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EDITORIAL COMMENT

Deeper Into Cardiac Amyloid

Potential for Improved Outcomes*

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Amyloidosis refers to a group of disorders characterized by deposition of autologous fibrillary proteins into the interstitium, leading to multiple-organ dysfunction (1). Depending upon the type, it can involve the skin, blood vessels, liver, kidney, nerves, heart, and other organs. The interstitial deposits increase the extravascular volume and may elicit a fibrotic response, parenchymal cell loss, and organ dysfunction. Amyloid deposits also have other nonfibrillary constituents, notable among which is serum amyloid P (SAP) component, as it lends itself to imaging and is a target for therapeutic intervention (2).

There are more than 30 different types of proteins associated with amyloid, and there are at least a dozen types of amyloidosis (2). The main types of systemic amyloidosis include: 1) AL amyloidosis due to monoclonal plasmacytoma in the bone marrow, resulting in excess production of monoclonal immunoglobulin light chains that are deposited in the interstitium along with SAP; 2) AA amyloidosis in response to chronic inflammation such as rheumatoid arthritis or tuberculosis with deposition of serum amyloid protein mostly in abdominal organs; 3) senile restrictive cardiomyopathy due to wild-type transthyretin deposits produced in the liver; 4) familial AF amyloid due to mutant transthyretin produced in the liver; and 5) AH amyloid, which occurs in dialysis patients because of B2-microglobulin deposits. AL amyloidosis is the most frequent type; it involves the heart in about 50% of cases and is amenable to chemotherapy in appropriately selected patients with positive outcomes. It is estimated that there are about 2,200 new cases of AL amyloid annually in the United States, but the incidence is likely underestimated because of lack of awareness, absence of sensitive detection tools, and vast underreporting (3). The prevalence of cardiac involvement is likely to be higher with better detection tools. Early detection may also enable a window of opportunity or a sweet spot when therapeutic ratio may be high, early enough in the disease process to maximize cure but not too late to be futile. In the late stage, the prognosis is poor, and therapy has little prospect of producing reversal of the disease process, thus exposing patients only to the risk of therapy. Cardiac involvement is usually diagnosed and staged on the basis of elevated serum levels of N-terminal pro-brain natriuretic peptide, cardiac troponin T, and free light-chain difference and increased left ventricular (LV) wall thickness of >12 mm in the absence of other causes (4). In addition, the presence of positive histological evidence of amyloid is required in tissues such as the rectum, abdominal fat pad, heart, and other areas (Mayo stage I: no elevation of N-terminal pro-brain natriuretic peptide or cardiac troponin T; stage II: elevation of N-terminal pro-brain natriuretic peptide or cardiac troponin T; stage III: elevation of both).

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In this issue of *iJACC*, Barros-Gomes et al. (5) of the Mayo Clinic describe the prognostic value of global longitudinal myocardial strain imaging in 150 patients with biopsy-proved AL amyloidosis, 63 with cardiac involvement as defined by the working group on amyloidosis and 87 with no evidence of cardiac involvement (extracardiac biopsy positive, cardiac markers and echocardiography negative). There was a typical LV base-to-apex strain gradient in both groups, with apical preservation of function. In addition, global strain was an independent predictor of survival in the entire cohort and more so in those with no evidence of cardiac involvement by other criteria, indicating that the strain measurement may be a sensitive tool for the early detection of cardiac

