Cardiovascular Magnetic Resonance in Cardiac Amyloidosis

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Cardiovascular magnetic resonance (CMR) has several advantages compared to TTE. In most centers, it is used for further investigation of subjects with suspected cardiac amyloidosis (CA) and in patients with confirmed systemic amyloidosis. On one hand, it offers unmatched precision when it comes to measurements, including the assessment of the right ventricle; on the other hand, there is a unique opportunity of tissue characterization.

Keywords: cardiac amyloidosis ; advanced imaging ; CMR

1. Chamber Quantification

Compared to TTE, CMR provides more precise information about structural and functional abnormalities. Cine images are acquired by merging a number of stationary images taken at different cardiac cycles. They are reconstructed to map views familiar from TTE studies (e.g., two-, three-, and four-chamber views or short-axis views). The recommended measurements do not greatly differ from TTE assessment and include wall thickness, function and mass of the left ventricle, stroke volume index to body-surface-area, atrial size, and the presence or absence of pericardial effusion [1]. Typical findings in ATTR CA are higher LV mass index, higher LV volumes, and lower LVEF [2][3].

In addition to standard measurements, there is a trend towards process optimization using complex computer software for fully automated measurements, often based on machine learning algorithms. However, these have not yet reached the routine clinical process, so conventional analysis methods are still required. Easy parameters derivate from CMR images independent of the aforementioned post-processing software needed to be found. The researchers evaluated the prognostic value of long-axis strain (LAS, image-based functional marker describing the percentage of longitudinal shortening of the left ventricle during systole) and previously mentioned myocardial contraction fraction (MCF) in 74 patients with AL. All-cause mortality (primary endpoint) was significantly higher in patients with low MCF. Both impaired LAS and MCF were preserved as predictors for all-cause mortality and heart transplant [4].

2. Strain Imaging

In analogy to speckle tracking in TTE, CMR uses feature tracking for strain analysis. ‘Feature’ refers to a certain myocardial pattern recognized and followed through a cardiac cycle by post-processing software to observe radial, circumferential, and longitudinal deformation of the myocardium. Like in STE, patients with CA being evaluated with CMR feature tracking typically show a pattern of relative apical sparing.

3. T1 Mapping

T1 mapping is an emerging tool used for tissue characterization and includes two sequences: native or pre-contrast T1 and post-contrast T1. Images are recommended to be acquired during diastole [5]. Variations of Look-Locker inversion recovery sequences were introduced to overcome issues with insufficient breath holding in patients. T1 relaxation times vary with magnetic field strength, and myocardial T1 relaxation times also depend on the patient’s age and sex [6]. Relaxation times are color-coded for every pixel and assembled on a two-dimensional plane, creating a T1 map [6].

Patients with systemic amyloidosis often have deposition of amyloid fibrils in the kidneys, leading to relevant renal dysfunction. This is an important limitation for the use of intravenous contrast agents. For the acquisition of native T1, none of them are necessary. It therefore takes an important diagnostic role when contrast agents are contraindicated. Native T1 displays not only extra- but also intra-cellular parts of the myocardium. Elevated T1 times are associated with the presence of CA. A very recent publication studied a large group of patients with suspected systemic amyloidosis. Though applied to selected individuals, high sensitivity and specificity were achieved (92% and 91%, respectively) [7].

T1 mapping is also believed to be a reliable tool for the monitoring of amyloid burden in AL during chemotherapy [8].

Extracellular volume (ECV) is defined as extracellular matrix, water, and intracapillary plasma volume. ECV, but also intracellular volume, are dynamic and vary for different physiological and pathophysiological processes. Combining pre- and post-contrast T1 mapping enables the calculation of ECV. The patient's hematocrit needs to be measured for that purpose. A normal ECV value for myocardium is around 25% [6]. The deposition of amyloid fibrils in CA leads to an increase of ECV.

Korthals et al. compared receiver operating curves of native T1 and ECV as well as longitudinal strain and were able to illustrate superior diagnostic performance of native T1 and ECV over longitudinal strain [9]. They earlier emphasized that special attention needs to be drawn towards choosing an adequate control group to define cut-off values [10]. Recommendations by the SCMR and the European Association for Cardiovascular Imaging (EACVI) stated that native T1 and ECV are increased before LGE, enabling earlier diagnosis of CA [11]. A meta-analysis by Pan et al. published in 2020 proved the diagnostic performance of ECV to be better than both native T1 and LGE. The same statement can be translated to the prognostic performance [12].

