



# The role of diagnostic modalities in differentiating hypertensive heart disease and hypertrophic cardiomyopathy: strategies in adults for potential application in paediatrics

## Review

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### Abstract

Hypertensive heart disease and hypertrophic cardiomyopathy both lead to left ventricular hypertrophy despite differing in aetiology. Elucidating the correct aetiology of the presenting hypertrophy can be a challenge for clinicians, especially in patients with overlapping risk factors. Furthermore, drugs typically used to combat hypertensive heart disease may be contraindicated for the treatment of hypertrophic cardiomyopathy, making the correct diagnosis imperative. In this review, we discuss characteristics of both hypertensive heart disease and hypertrophic cardiomyopathy that may enable clinicians to discriminate the two as causes of left ventricular hypertrophy. We summarise the current literature, which is primarily focused on adult populations, containing discriminative techniques available via diagnostic modalities such as electrocardiography, echocardiography, and cardiac MRI, noting strategies yet to be applied in paediatric populations. Finally, we review pharmacotherapy strategies for each disease with regard to pathophysiology.

## Introduction

Left ventricular hypertrophy due to hypertension, otherwise known as hypertensive heart disease, can be challenging to differentiate from other causes of left ventricular hypertrophy such as hypertrophic cardiomyopathy. This is especially true when conditions that manifest left ventricular hypertrophy are superimposed on one another; for example, differentiating hypertrophic cardiomyopathy versus hypertensive heart disease in the context of an obese patient.<sup>1</sup> A correct diagnosis of the cause of left ventricular hypertrophy is imperative, given that hypertrophic cardiomyopathy and hypertensive heart disease have differing prognoses and pharmacotherapy strategies.<sup>2</sup> There appears to be little published with regard to this clinical conundrum in children despite an abundance of evidence for the adult population.<sup>3</sup> In this review, we describe the available tools for the discrimination of hypertensive heart disease from hypertrophic cardiomyopathy and outline various management strategies through the lens of pathophysiology, discussing approaches utilised in adults that have potential application in paediatric populations.

## Comparing and contrasting left ventricular hypertrophy in the context of hypertensive heart disease and hypertrophic cardiomyopathy

### Hypertensive heart disease

A pathognomic feature of hypertensive heart disease is left ventricular hypertrophy, thought to be a response of the myocardium to chronically raised afterload.<sup>4</sup> Left ventricular remodelling is described in this setting by Laplace's law: increased afterload on the heart results in an increase in left ventricular pressure, which is proportional with left ventricle wall stress. As wall stress increases, there is worsened myocardial shortening and increased myocardial oxygen demand, which leads to compensation by the myocardium to normalise the wall stress.<sup>4</sup> Hypertrophy will increase the wall thickness and decrease the cavity radius, both acting within Laplace's law to decrease left ventricle wall stress.<sup>5,6</sup> Hypertrophy of the ventricular wall is a precursor in the pathogenesis of hypertensive heart disease: hypertrophy is followed by fibrotic accumulation, coronary abnormalities, and eventual heart failure.<sup>7</sup>

There are many potential causes for hypertension in children: renal disease, cardiovascular malformations, drugs and medications, malignancies, endocrine disorders, and genetic defects

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classify common conditions that result in paediatric hypertension. However, the majority (50–60%) are due to renal disease or renal artery stenosis.<sup>8</sup> Left ventricular hypertrophy in children (and adults) is highly correlated with hypertension. In children specifically, office blood pressure readings and 24-hour ambulatory blood pressure monitoring significantly correlate with left ventricular mass.<sup>9</sup> In a meta-analysis of populations of children with primary hypertension, 30.5% had hypertrophy.<sup>10,11</sup> The degree of hypertrophy typically considered to be abnormal is defined as a left ventricular mass to height raised to the 2.7<sup>th</sup> power being greater than the 95<sup>th</sup> percentile of healthy reference populations for both sex and age. Khoury *et al.* found that left ventricular mass normalised to height raised to the 2.7<sup>th</sup> power varied little after age 9, suggesting that cut-offs of either 40 g/m<sup>2.7</sup> and 45 g/m<sup>2.7</sup> for females and males could be used, respectively.<sup>12</sup> The American Academy of Pediatrics Fourth Report recommends a cut-off of 51 g/m<sup>2.7</sup> (the 99<sup>th</sup> percentile in children and adults) given its association with hypertension-related morbidity in adults.<sup>13</sup> This corresponds approximately to two standard deviations above the mean left ventricular mass index (+2.0 Z-score) measured by cardiac MRI.<sup>14</sup> There has since been some controversy over the methodology used to determine left ventricular mass index: Foster *et al.* suggested that normalising left ventricular mass to body surface area can lead to its underestimation, whereas normalisation by height can lead to its overestimation, advocating instead for indexation to lean body mass.<sup>15,16</sup> However, lean body mass is less practical to measure.<sup>15</sup> It is perhaps preferable to overestimate left ventricular hypertrophy with a more practical method as individuals approaching a higher percentile rank of ventricular mass index likely have higher blood pressure, given their high degree of association.

As opposed to the majority of hypertrophic cardiomyopathy cases, hypertensive heart disease usually presents with concentric, rather than asymmetric left ventricular hypertrophy.<sup>17</sup> However, as thickening of the myocardium can still be asymmetric in hypertensive heart disease (in about 21% of adult patients)<sup>18</sup>, morphological differences cannot definitively confirm one disease from the other. Depending on the severity of the hypertrophy, left ventricular outflow tract obstruction can also be observed in hypertensive heart disease. However, the prevalence of this phenomenon in the context of hypertensive heart disease has not been verified by a large-scale study in children or adults. Rather, it is thought to be extremely rare and has only been highlighted to date in case reports.<sup>19–21</sup> Increased wall stress on the left ventricle in hypertensive heart disease can activate biomechanical sensors which upregulate hypertrophic gene expression and activate myofibroblasts, subsequently depositing extracellular matrix proteins into the interstitium. This can yield fibrosis, which, similar to hypertrophic cardiomyopathy, results in both systolic and diastolic dysfunction.<sup>22</sup>

### Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is defined as hypertrophy of the left ventricular wall that is unexplained by the presence of other left ventricular hypertrophy-inducing conditions, including hypertension.<sup>17,23</sup> Hypertrophic cardiomyopathy is a disease of genetic origin, with a litany of sarcomeric and non-sarcomeric protein mutations implicated.<sup>23</sup> It is known that these mutations typically act in an autosomally dominant fashion.<sup>23,24</sup> The pathogenesis of hypertrophic cardiomyopathy is characterised by increased myocyte size, disorganised myocytes and sarcomeres, and worsening fibrosis due to the secretion of collagen from cardiac fibroblasts.<sup>24</sup> Myocardial fibrosis usually leads to diastolic dysfunction, with preserved ejection

fraction that persists until more end-stage disease.<sup>24,25</sup> Focal, asymmetric hypertrophy in various areas of the left ventricle is characteristic of hypertrophic cardiomyopathy, though more symmetric hypertrophy involving all portions of the left ventricular myocardium can also be observed. In addition to uniform septal thickness, hypertrophy can be focused in the base (simple sigmoid), mid-septum (catenoid), and apex (apical), with mid-septal thickening being most common.<sup>26</sup> While genetic testing can be helpful, it also has its limitations in the diagnosis of hypertrophic cardiomyopathy as only 27–60% of patients test gene positive.<sup>25,27–29</sup> Though hypertrophic cardiomyopathy can be passed to progeny in an autosomal dominant pattern, a negative family history does not rule out the disease, and significant variability exists with respect to penetrance and expression.<sup>30</sup> There is certainly more work needing to be done to understand the link between genotype and the manifested phenotype in the face of environmental influences.<sup>23</sup> Despite a negative genotype not ruling out a diagnosis of hypertrophic cardiomyopathy, a positive genotype can help as supporting evidence in the differentiation between hypertrophic cardiomyopathy and hypertensive heart disease.<sup>29</sup> Screening of individuals for highly pathogenic mutations can help guide clinical investigation, with cascade testing enabling clinicians to construct a genetic history of the patient which may corroborate a diagnosis of hypertrophic cardiomyopathy over hypertensive heart disease. However, caution should be exercised as the uncertain evidence of causality and the constellation of genetic variation can make genetic results hard to interpret.<sup>31</sup>

