



# The Depiction of Hypertension in Heart Imaging Examinations: An Up-to-Date Review of the Evidence

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**Abstract:** Hypertension is one of the main preventable cardiovascular (CV) risk factors all over the years, closely related to CV morbidity and mortality. One of the most common hypertensive target organ damages is hypertensive heart disease (HHD), including left ventricular hypertrophy, which progresses gradually and leads to systolic or diastolic dysfunction of the left ventricular, and finally to end-stage heart failure. Regarding its prevalence and the need for early diagnosis, assessment of heart imaging examination is of major importance. Echocardiography has been used as the standard imaging technique to evaluate HHD for years, providing an accurate evaluation of the left ventricular geometry, along with the systolic and diastolic function. However, nowadays there is a growing interest in cardiovascular magnetic resonance (CMR). Despite the importance of the use of echocardiography in everyday clinical practice, numerous studies have shown the superiority of CMR as an imaging technique for clinical and research purposes, mainly due to its strength to provide an unlimited area of view, as well as the identification and quantification of the type and extent of myocardial fibrosis. Hence, this review aims to analyze the importance of heart imaging in the hypertensive population, with a special interest in CMR imaging.

**Keywords:** hypertension, heart, MRI, CMR, ultrasound, hypertensive heart disease

## Introduction

Hypertension is one of the main preventable cardiovascular (CV) risk factors all over the years, closely related to CV morbidity and mortality. Despite numerous attempts from the scientific community and awareness programs, the prevalence is still extremely high globally.<sup>1</sup> In the United States, nearly half of the adults (47%) have hypertension, defined either as abnormal values of blood pressure or as the use of anti-hypertension treatment.<sup>2</sup> In Europe, the prevalence is lower but still remarkable, closing to 25%.<sup>3</sup> The control rates of the hypertensive population also seem to be dramatic; 25% of the population is reported to be uncontrolled and almost half of them live with blood pressure values higher than 140/90mmHg.<sup>2</sup> The high prevalence and uncontrolled cases lead to high rates of morbidity and mortality, but also a high cost for the health system for medication, hospitalization, and loss of working hours.<sup>1</sup>

Hypertensive heart disease (HHD) represents a range of target organ damages that includes left ventricular hypertrophy (LVH), systolic (LVSD), and diastolic (LVDD) dysfunction and their clinical outcomes such as heart failure and arrhythmias.<sup>4,5</sup> When blood pressure is increased higher than the normal values, there is a two-fold highest risk of heart failure in the male as well as a three-fold highest risk in the female population and enlarges, at least twice, the probability of acute myocardial infarction and stroke.<sup>4</sup>

LVH is the most common HHD and reports a reparative heart answer to lower at the minimum the wall stress, affecting the left ventricular and the ejection fraction and gradually leading to dilated heart failure.<sup>6</sup> However, different factors, including differences in pressure loading, co-morbidities, genes' impact, and the reaction between hormones and the nerve system may change the adaptation of the heart, specifically of the left ventricular, and lead to acceleration or

not of the LVH.<sup>7</sup> Furthermore, hypertensive patients can develop diastolic dysfunction and/or symptoms of heart failure even having normal ejection fraction, further correlated with remodeling of the extracellular matrix and an elevation in left ventricular filling pressure.<sup>8</sup>

A plethora of imaging examinations is available to evaluate and determine the existence of HHD.<sup>5</sup> Echocardiography has been the dominant imaging examination in the assessment of HHD for years, while nowadays there is a growing interest in cardiovascular magnetic resonance (CMR) imaging due to its potential to depict an unrestrained field of view and noninvasive tissue representation.<sup>5</sup> Hence, this review aims to analyze the current role of cardiovascular magnetic resonance (CMR) imaging in hypertensive patients. This study mainly focuses on CMR due to its high potential for clinical use in the future, as it provides accuracy and high-quality images, along with no exposure to ionized radiation. This study also aims to compare the advantages and limitations of CMR in clinical practice, so that we come to a conclusion about its position in everyday clinical practice.

