Multimodality imaging for the assessment of hypertensive heart disease

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Abstract

Left ventricular hypertrophy is one of the complications of systemic hypertension. However, it can be caused by several other conditions such as valvular, genetic, or infiltrative heart diseases. In clinical practice, it is important to establish the etiology of left ventricular hypertrophy accurately, but this is frequently challenging due to phenotype overlap. Multimodality imaging is currently employed in clinical practice, and echocardiography and cardiovascular magnetic resonance (CMR) provide valuable information in the case of left ventricular hypertrophy. Because of its tissue characterization capabilities, CMR can inform about myocardial fibrosis, edema, or infiltration; thus, it should be indicated whenever clinical or echocardiographic red flags indicate an alternative etiology of the left ventricular hypertrophy, other than hypertensive heart disease.

Systemic arterial hypertension (HTN) is highly prevalent worldwide, portending high morbidity and mortality. In Romania, the SEPHAR studies depicted an accurate picture of HTN prevalence, awareness, and control. Prevalence of hypertension in the Romanian population is 40.41%, awareness of hypertension is 69.55%, with 59.15% hypertensive individuals under current treatment with a control rate of 25% [1]. Long-standing HTN may damage several target organs such as the brain, eye, kidney and heart. Hypertensive heart disease (HHD) may be regarded as a continuum of damage of progressive severity beginning with diastolic dysfunction, left ventricular hypertrophy (LVH), with a proportion of patients developing left ventricular (LV) systolic dysfunction as the end stage of HHD. Clinically, patients may present initially with heart failure with preserved ejection fraction (HFpEF) and, if untreated, may develop heart failure with reduced ejection fraction (HFrEF).

Cardiovascular imaging is an essential tool for assessing the effects of uncontrolled high blood pressure (BP) on the heart. Currently, the concept of cardiovascular multimodality imaging is well established and accepted as the strategy of choice for the deep characterization of HHD. Echocardiography is the most widely employed imaging modality due to its availability, low costs, and the high amount of valuable information provided. Both two-dimensional (2D) and three-dimensional (3D) echocardiography are useful for defining cardiac chambers morphology and function. A complete echocardiography study should actively search for the following

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information that may reveal HTN induced changes on the heart: left atrial size and function, diastolic function, LV wall thickness, LV ejection fraction, aortic dimensions, and any evidence of concomitant valvular heart disease.

Deformation imaging with 2D and 3D strain echocardiography may provide useful insights on myocardial functional damage at a subclinical level.

When LVH is present, echocardiography alone may not be able to discern among several other etiologies of increased LV wall thickness. In these cases, multimodality imaging plays a key role by introducing cardiovascular magnetic resonance (CMR) imaging in the arena of accurate characterization of HHD. CMR is currently considered de gold standard for volumetric and functional chamber quantification. Independently of the acoustic window and without radiation, CMR offers the most accurate quantitative characterization of the heart. CMR is highly reproducible, with low intra-observer and inter-observer variability, which makes it an ideal tool for serial monitoring. However, the most important advantage of CMR over echocardiography is its capacity for tissue characterization. CMR can provide data on myocardial scar or focal fibrosis, diffuse interstitial fibrosis, myocardial edema, amyloid extracellular infiltration, or intracellular glycosphingolipids intracellular accumulation. As a result, CMR may non-invasively potentially differentiate among several etiologies of LVH, such as HHD, amyloidosis, Fabry's disease, or athlete's heart.

CMR morphological and functional assessment of hypertensive heart disease

Currently, steady-state free precession (SSFP) cine images are acquired for morphological assessment of LV. Short axis slices of 8–10 mm thickness are acquired, covering the entire LV from base to apex, with a 2 mm interslice gap. Wall thickness can be accurately measured in diastole in all myocardial segments. Moreover, in each of the short-axis slices, diastolic and systolic endocardial contours are traced in order to obtain LV end-diastolic and end-systolic volumes, respectively, as well as the LV ejection fraction (LVEF). By also tracking the epicardial contour, LV mass (LVM) is obtained. LVM assessment by CMR demonstrated high accuracy and reproducibility [2].