Hypertrophic cardiomyopathy generally can be categorised in two ways, that are not mutually exclusive: obstructive hypertrophic cardiomyopathy and non-obstructive hypertrophic cardiomyopathy, the former being more common.<sup>25</sup> Obstruction results from worsening hypertrophy of the left ventricular wall which creates narrowing of the left ventricular outflow tract such that velocity of flow through the tract becomes increased.<sup>25</sup> Described by Bernoulli's principle, the faster moving fluid constitutes a lesser pressure within the outflow tract, leading to suction on the anterior mitral valve leaflet during systole. This is known as systolic anterior motion of the mitral valve, which is a classic feature of obstructive hypertrophic cardiomyopathy but is also recognised to occur very rarely during hypertensive heart disease.<sup>19,32</sup> If the intracavitary pressure gradients become pronounced enough, the leaflet is moved into the outflow tract of the left ventricle and can make contact with the interventricular septum that results in further obstruction to blood flow.<sup>25,33</sup> This movement may result in mitral regurgitation due to the leaflet being unable to remain in the closed position during systole. Further, patients with hypertrophic cardiomyopathy often present with abnormalities of the mitral valve: roughly half present with elongated mitral valve leaflets, especially in the anterior leaflet, which may worsen the systolic anterior motion of the valve to cause obstruction.<sup>34</sup> Papillary muscles may also be higher in number, hypertrophied, and anteriorly displaced, which can also contribute to systolic anterior motion of the valve.<sup>34</sup>

### The role of diagnostic modalities in differentiation of hypertrophic cardiomyopathy and hypertensive heart disease

There are several tools available to clinicians which can help distinguish hypertensive heart disease from hypertrophic cardiomyopathy. Each comes with its own advantages and disadvantages; however, there are a variety of signs afforded by different diagnostic modalities which can suggest the aetiology of left

ventricular hypertrophy. In the following sections, the utility of each modality and their differentiative ability is described.

### The importance of physical examination and history in discrimination

The physical examination and history of the patient can be helpful in differentiating between left ventricular hypertrophy that is resultant from hypertrophic cardiomyopathy or hypertensive heart disease in some regards. Both diseases can present with the same myriad of symptoms once the degree of left ventricular hypertrophy is pronounced enough: dyspnea, chest pain, palpitations, dizziness, syncope, and audible S4 on auscultation (due to the hypertrophic and non-compliant ventricle) are readily observed.<sup>35–37</sup> However, given the rarity of these symptoms in children, these symptoms will more likely suggest hypertrophic cardiomyopathy over hypertensive heart disease. A family history of relatives either diagnosed with hypertrophic cardiomyopathy or hypertrophic cardiomyopathy-related adverse events like sudden cardiac death can be suggestive of hypertrophic cardiomyopathy over hypertensive heart disease. As a manifestation of uncontrolled hypertension, hypertensive heart disease may arise concomitantly with manifestations of other target organ damage such as retinopathy, which can suggest hypertensive heart disease over hypertrophic cardiomyopathy.<sup>37</sup> Guideline statements emphasise that 24-hour ambulatory blood pressure monitoring be carried out in order to confirm a diagnosis of hypertension and can facilitate the diagnosis of masked or nocturnal hypertension.<sup>38–40</sup> However, despite establishing the severity or length of hypertension in the individual, this cannot solely differentiate the patient as 30–50% of adult patients<sup>41</sup> and 10% of children<sup>42</sup> with hypertrophic cardiomyopathy are also hypertensive. Therefore, this finding should be considered in conjunction with other artefacts from the physical examination and findings from imaging investigations.

Various manoeuvres can be used to probe for a latent obstruction, the finding of which can be suggestive of hypertrophic cardiomyopathy given its rarity in cases of hypertensive heart disease.<sup>19</sup> Since intracavitary pressure gradients can be changed by altered preload and afterload, outflow tract obstruction can be dynamic, only presenting once aggravated. Thus, it is imperative to conduct tests that will provoke an underlying outflow tract obstruction – for this purpose, handgrip, squatting, standing up, or the Valsalva manoeuvre can be employed.<sup>25,33</sup> For example, the Valsalva manoeuvre will temporarily increase intrathoracic pressure, leading to a reduced venous return to the heart, reducing preload. Decreased preload reduces chamber size and exacerbates the narrowing in the outflow tract, increasing the pressure gradient across it and provoking an underlying obstruction. Conversely, squatting can increase the preload by moving blood out of the venous reservoir of the legs, while concomitantly increasing the systemic vascular resistance, reducing the left ventricular outflow tract obstruction. Similarly, cardiopulmonary exercise testing can also reveal a latent obstruction.<sup>43</sup> While there seems to be lacking reports of the proportion of children that suffer from latent or resting obstruction, data from adults allow us to infer that up to approximately two-thirds will develop outflow tract obstruction over the course of their lifetime.<sup>44</sup> Since not all patients present with a resting or latent obstruction, other diagnostic tools are necessary to further differentiate between hypertensive heart disease and non-obstructive hypertrophic cardiomyopathy. Cues are summarised in Table 1.

### Electrocardiography and telemetry

Electrocardiography is a valuable tool, known to have a high specificity in the diagnosis of left ventricular hypertrophy. In the context of the larger mass of the myocardium, the amplitude of the QRS complex will be increased. Furthermore, the abnormally thickened myocardium causes electric pulses from the electrocardiography to take longer to traverse the heart, which may manifest as a widening of the QRS complex. This affects repolarisation as well, apparent in ST segment abnormalities.<sup>45</sup>

Electrocardiography is widely available and low cost and has an abundance of defined clinical criteria that can be easily employed to diagnose left ventricular hypertrophy.<sup>16,46–48</sup> However, since left ventricular hypertrophy can manifest in both hypertrophic cardiomyopathy and hypertensive heart disease, electrocardiography should not be used alone in the classification of left ventricular hypertrophy's aetiology.<sup>16,45</sup> Even using electrocardiography to screen for left ventricular hypertrophy is limited, as the method suffers from low sensitivity even in populations at high risk for developing hypertrophy.<sup>49</sup> A variety of studies have analysed various electrocardiographic techniques, comparing their sensitivity and specificity. Varying slightly depending on population, age, and obesity, sensitivity and specificity for left ventricle hypertrophy appear to hover between 17–35% and 80–99%, respectively, using Sokolow-Lyon or Cornell voltage criteria.<sup>50–52</sup> A relatively new voltage criterion for left ventricular hypertrophy screening which boosts sensitivity is the Peguero-lo Presti criteria: in comparison with Cornell or Sokolow-Lyon criteria, the new criteria found a 70% sensitivity whilst retaining specificity at 89%.<sup>47</sup> A meta-analysis found that the Peguero-lo Presti criteria averaged a slightly lower sensitivity of 50%; however, this was still significantly greater than both the Sokolow-Lyon and Cornell criteria (found to be 29 and 24%, respectively).<sup>48</sup>

There are yet to be any studies which focus on determining discriminating markers between hypertensive heart disease and hypertrophic cardiomyopathy based solely on electrocardiography characteristics. However, a study by Forghani et al. found that a combination of electrocardiography and echocardiography data resulted in a heightened ability for a trained algorithm to classify patients between hypertensive heart disease and hypertrophic cardiomyopathy compared to the use of data from either modality alone.<sup>53</sup> This suggests that there may be some features of electrocardiography that are of discriminatory value between hypertensive heart disease and hypertrophic cardiomyopathy which could be elucidated in future studies. In fact, studies have suggested that Q-wave abnormalities can be of predictive value for genetic mutation carriers, with abnormalities being more frequent in female patients with hypertrophic cardiomyopathy.<sup>54,55</sup> However, these studies centre on populations of patients with hypertrophic cardiomyopathy and do not compare with populations with hypertensive heart disease. Another study reported that lengthened filtered P-wave duration and PR interval were significantly longer in individuals with hypertrophic cardiomyopathy.<sup>56</sup> Furthermore, the number of premature atrial complexes formed per hour with 24-hour Holter monitoring was significantly greater in individuals with hypertensive heart disease.<sup>56</sup> While receiver-operator curve analysis was not conducted for these parameters, they may be important discriminatory markers offered by electrocardiography and telemetry.