## Left Ventricular Hypertrophy

LVH is defined by an increase in LV mass with parallel thickening of the wall, being suspected either with electrocardiographic (ECG) criteria or by echocardiography or CMR. First reports have defined LVH as an absolute LV mass weighting more than 0.25 kg.<sup>9</sup> However, new data have changed things in everyday clinical practice, and gender-specific values have been introduced according to life years and body surface area or height, using CMR as the gold standard examination.<sup>10</sup>

Pathways that have been proposed for the population with LVH as a hypertension target organ damage are the enlargement of cardiac myocytes and the rising amount of interstitial and perivascular fibrosis. LVH is usually categorized as concentric hypertrophy, eccentric hypertrophy, or concentric remodeling.<sup>11</sup> Hence, when patients have an enlarged LV mass, estimation of relative wall thickness is necessary to classify if the patient has concentric or eccentric LVH. Concentric LVH is described as the condition in which LV mass enlarges and the walls are thickened in response to pressure overload and related to lower cardiac output. In eccentric hypertrophy, LV mass predominantly increases with chamber dilatation, with normal relative wall thickness. This is a usual finding in young adults and is correlated with higher cardiac output.<sup>12</sup> Concentric remodeling is characterized by normal LV mass but increased relative wall thickness.<sup>6</sup> LV hypertrophy with increased relative wall thickness characterizes concentric hypertrophy, while a normal value depicts eccentric hypertrophy.<sup>11</sup>

A recently published study trying to identify the prevalence of hypertension-mediated organ damage in more than 7000 hypertensive patients revealed that 20–40% of the study population had hypertension-mediated organ damage, including LVH.<sup>13</sup> In China, the prevalence of asymptomatic LVH is almost 30% in patients with hypertension, with this number getting lower among well-controlled patients.<sup>14</sup> Long-term hypertension consequences regarding LVH have also been detected, with hypertensive women having a higher risk for the development of LVH compared to men.<sup>15</sup> This association between the women population and LVM index alteration was not significant in the case of achieving systolic blood pressure <120 mmHg and <130 mmHg, providing a clear effect of hypertension despite age.<sup>15</sup> Furthermore, the pattern of hypertension plays an important role. Abnormalities and particularly an increase in circadian blood pressure variability seem to be associated with higher LV mass index.<sup>16</sup> Similarly, data show that patients with non-dipping status during 24h ambulatory BP monitoring have higher LV mass index compared to patients with dipping status.<sup>17</sup> Despite the well-established fact that hypertension and especially the increase in systolic blood pressure is correlated with LVH, there is also evidence that treatment plays a significant role.<sup>18</sup> Reduction in systolic blood pressure was one of the major predictors of left ventricular hypertrophy regression.<sup>18</sup> Moreover, research suggests that reverting LV mass through antihypertensive medication leads to a reduced risk of stroke, myocardial infarction, and all-cause mortality.<sup>19</sup> Hence, the heart evaluation of the hypertensive population seems of major importance as a target organ damage and as so the heart imaging.

Although signs of LVH on the electrocardiogram were found to be correlated with higher cardiovascular disease risk in the Framingham study,<sup>20</sup> it is totally accepted by physicians that the assessment of LVH through electrocardiogram is short of sensitivity and specificity, particularly in young aged men.<sup>21</sup> As a result, imaging examinations such as echocardiography and CMR are gaining place in the evaluation of the hypertensive population.

## Left Ventricular Systolic and Diastolic Dysfunction

Population having LVH remains asymptomatic for a long period of life, although the disease progresses gradually and leads to the development of systolic or diastolic dysfunction of the left ventricular and finally to end-stage heart failure. The mechanism is the same in the case of the hypertensive cause of LVH. Given the usual development of diastolic dysfunction before systolic dysfunction during myocardial disease, patients with systolic dysfunction generally have also diastolic dysfunction.<sup>22</sup>

Numerous echocardiographic techniques are used to assess the function of the left ventricular. Adults with LVEF less than 50% (independently of the existence of symptoms or not) have diastolic dysfunction due to impaired LV relaxation. Mitral inflow indices (peak early [E] and late [A] diastolic velocities) are extremely useful in this patient subgroup for estimating left atrial pressure. Even in the first stages of hypertension, there is modest “stiffening” and delayed relaxation of the myocardium which influences peak early filling (E-wave) and late diastolic filling (A-wave). The result of these pathophysiological changes is a reduced E/A ratio of transmitral flow velocity, which is detected with the pulse-wave Doppler. Modest diastolic dysfunction is expressed as a reduced E/A ratio, while progressive diastolic dysfunction could lead to pseudo-normalization of the E/A ratio.<sup>23</sup>