4. Late Gadolinium Enhancement

Gadolinium-based contrast agents (GBCA) are administered intravenously following predefined protocols. In the literature, cases of nephrogenic systemic fibrosis, a rare kidney disease with poor prognosis, after the use of GBCA are described. It remains a controversial subject [13]. Recent evidence reports deposition of gadolinium in the brain after administration of GBCA, irrespective of renal function and performance of the blood–brain barrier. There are no reports of neurologic deficits due to gadolinium deposition. As a consequence, monitoring of renal function is mandatory, and the use of cyclic GBCA instead of linear agents is recommended [14]. The high prevalence of renal disease in patients with suspected amyloidosis is an important limitation in the use of GBCA. Standards suggest that images are acquired more than ten minutes after the intravenous administration of the contrast agent. The recommended dose depends on the chosen agent and should be as low as possible considering the aforementioned potential complications [15].

Phase-sensitive inversion recovery (PSIR) is used to overcome problems with 'myocardial nulling'. Difficulties in 'myocardial nulling' are typical for CA and describe the challenge of finding an inversion time to differentiate the myocardium from the blood pool when acquiring images with GBCA [16].

Myocardial uptake of gadolinium is referred to as late gadolinium enhancement (LGE). The accumulation of amyloid fibrils leads to the expansion of extracellular space, where gadolinium uptake experiences regional differences depending on the extent of expansion. Patterns range from typically described subendocardial to diffuse, transmural, or patchy dispersion. Though discrimination between different types of CA is not reliably feasible, a study including almost one hundred patients with cardiac involvement of amyloidosis demonstrated that LGE is more extensive in patients with ATTR and there is a higher proportion of patients showing transmural patterns of LGE [2]. Transmural LGE patterns are suggestive for advanced stages of the disease [17]. To our knowledge, there is no established staging system involving LGE.

5. T2 Mapping

T2 mapping is another quantitative tool used for tissue characterization. T2 times are tissue-specific and enable differentiation between normal and abnormal myocardial tissue. Water has quite a long T2 time. Therefore, the tissue has a higher content of water, hence myocardial edema can be depicted by this technique. Reference values for T2 times are different for 1.5 and 3 T MRT scanners [18]. Kotecha et al. proved that T2 mapping can be used as an independent predictor of prognosis in patients with cardiac AL. The study also suggests that different types of CA are part of a heterogeneous group of diseases, since there are significant differences between untreated individuals with AL, treated AL, and ATTR [19].

A meta-analysis by Brownrigg et al. analyzed the performance of CMR in differentiating AL and ATTR (sensitivity and specificity of 28.1–99% and 11–60%, respectively) and compared CMR to scintigraphy (sensitivity and specificity of 88.6–90.9% and 91.5–97.1%, respectively) [20]. In summary, CMR is a useful diagnostic tool for evaluation of CA, but it does not currently allow the differentiation between the different types of amyloidosis.