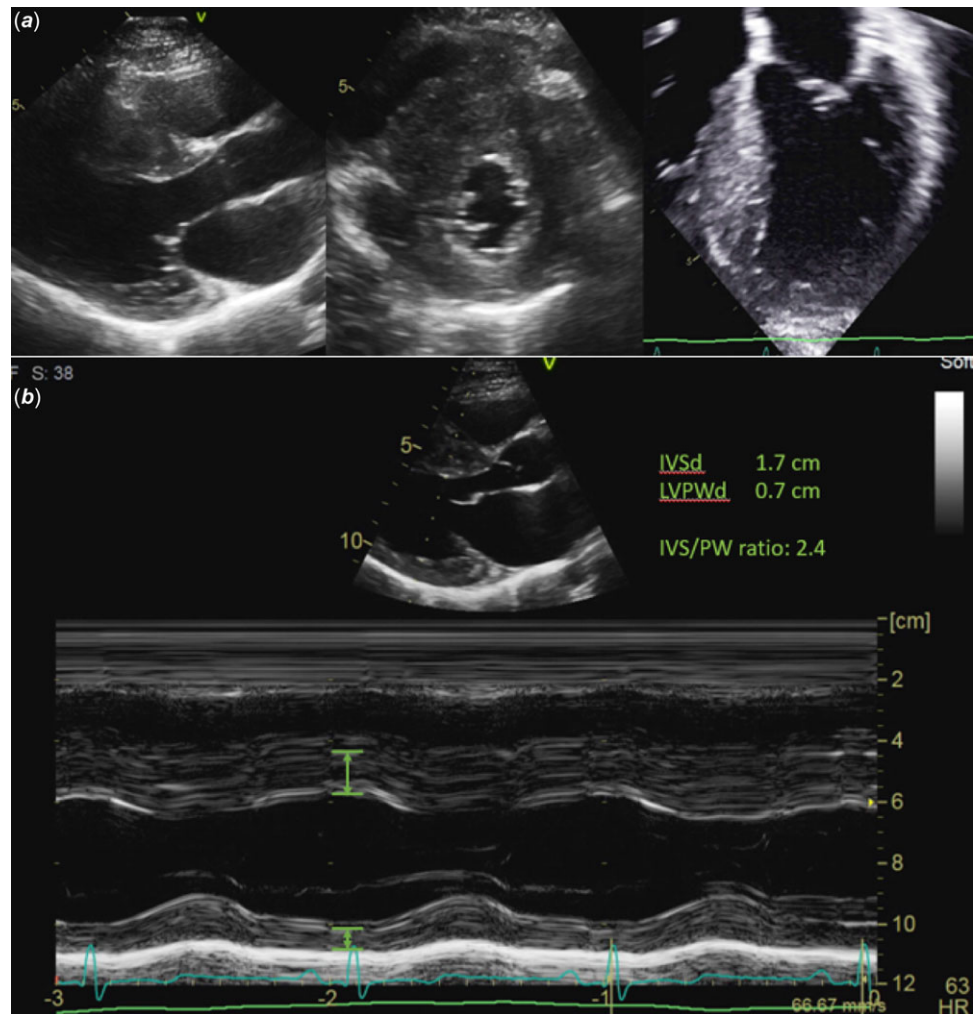
### Echocardiography

Echocardiography is the most widely used tool to investigate ventricular function as various modalities of echocardiography can

**Table 1.** Clinical clues to differentiate HCM from HHD

HHD suggestive	Inconclusive	HCM suggestive
<ul style="list-style-type: none"> <li>Concomitant evidence of alternate target organ damage (e.g. retinopathy)</li> <li>Improvement of LVH upon hypertension control</li> </ul>	<ul style="list-style-type: none"> <li>Hypertension</li> </ul>	<ul style="list-style-type: none"> <li>Family history of genetic mutation or SCD</li> <li>Resting or provokable obstruction</li> <li>No improvement in LVH upon hypertension control</li> <li>Absence of hypertension but ventricular hypertrophy symptoms</li> </ul>

HCM = hypertrophic cardiomyopathy; SCD = sudden cardiac death; LVH = left ventricular hypertrophy.

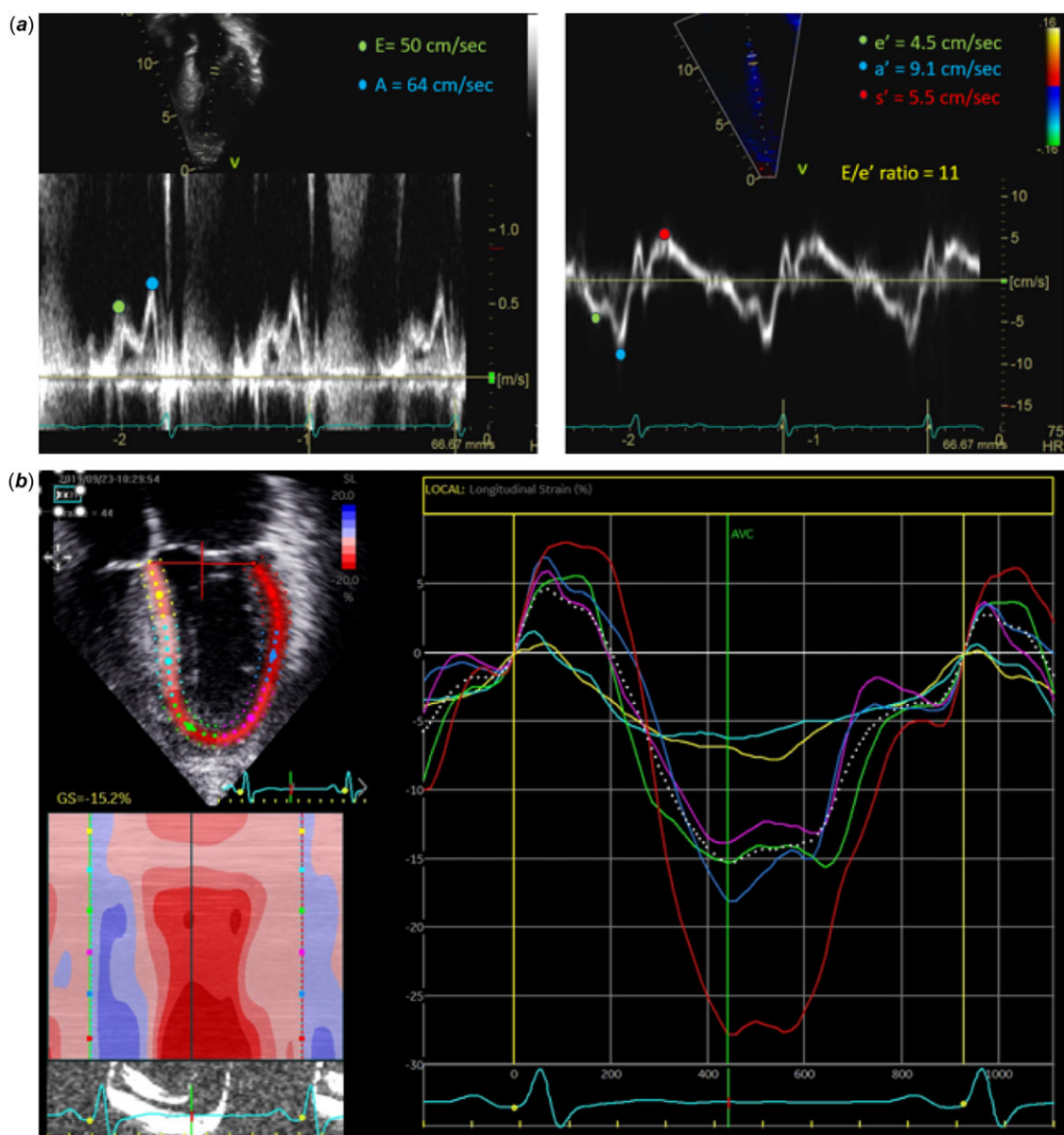


**Figure 1.** *a*) Asymmetric septal hypertrophy shown on transthoracic two-dimensional echocardiogram images of a teenager with hypertrophic cardiomyopathy. Views include parasternal long axis (left), short axis (middle), and apical four chamber (right). *b*) M-mode measurement of the end-diastolic septal and left ventricular posterior wall thickness in a teenager with hypertrophic cardiomyopathy with asymmetric septal hypertrophy.

provide information about left ventricle wall thickness, internal dimensions, volume, mass, ejection fraction, and pressure gradients<sup>57</sup> (Figures 1, 2, and 3). Indeed, this can help separate out individuals with obstructive hypertrophic cardiomyopathy by measuring pressure intracavitary pressure gradients towards the left ventricle outflow tract (> 30 mmHg); however, distinction between non-obstructive hypertrophic cardiomyopathy and hypertensive heart disease patients may be more challenging as the presence of an outflow tract obstruction is usually not present to suggest hypertrophic cardiomyopathy.<sup>58</sup> In hypertensive patients, left ventricle wall thickness is typically only mildly increased (< 13 mm) in adults; however, some patients can have a substantial hypertrophy up to 16 mm.<sup>58</sup> This provides some overlap with more severe left ventricle wall thicknesses typically

observed in patients with hypertrophic cardiomyopathy, where >15 mm is typically indicative of hypertrophic cardiomyopathy in adults.<sup>59</sup> This is further complicated by the ethnicity of the individual, as the prevalence and severity of left ventricular hypertrophy can differ depending on this variable. For example, it has been reported that left ventricular hypertrophy secondary to hypertension is more prevalent in African American individuals.<sup>7,60</sup>

