Whelan, MD
Helen J. Lachmann, MD
Ashutosh D. Wechalekar, MD
Peter Kellman, PhD
Julian D. Gillmore, MD, PhD
James C. Moon, MD
Philip N. Hawkins, PhD
Marianna Fontana, PhD*

FIGURE 1 Regression and Progression of Cardiac Amyloidosis by Cardiac Magnetic Resonance



Four-chamber cine **(left)**, corresponding LGE **(middle)**, and ECV **(right)** mapping before and after chemotherapy in 2 patients: 1 regressor **(top)** and 1 that progressed **(bottom)**. ECV = extracellular volume; LGE = late gadolinium enhancement.

*National Amyloidosis Centre, University College London
Royal Free Hospital
Rowland Hill Street
London NW3 2PF
United Kingdom
E-mail: m.fontana@ucl.ac.uk

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Atrial Strain Assessment in Left Ventricular Diastolic Dysfunction

We read with great interest the work by Mordi et al. (1), which was concerned with the ventricular mechanics in patients with heart failure and preserved ejection fraction (HFpEF) in the current issue of *iJACC*. The investigators nicely demonstrated the relevance of echocardiographic global longitudinal strain (GLS) at rest and cardiac magnetic resonance (CMR)–derived extracellular volume (ECV) in the identification of patients with left ventricular (LV) diastolic dysfunction. Both parameters possess additional value beyond commonly established parameters like LV ejection fraction and transmitral velocities, such as, E/E′ in the differentiation among patients with hypertensive heart disease, patients with HFpEF, and healthy control subjects (1).

While the investigators valued ventricular mechanics, evaluation of atrial physiology, with its 3 distinct phases (2) was not approached, although mounting evidence has suggested a pivotal role of atrial physiology in ventricular diastolic dysfunction (2). In addition to ventricular measurements, strain and strain rate parameters are available to assess atrial reservoir function (collection of pulmonary venous return during ventricular systole), conduit function (early diastolic blood passage for ventricular filling), and booster pump function (late diastolic augmentation of ventricular filling). Although the investigators demonstrated a strong correlation of GLS with exercise capacity as expressed by peak volume of oxygen and ventilatory response/volume of carbon dioxide, atrial conduit function was shown to be the most precise predictor of exercise intolerance, beyond invasively measured ventricular parameters of stiffness and relaxation (3). In addition, there is evidence to suggest an important role of stress testing in HFpEF because diagnostic accuracy of guideline-recommended echocardiographic assessments during stress was significantly increased, mainly due to improved sensitivity (4). Furthermore, Melenovsky et al. (5) identified an impaired atrial booster pump function during stress in HFpEF as a potential mechanism to explain cardiopulmonary decompensation in this condition.

In conclusion, the investigators should be commended for expanding the existing body of literature on assessment of ventricular mechanics and tissue characterization by a multiparametric imaging approach with echocardiography and CMR in diastolic dysfunction. Both resting GLS and ECV might improve diagnostic accuracy to detect early changes in subclinical diastolic dysfunction, which potentially could be further increased by assessments during physiological exercise and the application of additional left atrial strain assessments. A complete evaluation of diastolic dysfunction should therefore incorporate ventricular and atrial physiology at rest, and ideally, also under stress, to gain further insights into the complicated and heterogeneous nature of HFpEF.

Sören Jan Backhaus, MD
Andreas Schuster, MD, PhD, MBA*
*Department of Cardiology
Royal North Shore Hospital
The Kolling Institute
Northern Clinical School
University of Sydney
Sydney, Australia
E-mail: andreas_schuster@gmx.net

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THE AUTHORS REPLY:

We thank Drs. Backhaus and Schuster for their interest in our study (1). As they state, a multiparametric approach to the diagnosis of heart failure with