A cross-sectional study with the participation of 2000 adults, aged more than 45 years old, evaluated the prevalence of systolic and diastolic dysfunction in the Minnesota population. The existence of hypertension was found to be of major importance. Only 20% of patients without hypertension had abnormal diastolic function, while almost 50% of the hypertensive population could not preserve diastolic function with 10% to be recorded as having moderate or severe dysfunction.<sup>24</sup> The Cardiovascular Health Study examined elderly free of coronary heart disease, congestive HF, or atrial fibrillation. In this population, 5.5% of subjects showed asymptomatic LVSD, and the subsequent incidence of congestive HF approximated 3% per year.<sup>25</sup> A later published longitudinal study with a 17-year follow-up found that asymptomatic LVSD was present in 3.6% of untreated hypertensives at baseline. Subjects with asymptomatic LVSD showed to have a 9-fold higher risk of hospital admission for congestive heart failure over a mean follow-up period of 6 years compared with those having normal EF.<sup>26</sup>

Vice versa, lowering of blood pressure as well as antihypertensive treatment act positively. Meta-analytic data have proved the beneficial effect of antihypertensive treatment on LV mechanisms, as well as that the improvement in global longitudinal strain is mainly related to the reduction in LVM rather than SBP reduction on its own.<sup>27</sup> Furthermore, in patients receiving treatment for hypertension and specifically nitrendipine, the LVM was decreased by more than 10% during antihypertensive therapy, and diastolic function was improved.<sup>28</sup> This improvement is obvious independent of age. However, later research revealed that young adults answer better to antihypertensive therapy compared to older for the same reduction of systolic blood pressure. Other antihypertensive agents, mainly angiotensin receptor blockers<sup>29</sup> or calcium channel blockers such as amlodipine,<sup>30</sup> could also significantly reduce the LV mass index as well as the LV wall thickness.

## The Role of Echocardiography

M-mode echocardiography was the first method used to assess LV mass. However, as it only measures the LV in one dimension, studies have shown that M-mode echocardiography offers low accuracy and has gradually been replaced by measurements made using two-dimensional (2D) echocardiography.<sup>31</sup> 2D echocardiography permits more accurate and reproducible estimation of LV volume and mass and is mostly commonly calculated using the Devereux equation.<sup>32</sup> Finally, three-dimensional (3D) echocardiography is the most contemporary exam as provides advantages over M-mode and 2D methods. The major advantage is the upgrade in the provided accuracy of the echocardiographic heart evaluation, achieved by declining the need for geometric modeling and the provided faults through foreshortened views.<sup>33</sup> 3D echocardiography, especially when combined with detection algorithms, offers excellent correlation and low variability regarding end-diastolic volume, end-systolic volume, and ejection fraction. The results were found to be highly correlated with those from CMR.<sup>34</sup>

Animal studies were the first to report differences between the different types of echocardiography, despite the status of hypertension. Almost 100 dogs were studied by Tidholm et al to identify differences in the estimations of LV end-diastolic and end-systolic volume, as well as left atrial size. Both 2D, as well as 3D echocardiography, agreed in the estimation of diastolic and systolic volume, whereas M-mode overestimated the results. In comparison with 3D, the left

atrial/aortic ratio underestimated left atrial size, especially when the left atrial was enlarged.<sup>35</sup> The latest data from normal canine hearts showed that 3D has a lower intra- and inter-rater coefficient of variation when compared to 2D echocardiography. Regarding LV size, the inter-rater coefficient of variation for 3D was lower than 2D.<sup>36</sup>

LV geometry as assessed by relative wall thickness is possible to further independently classify LV systolic and diastolic functions in patients with hypertension, even when the assessment is conducted by M-mode echocardiography.<sup>37</sup> Similarly, the estimation of left ventricular mass by M-mode echocardiography in the Framingham study was found to be enough to offer prognostic information and to predict a higher incidence of clinical events, including fatal events, closely related to cardiovascular disease.<sup>7</sup> In native hypertensives, a 3D evaluation of the LV mass/end-diastolic volume ratio recognizes a higher prevalence of LV concentric geometry than the 2D wall thickness.<sup>38</sup> In general, the comparison of these strongly supports the superiority of 3D echocardiography in the hypertensive population, especially in those with established LVH, providing a more comprehensive metric of the left systolic function.<sup>39</sup>