Nonetheless, there exists a zone of uncertainty between 13 and 15 mm in left ventricle wall thickness which can make it hard to discern between hypertensive heart disease and non-obstructive hypertrophic cardiomyopathy based on wall thickness.<sup>2,17,25</sup> It is generally thought that hypertrophy due to hypertension is symmetric, whereas that in hypertrophic cardiomyopathy is asymmetric across regions of the myocardium.<sup>61</sup> However, there is still overlap between



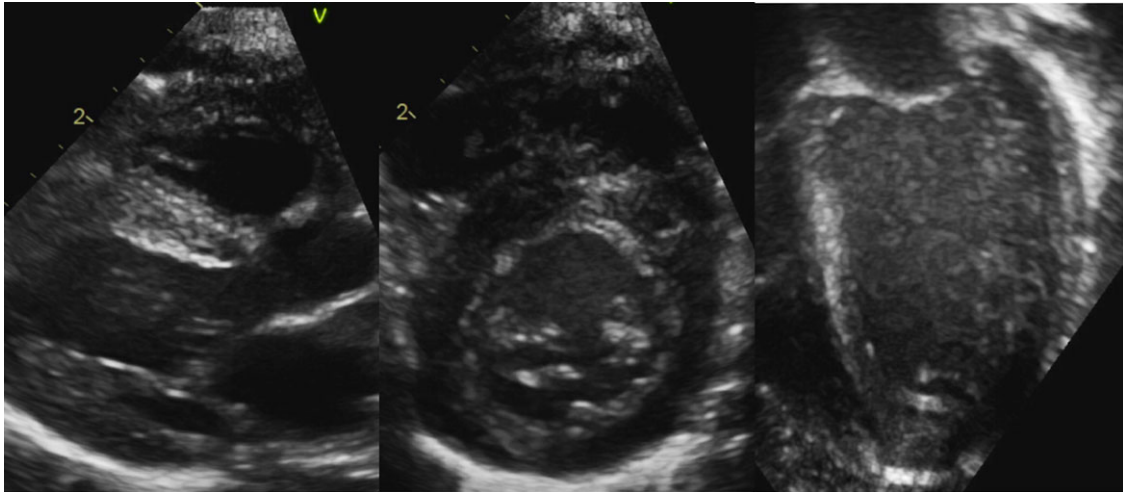
**Figure 2.** **a)** Illustrative left ventricular inflow pulse-wave Doppler (top left) and septal tissue Doppler (top right) velocities in a teenager with hypertrophic cardiomyopathy. Note the reduced  $e'$  TDI velocity with increased  $E/e'$  ratio. **b)** Speckle tracking echocardiography performed on a teenager with hypertrophic cardiomyopathy. Illustrated above is the left ventricular longitudinal strain obtained on an apical four-chamber image.

the two aetiologies: 13–31% of patients with hypertrophic cardiomyopathy show symmetrical hypertrophy and between 4 and 47% of hypertensive heart disease patients can present with asymmetrical hypertrophy.<sup>62</sup> These measurements have not been explored in the differentiation of the two conditions in paediatrics, but it is likely that general observations about the thickness of the myocardium in some regions cannot fully distinguish one aetiology from the other.

Atrial differences can perhaps be of discriminatory value on the basis of worsened left ventricle compliance and fibrosis in individuals with hypertrophic cardiomyopathy: one such study evaluated parameters of atrial remodelling between hypertensive heart disease and hypertrophic cardiomyopathy adults and found that left atrial volume index was larger in hypertrophic cardiomyopathy patients compared to patients with hypertensive heart disease.<sup>56</sup> In receiver–operator curve analysis, left atrial volume index of 31 mL/m<sup>2</sup> displayed an area under curve of 0.733,

with a sensitivity and specificity of 81.5% and 56.8%, respectively, for hypertrophic cardiomyopathy.<sup>56</sup>

Morphological parameters of the myocardium that may be used to differentiate hypertrophic cardiomyopathy patients from hypertensive heart disease patients have also been studied. For the left ventricle, Kato et al. conducted a study of 34 patients with left ventricular hypertrophy >13 mm in wall thickness suspected of either hypertensive heart disease or hypertrophic cardiomyopathy and analysed parameters that could differentiate the two groups. They found that maximal interventricular septum to posterior wall thickness ratio and utility in the discrimination between hypertensive heart disease and hypertrophic cardiomyopathy diagnoses.<sup>62</sup> A cut-off interventricular septum to posterior wall ratio of 1.3 was associated with a sensitivity, specificity, and predictive accuracy for hypertrophic cardiomyopathy of 65%, 100%, and 79.4%, respectively.<sup>62</sup> Other studies have found similarly that an



**Figure 3.** Transthoracic two-dimensional echocardiogram views of an infant with concentric left ventricular hypertrophy secondary systemic hypertension from renal disease. View include parasternal long axis (left), short axis (middle), apical four chamber (right).

interventricular septum to posterior wall ratio cut-off of about 1.3 holds good discriminatory utility, with sensitivity, specificity, and accuracy at 85.7%, 75%, and 80%, respectively.<sup>63</sup> In another cohort, interventricular septum to posterior wall ratio  $>1.35$  or simply interventricular septum thickness  $>1.65$  cm displayed discriminatory capability between hypertensive heart disease and hypertrophic cardiomyopathy with an area under curve of 0.979 and 0.951, respectively.<sup>64</sup> It is unclear if this ratio holds true for the paediatric population. For the right ventricle, another study focused on tricuspid annular motion velocity on the basis that right ventricle remodelling was observed to be more frequent in individuals with hypertrophic cardiomyopathy than hypertensive heart disease.<sup>65</sup> At a cut-off value of 8.0 cm/s, a sensitivity, specificity, and area under curve of 62%, 65%, and 0.686, respectively, was observed.<sup>66</sup>

Of particular interest in the diagnostic differentiation of left ventricular hypertrophy aetiology is tissue doppler imaging and speckle tracking echocardiography, which can measure the velocity of myocardial motion during systole and/or diastole and other parameters such as strain and strain rate.<sup>57,67</sup> Speckle tracking echocardiography utilises analysis of “speckles” which manifest on the image produced by the interaction of the ultrasound and myocardial fibres, allowing for measurements of myocardial strain and strain rate. This can be done in three spatial directions: longitudinal, radial, and circumferential strain, allowing for speckle tracking echocardiography to largely replace tissue doppler echocardiography for measurement of strain and strain rate.<sup>68,69</sup> The following studies mentioned use one of these two methodologies: it should be noted the two methods in children have shown good agreement in longitudinal and circumferential strain; however, radial strain and strain rate have been shown to be different between tissue doppler and speckle tracking.<sup>70</sup> Finally, 3D speckle tracking echocardiography is a relatively new development within echocardiography and is quickly becoming the gold standard for evaluation of cardiomyopathy. The accuracy of M-mode and 2D echocardiography is decreased in comparison with 3D echocardiography, given that the former assumes that size and shape of the ventricle are uniform.<sup>71</sup> However, 3D echocardiography allows direct observation of epi-endocardial boundaries, improving regional myocardial assessment.<sup>71,72</sup>

Strain values are anticipated to be more significantly reduced in patients with hypertrophic cardiomyopathy and especially within myocardial segments with a greater degree of fibrosis. In adults, mean values of systolic strain ( $\epsilon$ -sys) have even better discriminatory utility than interventricular septum to posterior wall thickness ratio: a systolic strain cut-off of  $-10.6\%$  had a sensitivity, specificity, and accuracy of 85%, 100%, and 91.2%, respectively.<sup>62</sup> Sun *et al.* reported that longitudinal strain was significantly lowered in hypertrophic cardiomyopathy patients versus hypertensive heart disease patients and varied within the endocardium, myocardium, and epicardium. They showed that endocardium/epicardium circumferential and longitudinal strain ratios had good differentiability between conditions, with area under curve of 0.92 and 0.90, respectively.<sup>73</sup> Subjects with hypertrophic cardiomyopathy had a significantly lower average global peak longitudinal systolic strain (GLS-avg) compared to other forms of left ventricular hypertrophy. It was shown that this parameter, at a cut-off value of  $-14.3\%$ , was able to distinguish hypertrophic cardiomyopathy from hypertensive heart disease, with a sensitivity, specificity, and predictive accuracy of 77%, 97%, and 87%, respectively.<sup>74</sup> These results were reinforced by another study comparing hypertensive heart disease to hypertrophic cardiomyopathy, which showed that a left ventricular global longitudinal strain below  $-12.5\%$  had an area under curve of 0.808 for differentiating hypertrophic cardiomyopathy from other left ventricular hypertrophy aetiologies.<sup>64</sup> They also found that an  $E/e'$  ratio of  $>11$  and had an area under curve of 0.865.<sup>64</sup> The usage of multiple parameters in conjunction is likely to provide greater discriminatory power; however, which parameters provide the most optimal discrimination for use of clinical resources is yet to be explored. Echocardiography parameters for adults are summarised in Table 2 and Figure 6.