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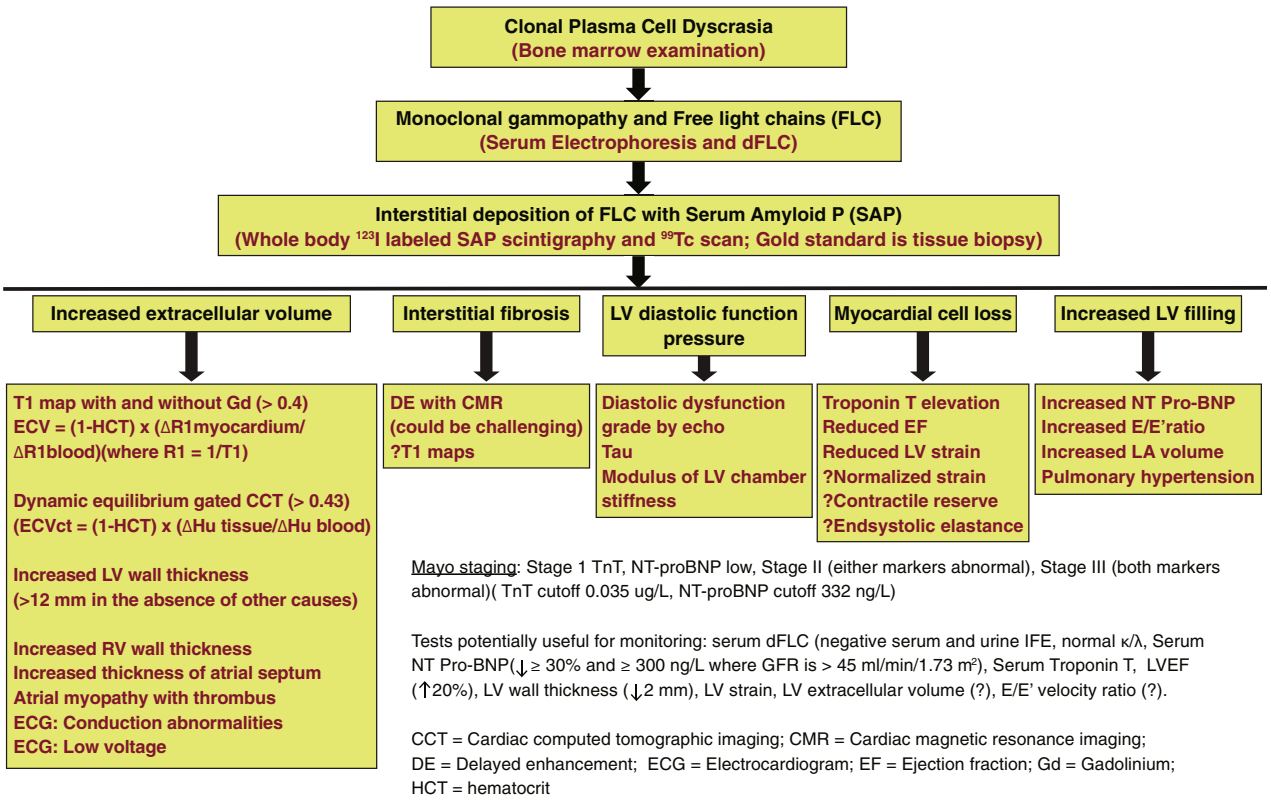
FIGURE 1 Imaging for Cardiac Amyloid



A flowchart schematically illustrating the steps and processes in the pathogenesis of AL cardiac amyloidosis and potential imaging techniques to characterize these steps.

deposits, though direct histological proof is not available in these patients. Because endomyocardial biopsy has sensitivity of nearly 100% for the detection of cardiac involvement, it would have been instructive to have such data to establish the myocardial strain level thresholds at which cardiac involvement is likely. This would allow earlier diagnosis and possibly earlier institution of disease-modifying therapies, as late detection of cardiac amyloidosis is associated with poor prognosis and potential lack of response to therapy. The goal would be to avoid reaching the phase in which LV ejection fraction drops or the myocardium is rendered stiff, resulting in restrictive physiology which bodes poor prognosis. Response to therapy is generally measured in terms of amount of reduction in free light-chain difference and improvements in LV wall thickness and ejection fraction. Global myocardial strain may be a better and more sensitive measure of response of the heart to therapy.