## Cardiovascular Magnetic Resonance, the Latest Trend

Despite the importance of the use of echocardiography in everyday clinical practice, numerous studies have shown the superiority of CMR as an imaging technique for clinic and research purposes.<sup>5</sup> One of the first studies in the field showed that the precision of LV mass by MRI was over twice that observed with the use of echocardiography. Furthermore, MRI provides better reliability regarding LV mass when compared to echocardiography.<sup>40</sup> A routine echocardiogram without contrast could not always eliminate the existence of hypertrophic cardiomyopathy. In that case, imaging with CMR or contrast echocardiography may be useful to diagnose the disease.<sup>41</sup>

Nowadays, CMR is used widely in clinical practice not only for the diagnosis but also for the management of CV diseases. However, there are no updated guidelines regarding when clinicians may refer their patients for CMR examination. The latest guidelines were published in 2004 and since then, they have not been revised.<sup>42</sup> In those recommendations, the statement for LVH is clear and considers CMR as the best technique to evaluate the LV mass and its alteration through the follow-up period, mainly due to its high reproducibility.<sup>42</sup> During CMR, short-axis cine “slices” with a steady-state-free precession sequence are acquired from the mitral valve annulus to the apex. At this sequence, LV volume and mass are assessed by using the endocardial and epicardial contours in the end-systole and end-diastole phases. Hence, no geometric assumptions are required, and body surface is not a restriction, even in patients presenting a distorted LV geometry.<sup>10</sup> The great contrast resolution between the blood and myocardium provided by the steady-state-free precession sequence helps the endocardial and epicardial easily be defined and ventricular volumes as well as mass to be assessed with an almost 5% variance, which is far apart from one of echocardiography.<sup>43</sup> The diastolic function could accurately be assessed by CMR, using contrast sequences across the mitral valve to give details for the early and late left ventricular filling status, improving the assessment of diastolic function.<sup>44</sup>

The latest research confirms the superiority of CMR compared to echocardiography as well as its necessity in the hypertensive population. Myocardial strain analysis as evaluated by CMR could provide evidence for asymptomatic LV dysfunction in patients with hypertension, which shadows an adverse long-term prognosis and must be taken into account not only for treatment purposes but also for prevention of heart failure manifestation.<sup>45,46</sup> Even if echocardiography strain analysis provides information about asymptomatic LV dysfunction, the diagnosis is not always accurate, especially in obese patients.<sup>47</sup> Thus, CMR should be considered in clinical practice in a hypertensive young population with obesity. Even in the case where differentiation between hypertrophic cardiomyopathy and HHD is difficult due to a similar myocardial hypertrophic phenotype on echocardiography, the evaluation of myocardial strain and torsion, through feature tracking CMR, could increase the diagnostic value.<sup>48</sup>

The most important limitation of echocardiography compared to CMR is the identification and quantification of the type and extent of myocardial fibrosis but also its progression through time. Myocardial fibrosis, resulting from increased myofibroblast activity and excessive extracellular matrix deposition and causing cardiac remodeling, is of major importance as it is the first step leading to CV disease and heart failure.<sup>49</sup> The newly published Multi-Ethnic Study of Atherosclerosis proved that the extracellular volume fraction evaluated by CMR, and as so myocardial fibrosis, is an independent prognostic marker of incident HF, atherosclerotic CV events, and all-cause mortality.<sup>50</sup> Even more, it is highly correlated with sudden cardiac death. Finnish-autopsy proved data, investigating the reasons for sudden cardiac

death in young subjects under the age of 40, revealed that primary myocardial fibrosis and HHD were some of the main reasons among the nonischemic causes.<sup>51</sup> Specifically, regarding hypertension, cardiac magnetic follow-up of new hypertensive swans showed that early myocardial interstitial fibrosis exists in HHD and as hypertension develops, fibrosis increases. As so, it must be evaluated even in the first stages of hypertension to be detected and prevent disease.<sup>52</sup> In humans, fibrosis seems also to be present during the early stages of hypertension in patients with a moderate degree of LVH after assessment with endomyocardial biopsy, the gold standard diagnostic procedure.<sup>53</sup> The REMODEL study showed that not only biopsy but also myocardial fibrosis on CMR is associated with adverse cardiac remodeling in the hypertensive population. CMR data were also linked to adverse outcomes such as acute coronary syndrome, heart failure hospitalization, stroke, and CV mortality; helping clinicians move a step further toward CMR as endomyocardial biopsy is impossible in everyday clinical practice and as so cannot guide treatment and prevention.<sup>54</sup>