Unfortunately, while all of these tools are also available in paediatrics, further study is needed to evaluate whether these parameters can provide equally successful discriminatory power in populations of children, as studies thus far have focused on adults. Studies have found between children with hypertension and healthy controls that global longitudinal strain, global radial strain, and global 3D strain were significantly different,<sup>75</sup> similarly to adults. This may suggest that the fibrotic pathology to the myocardium is similarly detected within paediatric populations as

opposed to adults via echocardiography; however, there are yet to be studies which compare parameters such as strain between hypertrophic cardiomyopathy and hypertensive heart disease in paediatrics. Further, differences in anatomical ratios such as interventricular septum to posterior wall thickness ratio may be altered in children and vary with age, making them difficult to compare between the two myocardial diseases. We advocate that these studies can improve the utility of echocardiography within this differential diagnosis in the paediatric population.

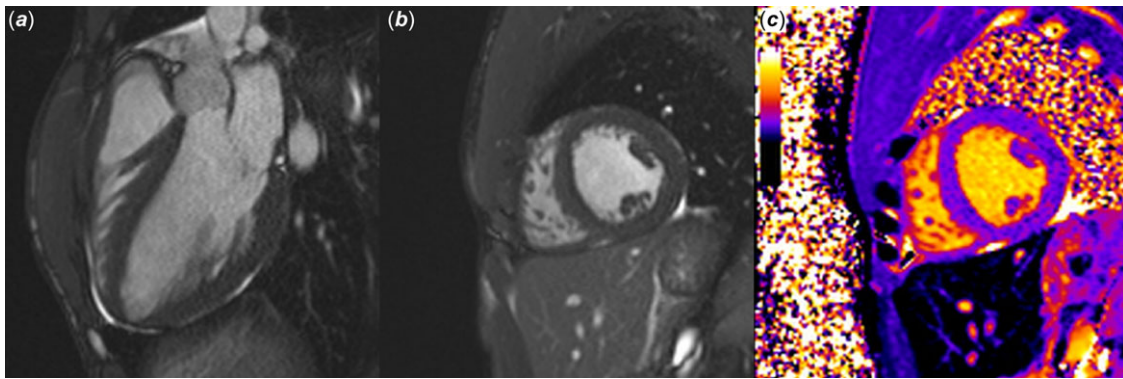
### Cardiac MRI

Cardiac MRI is the gold standard tool for validating myocardial morphology and function as it produces highly accurate and reproducible measurements, making it a good tool for monitoring left ventricular hypertrophy over time.<sup>59</sup> Echocardiography can be limited in full assessment of the left ventricle, especially within the basal anterolateral wall; however, studies have found that left ventricular mass measurement with echocardiography overestimated left ventricular mass in comparison with cardiac MRI.<sup>76</sup> By taking slices of the myocardium spanning the ventricle, volume is evaluated by contouring the endo- and epicardium, and using Simpson's rule to estimate myocardial volume, which can be multiplied by myocardial density to obtain mass. Regional morphology and wall thickness can be evaluated at each acquired slice, finding the myocardial segments with maximal wall thickness.<sup>77</sup> Compared to echocardiography, cardiac MRI has particular strength in myocardial tissue characterisation, which can be useful in determining the aetiology of left ventricular hypertrophy: this includes techniques such as late gadolinium enhancement, native T1 mapping, extracellular volume, and texture analysis, each of which have shown promise as discriminatory markers for left ventricular hypertrophy due to hypertrophic cardiomyopathy or hypertensive heart disease.<sup>3</sup> While it is a potent tool for non-invasive myocardial tissue assessment, cardiac MRI is not widely available, may be challenging for some individuals with claustrophobia, and requires sedation of younger children (typically < 8–10 years old) to limit movement.<sup>16</sup>

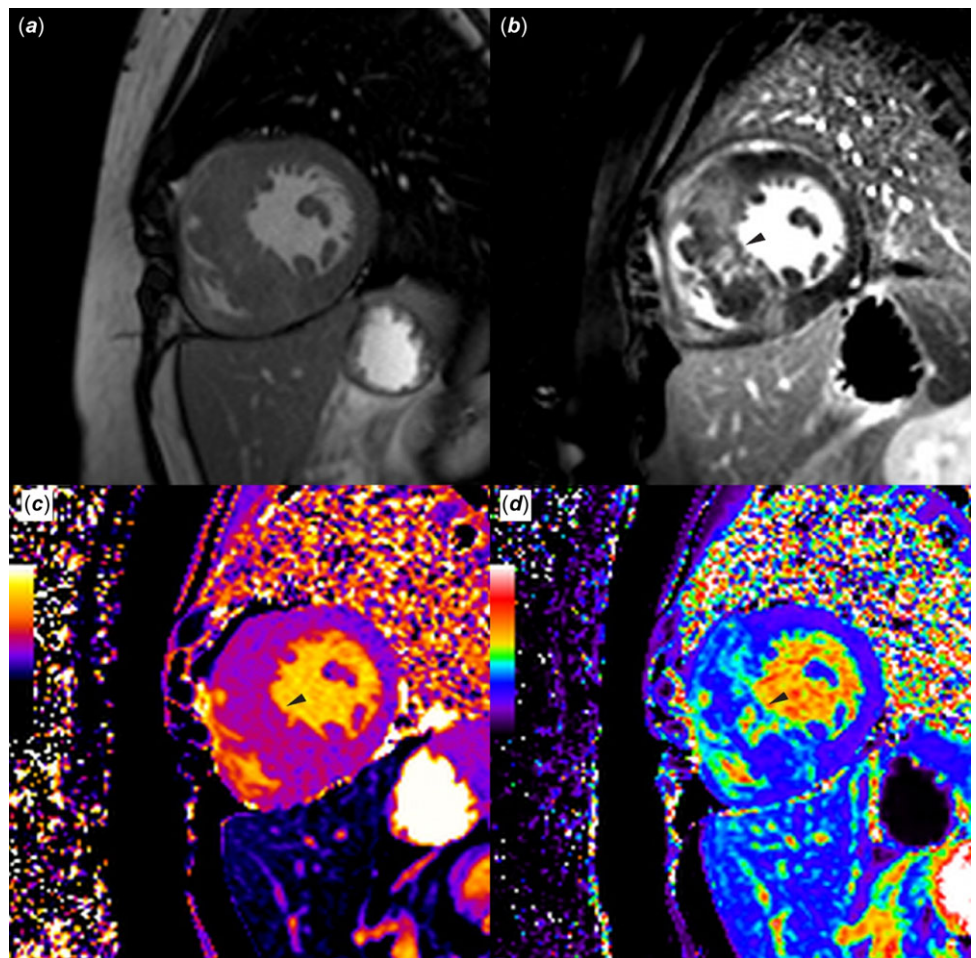
Late gadolinium enhancement on cardiac MRI has long been regarded as a potent way to assess fibrosis within the myocardium, as abnormal myocardium will retain the gadolinium-based contrast in the extracellular space for longer.<sup>78</sup> The extent of the enhancement correlates with areas of increased collagen deposition on histology.<sup>59</sup> This is especially pertinent for the identification of fibrotic conditions like hypertrophic cardiomyopathy and even risk stratifying hypertrophic cardiomyopathy patients, as worsened fibrosis has been associated with arrhythmia (within hypertrophic cardiomyopathy, most prevalently ventricular fibrillation followed by atrial fibrillation<sup>79</sup>) and sudden cardiac death.<sup>80,81</sup> Furthermore, the degree of fibrosis in patients with hypertensive heart disease is lesser than that in hypertrophic cardiomyopathy, making its quantification by late gadolinium enhancement a potentially powerful discriminatory tool. Indeed, it has been demonstrated that late gadolinium enhancement is more prevalent in individuals with hypertrophic cardiomyopathy and that late gadolinium enhancement can serve as a diagnostic index to categorise the two conditions when left ventricle wall thickness is >15 mm in adults.<sup>82,83</sup> While late gadolinium enhancement can manifest in both hypertensive heart disease and hypertrophic cardiomyopathy, hypertrophic cardiomyopathy patients feature a higher percentage of late gadolinium enhancement compared to other left ventricular hypertrophy aetiologies and it can be found characteristically in the mid-wall either anteroseptally or

