Title:

Cardiac amyloidosis – can imaging shed light on mechanisms and prognosis?

Authors:

Kristina H. Haugaa MD PhD^{abc}, Øyvind H. Lie MD PhD^{abc},

^a Department of Cardiology and Center for Cardiological Innovation, Oslo University Hospital, Rikshospitalet, Oslo, Norway

^b Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway

Author e-mail addresses:

kristina.haugaa@medisin.uio.no,

oyvind.haugen.lie@rr-research.no

Address for correspondence:

Associate professor Kristina H. Haugaa, MD, PhD

Department of Cardiology, Oslo University Hospital, Rikshospitalet

PO Box 4950 Nydalen, N-0424 Oslo, Norway.

Phone: +47 23 07 13 93 / Fax: +47 23 07 35 30

E-mail: krihauga@medisin.uio.no

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Cardiac amyloidosis is a malignant disease presenting with cardiac hypertrophy and heart failure. The condition is probably severely underdiagnosed. Imaging efforts have mainly focused on establishing the diagnosis of cardiac amyloidosis. The discrimination from other etiologies of hypertrophy can have important clinical implications. Sarcomere disease in genetic hypertrophic cardiomyopathy requires a different approach and management, and other causes of hypertrophy and heart failure may require specific treatments, highlighting the importance of correct diagnosis.

Also in subgroups of cardiac amyloidosis it is important to establish the correct etiology. Recognizing light chain amyloidosis (AL) triggers a search for an underlying malignant process, with potential therapeutic targets, albeit with a limited effect on the cardiac disease manifestation and the severe prognosis. The genetic form of transthyretin (TTR) amyloidosis also represents a severe diagnosis and may even require highest specialized treatment including liver transplantation. For the most common subtype, the TTR wild type amyloidosis (ATTRw), there have so far been limited therapeutic possibilities beyond traditional heart failure treatment. Therefore, cardiac imaging has primarily addressed differential diagnoses and optimization of heart failure treatment, and a few studies have reported the value in estimating myocardial amyloid burden (1), and strict prognostication (2). Importantly, recent reports indicate a promising therapy of ATTRw (3). This perspective urges for further knowledge of amyloid disease progression and markers of adverse outcome.

In this issue of the EHJ CVI, Binder and Bonderman et al (ref present issue) present their single center study on 122 patients with cardiac amyloidosis investigated with comprehensive echocardiography including speckle tracking strain and CMR. They compared right ventricular (RV) and left ventricular (LV) parameters in patients with AL and ATTRw, their association with heart failure symptoms, and their ability to predict cardiac outcome. During follow up, 29% of TTR patients and 38% of AL patients reached the combined outcome

endpoint, defined as cardiac death and hospitalization for heart failure. In patients with ATTRw, only RV free wall strain was an independent predictor of outcome. In AL on the other hand, LV function was more important for prognosis, with LV global longitudinal strain (GLS) as a strong and independent marker of outcome in line with previous reports (4). The authors concluded that mechanisms underlying heart failure in cardiac amyloidosis may differ between ATTRw and AL, which may have substantial implications considering emerging therapies for both subtypes of cardiac amyloidosis.

Patients with AL were younger, had less comorbidities and milder septal hypertrophy compared to patients with ATTRw although they had higher event rate. When reviewing the provided data, parameters of LV and RV function were strikingly similar between the two patient groups, despite ATTRw-patients being 10 years older. This highlights the more malignant nature of AL-amyloidosis, but also highlights the similarities between the two entities. The less severe prognosis in ATTRw could explain the stronger prognostic value of RV function in ATTRw. Considering RV affection as a late finding in cardiac amyloidosis, the less severe course of disease in ATTRw could allow patients to develop RV dysfunction as a long-standing disease phenomenon. The longer remodeling phase would also allow for adaptation of the RV as compared to patients with AL. In AL patients, LV function seemed to be instrumental for symptomatology and prognosis, and RV affection did not seem to affect outcome. The authors themselves point out the missing causal link; it cannot be inferred whether RV dysfunction is the reason for or a consequence of worse prognosis in ATTRw-patients.

To further clarify these interpretations, serial measurements of cardiac function and rate of disease progression would be appropriate. In a large previous study of predictors of all-cause mortality in patients with AL, indexed stroke volume had similar predictive abilities as

speckle tracking strain parameters (2). This observation was not as prominent in the present study but should be kept in mind.

A couple of questions remain. The presented cut off values for RV and LV strain values indicating prognosis in the presented paper should be validated and tested for clinical relevance. Moreover, the older age of the ATTRw-patients compared to the AL-patients, leads to speculations on how the prognostic value of RV dysfunction is modulated by age in the total population. These and other questions lie within the inherent limitations of the provided data and were clearly outside of the primary scope of the authors.

The study is important by providing the idea that different markers of cardiac function may be appropriate for prognosis in AL versus ATTRw patients, underscoring the importance of biventricular assessment in both subgroups of patients. While we are not certain that the provided data reflect fundamental differences in cardiac structural phenotypes between ATTRw and AL patients, clinical predictors of outcome are welcomed. This work also generates an intriguing hypothesis that there may be adaptive mechanisms in ATTRw that AL-patients are less able to utilize and which future studies should be aware of. We are looking forward to the introduction of medical therapy to help patients with amyloidosis and studies showing how intervention affects the trajectory of RV and LV function. Prognosis will probably remain different between the two subtypes, and the knowledge of specific prognostic markers in amyloidosis is important. We consider the present study an important piece of this puzzle.

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