Rodrigues *et al.* described four LV phenotypes in HTN patients: normal, concentric remodeling with normal LVM but elevated M/V, concentric LV hypertrophy (LVH) with elevated LVM but the normal indexed end-diastolic volume (EDV), and eccentric LVH with elevated LVM and EDV [3]. They showed that myocardial interstitial fibrosis varies across hypertensive LV phenotypes with functional consequences. Eccentric LVH had the most fibrosis and

systolic impairment. Concentric remodeling was only associated with abnormal aortic function [3].

Approximately one-fifth of the patients with HHD have asymmetrical septal hypertrophy. Whenever asymmetrical septal hypertrophy is encountered in HHD, it always exclusively involves the basal or mid septum [4]. Furthermore, asymmetric HHD is characterized by a reduced aorto-septal angle and aortic distensibility [4].

## CMR tissue characterization of left ventricular hypertrophy

LVH is frequently encountered in clinical practice, with HHD being just one of the several other possible etiologies. HHD-associated LVH must be differentiated from other conditions such as sarcomeric hypertrophic cardiomyopathy (HCM), end-stage renal disease-associated cardiomyopathy, cardiac amyloidosis, Fabry's disease, or even athlete's heart. The tissue characterization capabilities of CMR are essential for differentiating among LVH etiologies. Currently, tissue characterization is performed through late Gadolinium enhancement (LGE) sequences and native T1 and T2 mapping, and post-contrast T1 mapping with the possibility of assessing extracellular volume.

LGE imaging is based on the paramagnetic properties of Gadolinium-based contrast agents (GBCA), which have a high affinity for the extracellular space resulting in accumulation in tissues with a high relative interstitial component such as focal fibrosis. Thus, in LGE sequences, myocardial scars or focal fibrosis will appear bright.

As opposed to focal fibrosis, diffuse interstitial fibrosis can be quantified through T1 mapping techniques [5]. T1 mapping measures the longitudinal relaxation time of the myocardium and displays it in a pixel-wise manner. High native T1 values are encountered with myocardial fibrosis, edema or amyloid deposition. On the other hand, low native T1 values are suggestive of lipid overload (Anderson-Fabry disease) and iron overload. Contrast-enhanced T1 mapping is used for calculating the extracellular volume (ECV) fraction in combination with native T1 mapping and the patient's hematocrit value [5].