inferoseptally.<sup>84</sup> This is reflected by late gadolinium enhancement prevalence as well: in hypertrophic cardiomyopathy, it is thought to manifest in roughly 76% of adult patients, but in hypertensive heart disease around 50% of symptomatic adult patients.<sup>84,85</sup> In the paediatric population, reported late gadolinium enhancement prevalence was reported by one study to be as high as 92%, which is notably on par with the also high prevalence in adults.<sup>86</sup> However, other studies with similar cohort sizes have found lower prevalence of late gadolinium enhancement within paediatric hypertrophic cardiomyopathy cohorts, outside of this study ranging from 18 to 82%.<sup>87–90</sup> The percentage of enhanced myocardium also seems to be similar to adults, with median percent late gadolinium enhancement burden of roughly 3.3–9%.<sup>84,86</sup> Neisius et al. sought to utilise late gadolinium enhancement to discriminate patients with either hypertrophic cardiomyopathy or hypertensive heart disease, reporting that while prevalence, late gadolinium enhancement volume, and percent late gadolinium enhancement were increased significantly in hypertrophic cardiomyopathy patients, use of these parameters alone found a relatively lower area under curve of 0.656–0.680<sup>91</sup> in discriminating hypertrophic cardiomyopathy from hypertensive heart disease. Therefore, it seems that late gadolinium enhancement should be used in combination with other parameters. Subsequent studies demonstrated that the use of other parameters together with late gadolinium enhancement could provide excellent discrimination of hypertensive heart disease and hypertrophic cardiomyopathy. One study showed that atypical late gadolinium enhancement score with percent normal myocardial strain produced a high discrimination area under curve (0.92) for determining hypertensive heart disease from hypertrophic cardiomyopathy.<sup>82</sup> Another study by Liu et al. used segmental strain analysis and found that global radial strain and mid-interventricular septum late gadolinium enhancement were significantly increased in the hypertrophic cardiomyopathy group compared to the hypertensive heart disease group. Combining global radial strain and late gadolinium enhancement within the mid-interventricular septum at cut-off values of 8.87% and 3.87%, respectively, yielded good discriminatory ability between hypertrophic cardiomyopathy and hypertensive heart disease (area under curve = 0.835) in multivariate analysis.<sup>92</sup> Studies evaluating the use of these metrics for discrimination of the two myocardial diseases in paediatric populations alone and especially in concert are lacking, however.

T1 mapping, measuring myocardial longitudinal relaxation, is another tissue characteristic parameter of interest on cardiac MRI (Figures 4 & 5). Typical cardiac MRI fibrosis imaging using late gadolinium enhancement relies on creating a signal difference between areas of fibrosis and normal tissue; however, if all myocardial tissue had diffuse fibrosis, such signal differences would not exist and the myocardium would appear “normal.” T1 mapping is able to overcome this limitation, as it can directly measure the myocardial T1 values, which will vary with disease. It was hypothesised to be able to distinguish hypertrophic cardiomyopathy from hypertensive heart disease on the basis that hypertensive heart disease would demonstrate a more diffuse interstitial fibrosis that lacks vivid enhancement under gadolinium contrast but could still be picked up by T1 mapping.<sup>77</sup> T1 mapping can also be performed before and after gadolinium administration to obtain the extracellular volume fraction, as gadolinium contrast agent will infiltrate the interstitial space proportional to its size, such that the difference between pre- and post-contrast T1 mapping values will determine the extracellular volume fraction.<sup>93</sup> In paediatric populations, mean native T1 scores and extracellular



**Figure 4.** Representative images from a 16-year-old male referred for assessment of left ventricular hypertrophy (LVH) without clear diagnosis of cardiomyopathy or hypertensive heart disease. Still images from cine imaging in: **a)** three-chamber view and **b)** short-axis slice in the mid-ventricular level show normal left ventricular chamber size with mild concentric LVH (maximum septal thickness 12 mm). **c)** A normal T1 map, with a mid-ventricular septal T1 value of 942 ms, within normal for the sequence type. Late gadolinium enhancement imaging was not performed due to perceived low yield given overall normal appearance of myocardium during examination, without specific features suggestive of hypertrophic cardiomyopathy.

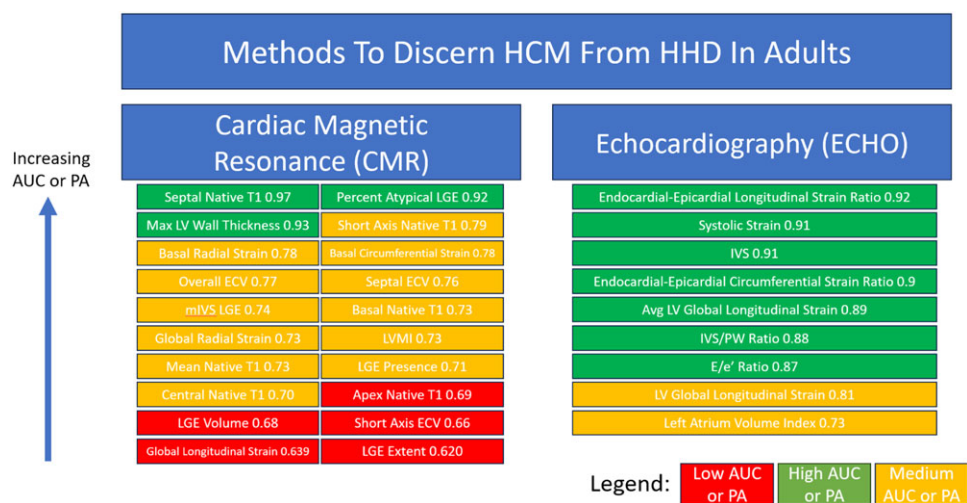


**Figure 5.** Representative images from a 17-year-old female referred for follow-up cardiac MRI assessment with a known diagnosis of severe hypertrophic cardiomyopathy. **a)** Still images from cine imaging in short-axis slice in the mid-ventricular level show normal left ventricular chamber size with severe asymmetric left ventricular hypertrophy (LVH) (maximum septal thickness 29 mm). **b)** Late gadolinium enhancement imaging showed diffuse and patchy enhancement of the interventricular septum (arrowhead). Overall fibrosis burden by semiquantitative late gadolinium enhancement (LGE) was approximately 33% of the myocardial mass. **c)** T1 mapping, pre-contrast, shows borderline elevated T1 value of 1068 ms in the septum (arrowhead). **d)** Extracellular volume fraction (ECV) map shows elevated ECV of 39% in the same septal region (arrowhead).

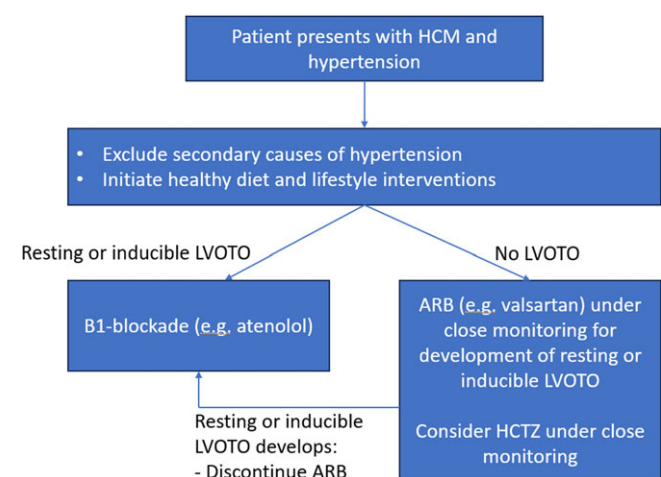
volume are significantly higher than non-hypertrophied controls; however, no comparison is made to hypertensive heart disease.<sup>94</sup> In adults, one such study found in univariate analysis that mean native T1 and extracellular volume could produce area under curves of 0.726 and 0.772, respectively.<sup>95</sup> In a larger powered study, however, Hinojar *et al.* reported in 2015 that T1 mapping displayed excellent discrimination between hypertrophic cardiomyopathy

and hypertensive heart disease. In univariate analysis, septal native T1 had high area under curve at 0.97, suggesting that the region of the myocardium in which T1 mapping is performed is relevant. In multivariate analysis, native T1 displayed a diagnostic accuracy of 97%. Furthermore, native T1 was increased in hypertrophic cardiomyopathy genotype positive phenotype negative patients, reflecting the ability of T1 mapping to detect even subtle disease





**Figure 6.** Schematic representation of techniques to discriminate HCM from HHD from either CMR or ECHO. Techniques are ranked by AUC or PA (averaged if multiple studies) and colour-coded by high ( $\geq 0.85$ ), medium ( $< 0.85 - \geq 0.7$ ), or low ( $< 0.7$ ) average AUC or PA. HCM = hypertrophic cardiomyopathy; HHD = hypertensive heart disease; ECHO = echocardiography; CMR = cardiac magnetic resonance; AUC = area under curve; PA = predictive accuracy.