There are tests available now to diagnose or assess different steps in the pathogenesis of cardiac amyloidosis, starting from detection of clonal plasmal cell proliferation and its burden in the bone marrow, to light chain production, its incorporation into the interstitium, expansion of LV extracellular volume (ECV), its deleterious effect on myocyte function and survival causing systolic and diastolic dysfunction and production of heart failure state (**Figure 1**) (2,4). Many of these may not only allow early detection of the disease but may serve as reliable tools for monitoring of therapeutic response as well. Expansion of ECV is potentially detectable by dynamic equilibrium contrast computed tomography, making use of myocardial attenuation with contrast in relation to the blood pool (6). ECV expansion is also detectable by T1 maps of the left ventricle with and without contrast (7). On delayed enhancement magnetic resonance scanning of the heart, difficulty to null the myocardium or paradoxic nulling of the LV cavity before the myocardium reflects extreme expansion of ECV (2). Strain is afterload dependent, and wall stress is a measure of afterload. Strain normalized to wall stress to adjust for the effect of afterload may perform

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better than unadjusted strain. Assessment of LV contractile reserve in response to inotropic stimulation tests maximal myocardial performance. Other potentially useful tools for early detection may include assessment of LV end-systolic elastance, more precise measures of relaxation that would approximate tau, assessment of LV stiffness, and detection of SAP in the myocardium.

AL amyloidosis is treated mainly with chemotherapy, which is aimed at suppressing or eradicating the underlying plasma cell clone that secretes the amyloid-forming immunoglobulin light chain. In recent years, prognosis of the disease has improved by this approach followed by autologous peripheral blood stem cell transplantation (8). Novel agents such as thalidomide, lenalidomide, and the proteasome inhibitor bortezomib in combination with dexamethasone have shown encouraging results (8). These therapies reduce the production of amyloid protein but do not increase the clearance of amyloid from the tissues. SAP protein is an important component of all amyloid fibrils that helps stabilize the fibrils, making them resistant to proteolysis. Strategies to reduce SAP levels have shown promising results in mice (9). Cardiac transplantation followed by autologous stem cell transplantation has been shown to be associated with better survival in selected patients with cardiac amyloidosis (10). Amyloid imaging of heart could play a key role not only in the early diagnosis and staging but also in patient selection for various therapeutic interventions with close monitoring of response to verify efficacy.

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REFERENCES

1. Falk RH. Diagnosis and management of the cardiac amyloidoses. Circulation 2005;112:2047–60.

2. Banypersad SM, Moon JC, Whelan C, Hawkins PN, Wechalekar AD. Updates in cardiac amyloidosis: a review. J Am Heart Assoc 2012;1:e000364.

3. Kyle RA, Linos A, Beard CM, et al. Incidence and natural history of primary systemic amyloidosis in Olmstead County, Minnesota 1950 through 1989. Blood 1992;79:1817–22.

4. Gertz MA. Immunoglobulin light chain amyloidosis: 2011 update on diagnosis, risk stratification and management. Am J Hematol 2011;86:180–6.

5. Barros-Gomes S, Williams B, Nhola LF, et al. Prognosis of light chain amyloidosis with preserved LVEF: added value of 2D speckle-tracking echocardiography to the current prognostic staging system. J Am Coll Cardiol Img 2017;10:398–407.

6. Treibel TA, Bandula S, Fontana M, et al. Extracellular volume quantification by dynamic equilibrium cardiac computed tomography in cardiac amyloidosis. J Cardiovasc Comput Tomogr 2015;9:585–92.

7. Moon JC, Messroghli DR, Kellman P, et al. Myocardial T1 mapping and extracellular volume quantification: a Society for Cardiovascular Magnetic Resonance (SCMR) and CMR Working Group of the European Society of Cardiology consensus statement. J Cardiovasc Magn Reson 2013;15:92.

8. Wechalekar AD, Gillmore JD, Bird J, et al., for the BCSH Committee. Guidelines on the management of AL amyloidosis. Br J Haematol 2015;168:186–206.

9. Bodin K, Ellmerich S, Kahan MC, et al. Antibodies to human serum amyloid P component eliminate visceral amyloid deposits. Nature 2010;468:93–7.

10. Dey BR, Chung SS, Spitzer TR, et al. Cardiac transplantation followed by dose-intensive melphalan and autologous stem-cell transplantation for light chain amyloidosis and heart failure. Transplantation 2010;90:905–11.

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