CMR appearances in various LVH etiologies

LVH due to HHD may be concentric or located only at the basal interventricular septum. LGE sequences may be normal or show focal fibrosis areas with a non-coronary distribution (Figure 1). T1 mapping usually shows higher myocardial native T1 values in
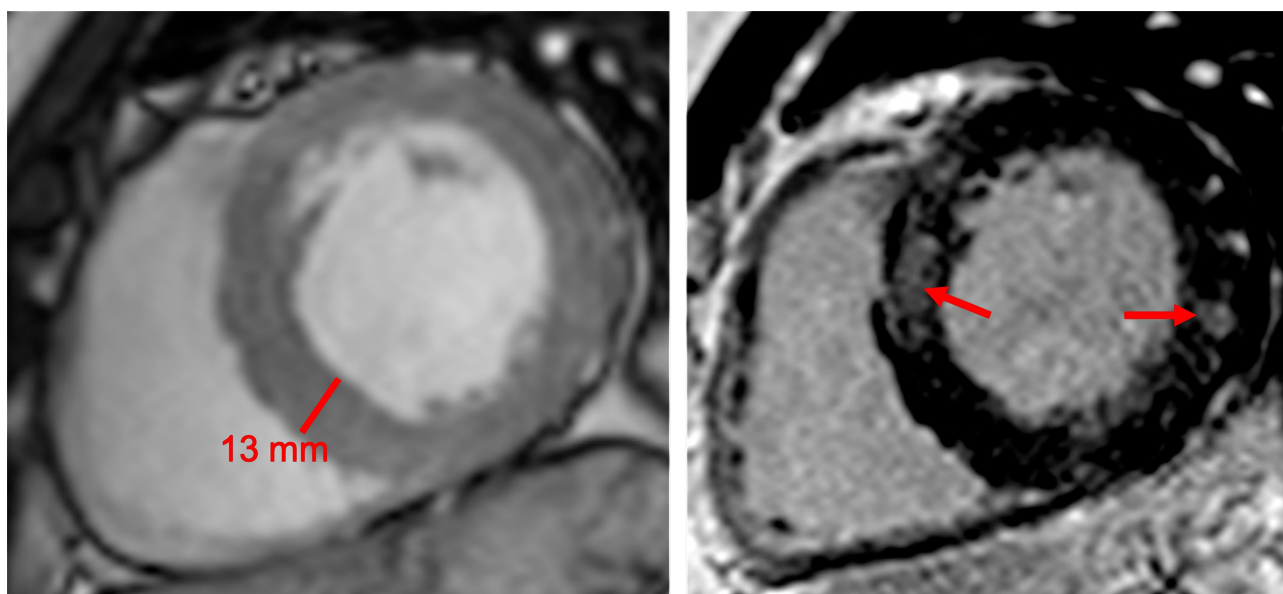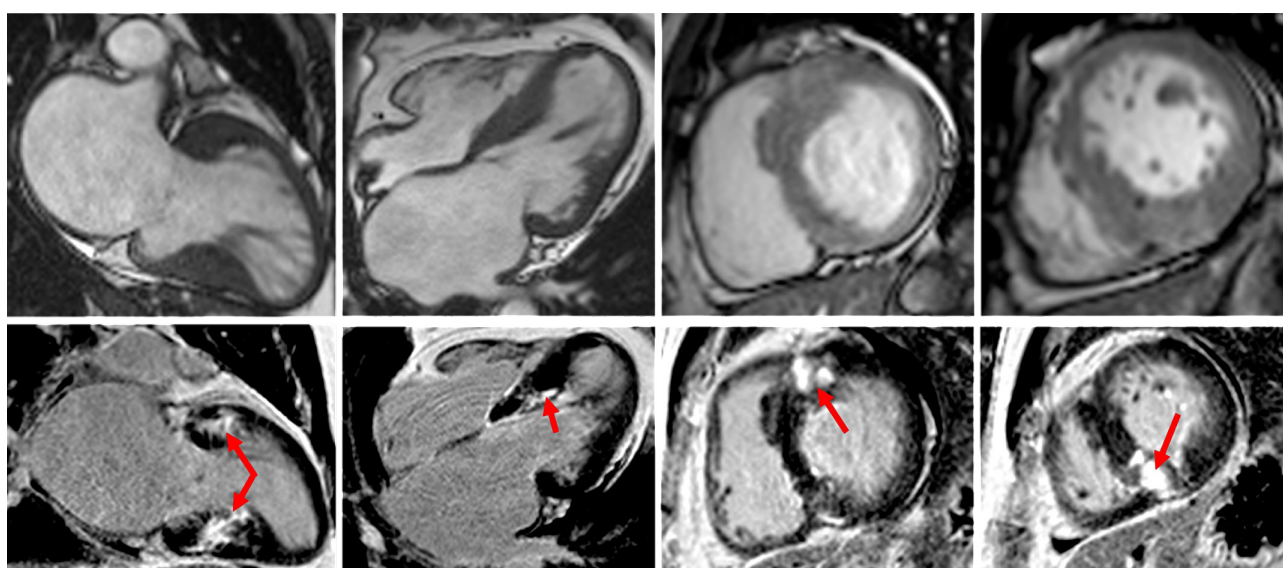
Figure 1. Cardiovascular magnetic resonance in a patient with long standing arterial hypertension due to hyperaldosteronism. *Left*: steady-state free precession (SSFP) cine diastolic frame in short axis view showing concentric left ventricle hypertrophy with a maximal thickness of interventricular septum of 13mm. *Right*: late Gadolinium enhancement in the same view showing areas of mid-myocardial focal fibrosis with a non-coronary distribution in the interventricular septum and lateral wall (red arrows).

hypertensive patients compared to controls. Also, hypertensive patients with LVH have higher ECV (0.28±0.03) compared with HTN non-LVH subjects (0.26±0.02) or controls [6].

Sarcomeric HCM may present as asymmetrical hypertrophy, but it also may have concentrical, symmetrical hypertrophy. LGE imaging may show fibrosis of the hypertrophied segments and non-specific fibrosis at right ventricular insertion points (Figure 2).