**Figure 7.** Flowchart for proposed treatment/management recommendations for patients with overlapping HCM and hypertension. HCM = hypertrophic cardiomyopathy; LVOTO = left ventricular outflow tract obstruction; ARB = angiotensin receptor blocker; HCTZ = hydrochlorothiazide.

potentially before complete manifestation.<sup>96,97</sup> This is corroborated by another study which applied texture analysis within T1 maps with extracellular volume, with their model providing good area under curves of 0.969 for the T1 map and 0.964 for extracellular volume.<sup>98</sup> Cardiac MRI parameters of utility within adults are summarised in Table 3 and Figure 6.

As emphasised within the echocardiography section, a similar problem within the cardiac MRI literature prevails. Though markers derived from echocardiography and cardiac MRI like interventricular septum to posterior wall thickness ratio, strain values, and T1 mapping have been demonstrated as valuable discriminators between hypertrophic cardiomyopathy and hypertensive heart disease in adults, there continues to be a lack of data for such a comparison in children.<sup>16</sup> While there are many studies within children that outline key myocardial parameters between healthy controls and children with either hypertrophic cardiomyopathy, there continues to be a lack of reproduction of studies that directly compare hypertensive heart disease with hypertrophic cardiomyopathy to differentiate them. It appears that in the context of paediatric hypertrophic cardiomyopathy, cardiac MRI parameters such as late gadolinium enhancement extent and

prevalence<sup>87,89,99</sup>, global and longitudinal strain and strain rate<sup>99,100</sup>, and T1 relaxation times<sup>94</sup> are similarly affected in paediatrics as in adults. There is a paucity of cardiac MRI studies of children with hypertensive heart disease; however, given that fibrosis has been shown to be detectable using parameters such as T1 relaxation time and late gadolinium enhancement within paediatric hypertrophic cardiomyopathy, these tools are presumably also relevant in the context of paediatric hypertensive heart disease. What stands to be investigated is whether differences in cardiac MRI parameters between the two myocardial diseases enable differentiability: to our knowledge, no cardiac MRI study or echocardiography study has made this comparison specifically within paediatrics. The lack of multicentre cardiac MRI studies has been acknowledged recently within the literature, with myocardial disease being scored as a high priority for surveyed investigators.<sup>101</sup> Thus, this may constitute important study that can provide an extra tool for distinguishing these two myocardial diseases in children.

It should also be acknowledged that discriminatory parameters, either in the case of cardiac MRI or echocardiography, may vary between cohorts studied. Thus, one-off, single-centre studies of the application of such parameters should be interpreted with caution. However, comparison of parameters within cohorts can be informative of which parameters may hold better utility and can be built upon with higher powered studies in the future.

### Management techniques of left ventricular hypertrophy through the lens of pathophysiology

Given that about 31.5% of the world's population suffers from hypertension, there is bound to be a significant proportion of patients with hypertrophic cardiomyopathy that presumably also have hypertension concomitantly.<sup>33,102,103</sup> This is especially pertinent in obese patients. In a cohort of children (ages 2–20) with hypertrophic cardiomyopathy, roughly 140/504 (28%) had concomitant obesity and though not measured, it is likely that a proportion of them also had hypertension given the association<sup>1,104</sup> and previous studies in both children and adults that have reported hypertension in 10–50% of individuals.<sup>41,42</sup> Thus, obesity, hypertension, and hypertrophic cardiomyopathy are commonly superimposed in both children and adults.

An overlap between hypertension and hypertrophic cardiomyopathy complicates treatment, as typical first-line antihypertensive

**Table 2.** Summary table of echocardiographic parameters of discriminatory value between HCM and HHD

Parameter	Study and participants	Mean age of HCM and HHD participants (years)	Cut-off value	Sensitivity	Specificity	AUC (no units) or PA (%)
<b>Strain</b>						
Systolic strain (E-sys) (%)	Kato <i>et al.</i> <sup>62</sup> <i>n</i> = 20 HCM <i>n</i> = 14 HHD	53.2	−10.6	85.0%	100%	91.2%
Endocardial to epicardial LS ratio	Sun <i>et al.</i> <sup>73</sup> <i>n</i> = 80 HCM <i>n</i> = 80 HHD	50.7	1.39	87.2%	85.7%	0.92
Endocardial to epicardial CS ratio	Sun <i>et al.</i> <sup>73</sup> As above	As above	2.32	92.1%	77.2%	0.90
LV GLS	Ozer <i>et al.</i> <sup>64</sup> <i>n</i> = 20 HCM <i>n</i> = 25 HHD	49.7	−12.5%	64%	70%	0.808
Average LV GLS	Afonso <i>et al.</i> <sup>74</sup> <i>n</i> = 56 HCM <i>n</i> = 27 HHD	52.5	−14.3%	77%	97%	0.893, 87%
<b>Myocardial and atrial measurements</b>						
LAVI	Servatius <i>et al.</i> <sup>56</sup> <i>n</i> = 27 HCM <i>n</i> = 324 HHD	73.1	31 mL/m <sup>2</sup>	81.5%	56.8%	0.733
IVS/PW ratio	Minoshima <i>et al.</i> <sup>63</sup> <i>n</i> = 14 HCM <i>n</i> = 16 HHD	62.2	1.29	75%	80%	80%
IVS/PW ratio	Ozer <i>et al.</i> <sup>64</sup> As above	As above	1.35	80%	99%	0.979
IVS/PW ratio	Kato <i>et al.</i> <sup>62</sup> As above	As above	1.3	65%	100%	79.4%
IVS	Ozer <i>et al.</i> <sup>64</sup> As above	As above	1.65 mm	80%	96%	0.951
IVS	Servatius <i>et al.</i> <sup>56</sup> As above	As above	14 mm	85.2%	71.9%	0.863
E/e' ratio	Ozer <i>et al.</i> <sup>64</sup> As above	As above	11	80%	79%	0.865

HCM = hypertrophic cardiomyopathy; LS, longitudinal strain; GLS, global longitudinal strain; CS, circumferential strain; LAVI, left atrium volume index; IVS, interventricular septum; PW, posterior wall; HHD = hypertensive heart disease; AUC = area under curve; PA = predictive accuracy.

medications such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, thiazides like hydrochlorothiazide, or the calcium channel blocker amlodipine are typically contraindicated in obstructive hypertrophic cardiomyopathy. A change in afterload, such as seen with angiotensin-converting enzyme inhibitors, can exacerbate intracavitary pressure gradients that perpetuate systolic anterior motion and obstruction of the left ventricle outflow tract.<sup>25,105</sup> Dihydropyridine calcium channel blockers (such as amlodipine or nifedipine) enable vasorelaxation to treat high blood pressure and will decrease afterload on the heart, which may worsen the pressure gradient by facilitating higher ejection velocity through the left ventricle outflow tract.<sup>25</sup> In symptomatic patients with obstructive hypertrophic cardiomyopathy, exacerbation of the obstruction can usually be avoided by using diuretics (typically hydrochlorothiazide); however, a further reduction in preload due to diuretics can reduce already impaired diastolic filling.<sup>106</sup> Therefore, management of hypertension in patients with hypertrophic cardiomyopathy can be a challenge.

Patients with hypertrophic cardiomyopathy who have latent gradients that only yield obstruction once provoked can suffer in

these circumstances, as changes in these gradients due to the addition of antihypertensives may lead to resting obstruction. These drugs may already have been started in some individuals who are hypertensive to prevent target organ damage either prior to left ventricular hypertrophy being diagnosed or because they are thought to have hypertensive heart disease.<sup>103</sup> This is why the discrimination of the aetiology of any observable left ventricular hypertrophy is important, and one should not simply prescribe antihypertensives and monitor whether hypertrophy regresses to determine the diagnosis without first conducting investigation.