However, CMR has limitations, like any other imaging method. This is probably the reason why it is not yet as widely used in clinical practice as the cardiac CT or the ECG. The main disadvantages of CMR in terms of imaging derive from spatial and temporal resolution limitations. For this reason, new techniques such as compressed sensing and parallel imaging are currently being applied in various sequences, to provide the best quality of images and minimal artifacts possible.<sup>55,56</sup> The lack of standardized protocols that result in variations of the CMR values, based on the equipment of the institution or the sequences used for imaging, is also a burden to the wide clinical application of CMR. However, nowadays efforts are being made towards the publication of guidelines for standardized protocols of CMR imaging, as well as image interpretation and the post-processing of them.<sup>57</sup> Furthermore, the usual MRI limitations also apply, including longer duration of the examination, possible claustrophobia feeling, or panic attacks of patients with a relative history, with high cost. Finally, some patients may not be able to have CMR, due to certain types of medical devices, including implantable defibrillators, pacemakers, or artificial heart valves, while there may be a potential distortion of the image of patients with metal foreign bodies, such as surgical clips. However, with technological evolution, scientists expect to overcome these problems in the next few years.<sup>55,56</sup>

This study is a narrative review, where studies included were pooled from electronic databases. The authors have attempted to include the most up-to-date studies and information available so that the results are as complete and non-biased as possible while highlighting the importance of the CMR technique in everyday clinical practice. However, there are also certain limitations of this study. First, due to the narrative character of this study, there is always the risk of not including certain studies or published data in our results, as this is not a systematic review with a protocol published in advance or a specific search protocol to search all the databases available. In addition, this study only presents qualitative results and not quantitative ones. Overall, this study presents results from a wide variety of studies, including all the key points that need to be highlighted in this specific scientific query.

## Conclusion

The epidemic of hypertension and related target organ damage, such as HHD, have indicated the need and use of different imaging techniques. The establishment of echocardiography over the last decades enlightened the morphological and pathophysiological changes associated with HHD. Extensive evaluation of LVH and systolic as well as diastolic function provides a better evaluation of the hypertensive population and helps clinicians to make choices for the management of follow-up of these patients.

Furthermore, CMR is a relatively new and interesting imaging examination as it is not obstructed by acoustic windows and gives the most precise and repeatable measures of LV function and mass, especially in the obese population. CMR also offers the differentiation of different types of cardiomyopathies in a more accurate and detailed way and as so the identification specifically of HHD. Most importantly, CMR detects myocardial fibrosis even in primary disease, used as a useful tool for predicting fatal and nonfatal CV events. CMR may be a diagnostic exam of higher cost and complexity, but it offers images with significant details that may lead to better and easier diagnosis and follow-up of the patients. Thus, CMR could be implemented in daily clinical practice in the future, especially if the scientists could overcome the potentially modifiable demerits of this technique. However, guidelines for the use of CMR have not been updated since 2004. Besides, this research lacks evidence regarding the use of CMR in the hypertensive population and its difference compared to echocardiography. Future research should be focused on how the hypertensive population (and

especially the naïve patients) should be evaluated for HHD using either echocardiography or CMR and with which technique and when the follow-up should be performed.

## Abbreviations

CV, Cardiovascular; HHD, Hypertensive Heart Disease; LVH, Left Ventricular Hypertrophy; LVSD, Left Ventricular Systolic Dysfunction; LVDD, Left Ventricular Diastolic Dysfunction; HFNEF, Heart Failure with Normal Ejection Fraction; CMR, Cardiovascular Magnetic Resonance; 2D, Two-Dimensional; 3D, Three-Dimensional.

## Disclosure

The authors report no conflicts of interest in this work.

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