Cardiac amyloidosis usually presents with LVH, which may be symmetrical or may affect only the interventricular septum. It is characterized by very high native T1 and ECV values reflecting interstitial expansion due to extracellular amyloid deposition [7]. LGE imaging has a pathognomonic ap-
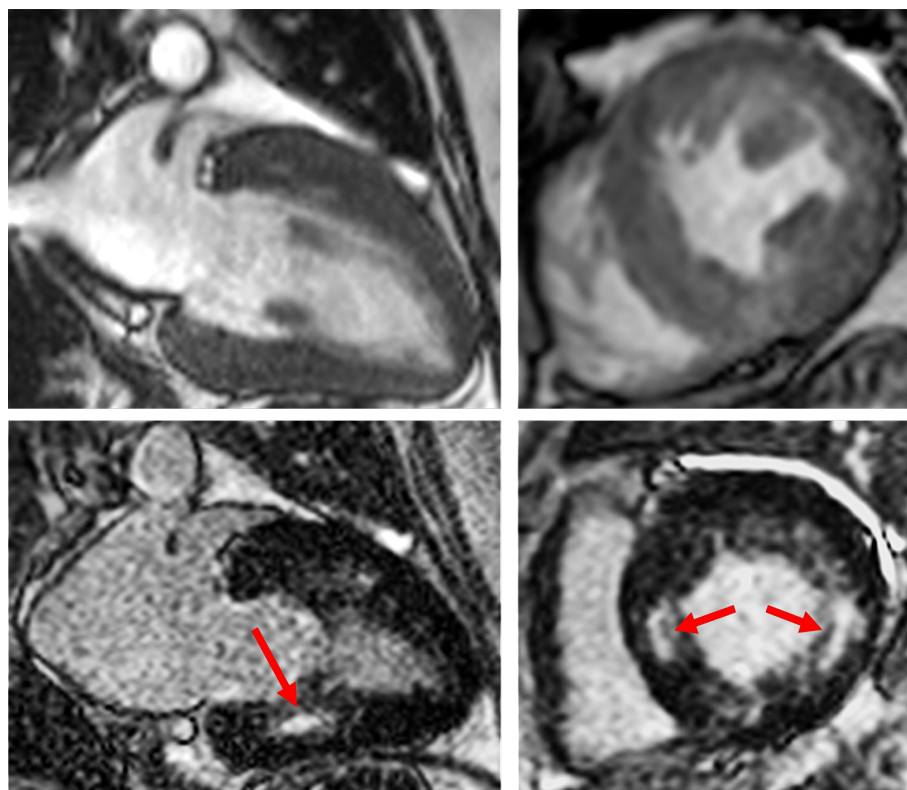