Negative inotropes like beta blockers and non-dihydropyridine calcium channel blockers (such as verapamil and diltiazem) can be useful in the treatment of both hypertensive heart disease and hypertrophic cardiomyopathy, as they can decrease contractility and thus underlying intraventricular pressure gradients. Indirectly, they may reduce blood pressure which can take away the hypertrophic stimulus. In the case of obstruction in hypertrophic cardiomyopathy patients, the sweeping of the mitral valve into the left ventricle outflow tract is specifically due to the velocity of fluid flow in the left ventricle outflow tract and the force of the flow on

**Table 3.** Summary of cardiac MRI parameters of discriminatory value between HCM and HHD

Parameter	Study and participants	Mean age of HCM and HHD participants (years)	Cut-off value	Specificity	Sensitivity	AUC
Mass indexation and wall thickness						
LVMI	Neisius et al. 2019 <sup>91</sup> N = 107 HCM N = 53 HHD	56.7	65.2 g/m <sup>2</sup>	66%	49%	0.643
LVMI	Hinojar et al. 2015 <sup>96</sup> N = 95 HCM N = 69 HHD	55.7	84 g/m <sup>2</sup>	64%	80%	0.82
Max LVWT	Hinojar et al. 2015 <sup>96</sup> Participants as above	As above	16 mm	84%	91%	0.93
Strain values						
GLS	Neisius et al. 2019 <sup>91</sup> Participants as above	As above	-15.7%	72%	58%	0.639
GRS	Liu et al. 2022 <sup>92</sup> N = 56 HCM N = 45 HHD	52.0	16.27%	75.44%	62.22%	0.734
BRS	Liu et al. 2022 <sup>92</sup> Participants as above	As above	18.09%	78.95%	68.89%	0.781
BCS	Liu et al. 2022 <sup>92</sup> Participants as above	As above	-11.59%	84.21%	62.22%	0.776
LGE						
LGE presence	Neisius et al. 2019 <sup>91</sup> Participants as above	As above	-	74%	58%	0.656
LGE presence	Hinojar et al. 2015 <sup>96</sup> Participants as above	As above	-	68%	76%	0.76
LGE extent	Liu et al. 2022 <sup>92</sup> Participants as above	As above	5.17%	63.16%	64.44%	0.619
LGE miVS	Liu et al. 2022 <sup>92</sup> Participants as above	As above	3.43%	64.91%	77.78%	0.735
LGE volume	Neisius et al. 2019 <sup>91</sup> Participants as above	As above	0.15 mL	79%	56%	0.68
% normal myocardium and atypical LGE	Giusca et al. 2021 <sup>82</sup> N = 45 HCM N = 228 HHD	64.5	N/R	98%	82%	0.92
T1 values						
Basal native T1 (3T)	Liang et al. 2022 <sup>95</sup> N = 38 HCM N = 35 HHD	50.4	1282 ms	63.16%	89.66%	0.733
Central native T1 (3T)	Liang et al. 2022 <sup>95</sup> Participants as above	As above	1236 ms	86.84%	77.41%	0.704
Apex native T1 (3T)	Liang et al. 2022 <sup>95</sup> Participants as above	As above	1267 ms	65.79%	75.86%	0.693
Mean native T1 (3T)	Liang et al. 2022 <sup>95</sup> Participants as above	As above	1282 ms	63.16%	89.66%	0.726
Septal native T1 (3T)	Hinojar et al. 2015 <sup>96</sup> Participants as above	As above	1110 ms	98%	96%	0.97
SAX native T1 (3T)	Hinojar et al. 2015 <sup>96</sup> Participants as above	As above	1067 ms	77%	71%	0.79
Global native T1 (3T)	Neisius et al. 2019 <sup>91</sup> Participants as above	As above	1097 ms	97%	50%	0.718
ECV						
Septal ECV	Hinojar et al. 2015 <sup>96</sup> Participants as above	As above	29%	71%	76%	0.76

(Continued)

**Table 3.** (Continued)

Parameter	Study and participants	Mean age of HCM and HHD participants (years)	Cut-off value	Specificity	Sensitivity	AUC
SAX ECV	Hinojar <i>et al.</i> <sup>96</sup> Participants as above	As above	30%	63%	70%	0.66
Overall ECV	Liang <i>et al.</i> 2022 <sup>95</sup> Participants as above	As above	28.8%	85%	62.07%	0.772

HCM = hypertrophic cardiomyopathy; GLS = global longitudinal strain; GRS = global radial strain; BRS = basal radial strain; BCS = basal circumferential strain; ECV = extracellular volume fraction; SAX = short-axis slice; LVMI = left ventricular mass index; LVWT = left ventricular wall thickness; LGE = late gadolinium enhancement; mLVS = mid-interventricular septum.

the valve.<sup>25,103,107</sup> Negative inotropes will decrease the left ventricle ejection velocity and thus exponentially reduce the force on the mitral valve such that systolic anterior motion is lessened. This yields a delay of mitral–septal contact during systole which would further decrease the left ventricle outflow tract pressure gradient.<sup>103</sup> Furthermore, negative inotropes can decrease heart rate, enabling a prolonged diastolic filling period which is usually impaired during hypertrophic cardiomyopathy.<sup>106</sup> Care must be exercised when choosing beta blockers, however; non-selective beta antagonism can result in unopposed alpha-receptor stimulation, leading to a net effect of vasoconstriction which can increase afterload. For this reason, selective beta-1 blockade (via drugs like atenolol or metoprolol) are used in the case of hypertrophic cardiomyopathy as they can reduce cardiac contractility whilst preserving sympathetic tone of the vessels. Conversely, alpha blockers are also not typically used in the context of suspected hypertrophic cardiomyopathy due to a lack of opposition to beta-2 signalling, which will cause vasodilation.<sup>103</sup>

Despite thiazides and angiotensin receptor blockers typically being contraindicated in individuals with obstructive hypertrophic cardiomyopathy, there has been some investigation into these drugs in the context of non-obstructive hypertrophic cardiomyopathy that may also be used in the context of hypertensive heart disease. Blood pressure-independent effects have also been documented. Angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, and thiazides all seem to have similar blood pressure controlling effects which can reduce cardiovascular risk proportional to this reduction<sup>108</sup>, yet despite this similarity, thiazides display additional reduction of cardiovascular risks compared to other antihypertensives according to the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial.<sup>109</sup> This is perhaps due to potential blood pressure-independent effects that mitigate hypertrophic signalling by thiazide medications.<sup>110,111</sup> The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study showed that treatment with hydrochlorothiazide along with losartan provided increased regression of electrocardiography measured left ventricular hypertrophy independently of blood pressure reducing effects.<sup>113,112</sup> Utilisation of hydrochlorothiazide may be especially pertinent in the case of the obese hypertrophic cardiomyopathy patient and particularly children, as both hypertension and hypertrophic signals are present and progressive disease can be prevented. When considering the use of hydrochlorothiazide for the treatment of hypertension in patients with hypertrophic cardiomyopathy, the general approach is to start a low dose and titrate slowly to ensure that there are no consequences due to the diuretic effect of hydrochlorothiazide.

These blood pressure-independent effects on fibrotic and hypertrophic signalling also prompted investigation into valsartan.

The VANISH trial evaluated the use of the angiotensin receptor blocker valsartan in adult and children with early-stage hypertrophic cardiomyopathy found that daily administration of valsartan was able to benefit patients in a variety of parameters such as cardiac structure and function.<sup>113</sup> A recent systematic review of clinical trials utilising angiotensin receptor blockers, including losartan or valsartan, has indicated that angiotensin receptor blocker treatment was significantly associated with reduced blood pressure as well as reduced left ventricle mass in patients with hypertrophic cardiomyopathy.<sup>114</sup> Though the medication is typically contraindicated in patients with potential dynamic obstruction, it may be of use in patients with non-obstructive hypertrophic cardiomyopathy.

Given the variety of options available, it is up to the treating physician to use discretion and change treatment depending on the response of the patient, as this will provide key information on the aetiology of left ventricular hypertrophy. Repeat imaging and ambulatory blood pressure monitoring are necessary to continuously evaluate the response to treatment and whether blood pressure is being controlled. The response towards antihypertensive therapy may differ between patient groups that may or may not be at high cardiovascular risk; therefore, a tailored approach to management should be considered when treating hypertension. Regression of left ventricular hypertrophy concomitantly with blood pressure reduction would suggest hypertensive heart disease (readers are directed to Khoury and Urbina 2021 for more discussion of regression of left ventricular hypertrophy under antihypertensive management).<sup>40</sup> Alternatively, provocation of obstruction or lack of left ventricular hypertrophy regression or fibrosis reduction with blood pressure control would instead indicate hypertrophic cardiomyopathy. These are the final indicators that will ultimately classify a patient into either myocardial category. A proposed treatment strategy which follows how patients are handled at our centre is included (Figure 7).

## Conclusion

Hypertrophic cardiomyopathy and hypertension are both common causes of left ventricular hypertrophy in children and adolescents. As the management strategies for these disease processes are different (and commonly contrary to each other), establishing diagnostic certainty is an important priority. The clinician must use all tools available at their disposal, including differentiating factors in the history and physical examination and diagnostic confirmation testing such as ambulatory blood pressure monitoring and genetic testing. Echocardiography and MRI are effective tools to differentiate hypertensive heart disease from hypertrophic cardiomyopathy, with exciting new cardiac MRI techniques showing high utility for discriminating between the

myocardial pathologies. While these techniques are well studied in adults, we note that there is a lack of replication in children where myocardial dimensions and characteristics may be altered: further studies are needed to characterise important cut-offs in children. This is especially significant for treatment choice as latent obstructions must not be aggravated. As angiotensin receptor blockers may serve as an important prevention modality for target organ damage, elucidating the proper indications for pharmacological therapy is of great importance. We must continue to use the tools at our disposal to differentiate these presentations in order to provide the best treatment for patients.

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