References

1. Dorbala, S.; Ando, Y.; Bokhari, S.; Dispenzieri, A.; Falk, R.H.; Ferrari, V.A.; Fontana, M.; Gheysens, O.; Gillmore, J.D.; Glaudemans, A.W.J.M.; et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis: Part 1 of 2—Evidence Base and Standardized Methods of Imaging. Circ. Cardiovasc. Imaging 2021, 14, e000029.
2. Dungu, J.N.; Valencia, O.; Pinney, J.H.; Gibbs, S.D.; Rowczenio, D.; Gilbertson, J.A.; Lachmann, H.; Wechalekar, A.; Gillmore, J.D.; Whelan, C.J.; et al. CMR-Based Differentiation of AL and ATTR Cardiac Amyloidosis. JACC Cardiovasc. Imaging 2014, 7, 133–142.
3. Ben Zadok, O.I.; Vaturi, M.; Vaxman, I.; Iakobishvili, Z.; Rhurman-Shahar, N.; Kornowski, R.; Hamdan, A. Differences in the characteristics and contemporary cardiac outcomes of patients with light-chain versus transthyretin cardiac amyloidosis. PLoS ONE 2021, 16, e0255487.
4. Arenja, N.; Andre, F.; Riffel, J.H.; Siepen, F.A.D.; Hegenbart, U.; Schönland, S.; Kristen, A.V.; Katus, H.A.; Buss, S.J. Prognostic value of novel imaging parameters derived from standard cardiovascular magnetic resonance in high risk patients with systemic light chain amyloidosis. J. Cardiovasc. Magn. Reson. 2019, 21, 53.
5. Yilmaz, A.; Kindermann, I.; Kindermann, M.; Mahfoud, F.; Ukena, C.; Athanasiadis, A.; Hill, S.; Mahrholdt, H.; Voehringer, M.; Schieber, M.; et al. Comparative Evaluation of Left and Right Ventricular Endomyocardial Biopsy: Differences in Complication Rate and Diagnostic Performance. Circulation 2010, 122, 900–909.
6. Williams, L.K.; Forero, J.F.; Popovic, Z.B.; Phelan, D.; Delgado, D.; Rakowski, H.; Wintersperger, B.J.; Thavendiranathan, P. Patterns of CMR measured longitudinal strain and its association with late gadolinium enhancement in patients with cardiac amyloidosis and its mimics. J. Cardiovasc. Magn. Reson. 2017, 19, 61.
7. Baggiano, A.; Boldrini, M.; Martinez-Naharro, A.; Kotecha, T.; Petrie, A.; Rezk, T.; Gritti, M.; Quarta, C.; Knight, D.S.; Wechalekar, A.D.; et al. Noncontrast Magnetic Resonance for the Diagnosis of Cardiac Amyloidosis. JACC Cardiovasc. Imaging 2020, 13, 69–80.
8. Martinez-Naharro, A.; Abdel-Gadir, A.; Treibel, T.; Zumbo, G.; Knight, D.S.; Rosmini, S.; Lane, T.; Mahmood, S.; Sachchithanantham, S.; Whelan, C.J.; et al. CMR-Verified Regression of Cardiac AL Amyloid After Chemotherapy. JACC Cardiovasc. Imaging 2018, 11, 152–154.
9. Korthals, D.; Chatzantonis, G.; Bietenbeck, M.; Meier, C.; Stalling, P.; Yilmaz, A. CMR-based T1-mapping offers superior diagnostic value compared to longitudinal strain-based assessment of relative apical sparing in cardiac amyloidosis. Sci. Rep. 2021, 11, 15521.
10. Korthals, D.; Chatzantonis, G.; Bietenbeck, M.; Meier, C.; Florian, A.; Yilmaz, A. Ruling in or out the presence of cardiac amyloidosis based on cut-off values using T1-mapping–caution is required regarding the control group. Eur. Heart J. 2020, 41, ehaa946.2119.
11. Messroghli, D.R.; Moon, J.C.; Ferreira, V.M.; Grosse-Wortmann, L.; He, T.; Kellman, P.; Mascherbauer, J.; Nezafat, R.; Salerno, M.; Schelbert, E.B.; et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). J. Cardiovasc. Magn. Reson. 2017, 19, 75.
12. Pan, J.A.; Kerwin, M.J.; Salerno, M. Native T1 Mapping, Extracellular Volume Mapping, and Late Gadolinium Enhancement in Cardiac Amyloidosis. JACC Cardiovasc. Imaging 2020, 13, 1299–1310.
13. Bennett, C.L.; Qureshi, Z.P.; Sartor, A.O.; Norris, L.; Murday, A.; Xirasagar, S.; Thomsen, H.S. Gadolinium-induced nephrogenic systemic fibrosis: The rise and fall of an iatrogenic disease. Clin. Kidney J. 2012, 5, 82–88.
14. Mathur, M.; Jones, J.R.; Weinreb, J.C. Gadolinium Deposition and Nephrogenic Systemic Fibrosis: A Radiologist's Primer. RadioGraphics 2020, 40, 153–162.
15. Feng, D.; Edwards, W.D.; Oh, J.K.; Chandrasekaran, K.; Grogan, M.; Martinez, M.W.; Syed, I.I.; Hughes, D.A.; Lust, J.A.; Jaffe, A.S.; et al. Intracardiac Thrombosis and Embolism in Patients With Cardiac Amyloidosis. Circulation 2007, 116, 2420–2426.
16. Fontana, M.; Pica, S.; Réant, P.; Abdel-Gadir, A.; Treibel, T.; Banypersad, S.M.; Maestrini, V.; Bulluck, H.; Lane, T.L.; Lachmann, H.; et al. LGE-PSIR is an independent predictor of mortality in cardiac amyloidosis: A 250 patient prospective study. J. Cardiovasc. Magn. Reson. 2015, 17, 1–2.
17. Fontana, M.; Pica, S.; Reant, P.; Abdel-Gadir, A.; Treibel, T.A.; Banypersad, S.M.; Maestrini, V.; Barcella, W.; Rosmini, S.; Bulluck, H.; et al. Prognostic Value of Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in Cardiac Amyloidosis. Circulation 2015, 132, 1570–1579.

18. Kim, P.K.; Hong, Y.; Im, D.J.; Suh, Y.J.; Park, C.H.; Kim, J.Y.; Chang, S.; Lee, H.-J.; Hur, J.; Kim, Y.J.; et al. Myocardial T1 and T2 Mapping: Techniques and Clinical Applications. Korean J. Radiol. 2017, 18, 113.
19. Kotecha, T.; Martinez-Naharro, A.; Treibel, T.; Francis, R.; Nordin, S.; Abdel-Gadir, A.; Knight, D.S.; Zumbo, G.; Rosmini, S.; Maestrini, V.; et al. Myocardial Edema and Prognosis in Amyloidosis. J. Am. Coll. Cardiol. 2018, 71, 2919–2931.
20. Brownrigg, J.; Lorenzini, M.; Lumley, M.; Elliott, P. Diagnostic performance of imaging investigations in detecting and differentiating cardiac amyloidosis: A systematic review and meta-analysis. ESC Heart Fail. 2019, 6, 1041–1051.