Figure 2. Cardiovascular magnetic resonance in a patient with sarcomeric hypertrophic cardiomyopathy. *Upper row*: steady-state free precession (SSFP) cine diastolic frames showing focal hypertrophy of the basal antero-septum and mid infero-septum and inferior walls. *Lower row*: late Gadolinium enhancement imaging showing focal fibrosis of the hypertrophied myocardial segments.
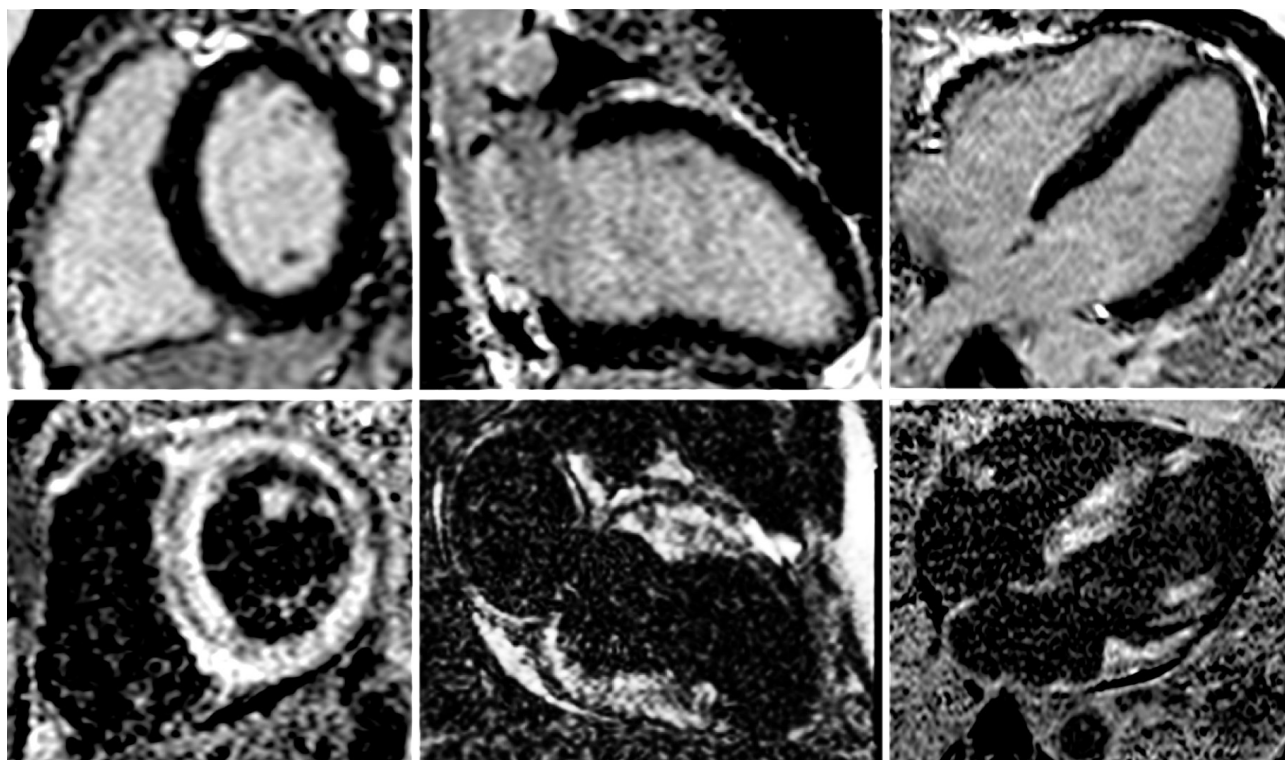
Figure 3. Cardiovascular magnetic resonance late Gadolinium enhancement (LGE) imaging in a healthy subject (*upper row*) and in a patient with cardiac amyloidosis (*lower row*). The healthy subject displays normal myocardium with no areas of hyperenhancement. On the contrary, the patient with cardiac amyloidosis shows diffuse, transmural hyperenhancement located mainly at the base and mid-ventricular walls with relative sparing of the apex.

Figure 4. Cardiovascular magnetic resonance in a patient with Fabry's disease. *Upper row*: steady-state free precession (SSFP) cine diastolic frames in 2-chamber long-axis and short-axis views, respectively, showing concentric left ventricular hypertrophy. *Lower row*: late Gadolinium enhancement (LGE) imaging in the same views showing areas of focal fibrosis with a non-coronary distribution.

pearance of diffuse, transmural, or subendocardial enhancement, sometimes sparing the ventricular apex (Figure 3).

Fabry's disease may present with LVH in advanced stages. Due to intracellular glycosphingolipid accumulation, the native T1 myocardial values are characteristically low. LGE imaging may be normal or may show areas of focal fibrosis with a non-coronary distribution (Figure 4).

Theoretically, the above-mentioned findings may help differentiate among various etiologies of LVH. However, in clinical practice, there is frequent overlap between CMR phenotypes. Careful analysis of the history, physical exam, ECG, and blood tests are usually sufficient to establish an accurate diagnosis in a non-invasive manner.

How to implement multimodality imaging in the daily clinical care of patients with hypertensive heart disease?

Currently, imaging modalities other than echocardiography have become more widely available. CMR practice requires very well-trained physicians with a high volume of cases experience and also high-costs infrastructure. LVH characterization is one of the main indications for CMR imaging. Not all patients with LVH should undergo CMR imaging, but careful assessment of any of the clinical red flags indicating any specific etiology other than HHD should indicate the need for CMR assessment.

Future studies are needed to establish the prognostic value of focal fibrosis on LGE imaging or diffuse interstitial fibrosis quantified by T1 mapping in HHD. Until then, the discriminative power of multimodality imaging among LVH etiologies recommends it for more frequent implementation in clinical practice.

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