Chapter 16
Cardiac Hypertrophy and Hypertrophic Cardiomyopathy: Introduction and Management

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Abstract The magnitude of hypertrophic response of the left ventricle to pressure overload is variable and likely is mediated by genetic factors as well as other identified mechanisms. Myocardial hypertrophy is a common phenotype of multiple cardiac disease entities. Left ventricular hypertrophy (LVH) causes significant morbidity and mortality in adults. Increased pressure overload is a key stimulus for the development of LVH in hypertensive patients as well as in those with aortic valve stenosis through several molecular mechanisms. Hypertrophic cardiomyopathy (HCM) is present in 1 in 500 people in the general population and is the most common genetically transmitted cardiomyopathy. HCM can be caused by more than 1,400 different mutations and is transmitted in an autosomal dominant pattern. Many individuals affected by HCM are undiagnosed, and most do not experience lethal events or symptoms. However, those who develop symptoms such as dyspnea, angina, and lightheadedness can experience functional disability secondary to heart failure and stroke as well as to sudden cardiac death (SCD). The majority of HCM patients are treated medically with the initial aim of reduction of symptoms along with reducing the risk for SCD. Therapy of patients with HCM can be classified into medical, interventional/device, and surgical treatments.

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16.1 Part I: Introduction to Cardiac Hypertrophy and Hypertrophic Cardiomyopathy

Patients develop left ventricular hypertrophy (LVH) secondary to left ventricular (LV) pressure overload. However, the magnitude of hypertrophic response of the LV to pressure overload is variable and likely is mediated by genetic factors as well as other pathophysiological mechanisms. One in three Americans suffers from systemic hypertension. Of these, about 40 % have secondary LVH. Causes of LV pressure overload include, in addition to systemic hypertension, aortic stenosis, discrete subvalvular aortic stenosis (DSAS), supravalvular aortic stenosis, aortic coarctation, HCM, and hypertensive HCM. Cardiac hypertrophy may lead to LV diastolic dysfunction, which is a major cause of congestive heart failure (CHF). In addition, an increase in LV mass due to LVH is associated with an increased risk of sudden death [1, 2].

16.1.1 Pathophysiologic Mechanisms of Myocardial Hypertrophy

Myocardial hypertrophy is a common phenotype of multiple cardiac disease entities. Although, right ventricular hypertrophy is a relatively common finding in LVH [3, 4], it is the latter that causes the vast majority of hypertrophy-associated morbidity and mortality in adults. Adaptive (and sometimes maladaptive) responses to hemodynamic load (i.e., athlete's heart, hypertensive heart disease, valvular disease) have a different underlying pathophysiology, when compared with infiltrative cardiomyopathies (i.e., amyloidosis, Fabry disease, mucopolysaccharidosis), mitochondrial disorders, and familial hypertrophic cardiomyopathies. What these disease entities do have in common is that our understanding of their putative mechanisms is far from complete. More recently some overlap of genetic and molecular mechanisms of different types of cardiomyopathies have been identified [5]. Table 16.1 summarizes causes and clinical findings of myocardial hypertrophy. In this chapter, we present the pathophysiology of the two most common pathological forms of myocardial hypertrophy in more detail: (1) hypertensive heart disease and (2) familial hypertrophic cardiomyopathies (HCM), the latter of which is the primary focus of this chapter.

Macroscopically, LVH is an increase of myocardial muscle mass. On a cellular level, there is considerable evidence that hypertrophy is caused by re-expression of many fetal genes and downregulation of adult genes. Re-expression of β-myosin heavy chain—most commonly found in areas of fibrosis and perivascular myocardial regions— and atrial natriuretic factor and α-skeletal actin is thought of as

Table 16.1 Overview and characteristics of diseases associated with left ventricular hypertrophy

	Athlete's heart	**Hypertensive heart disease**	**Hypertrophic cardiomyopathy**	**Cardiac amyloidosis**	**Mitochondrial myopathy**	**Mucopolysaccharidosis**	**Anderson-Fabry disease**
Onset age	Adolescence/ adulthood	Adulthood	Adolescence/ adulthood	Adulthood	Early childhood/ adolescence	Early childhood/ adolescence	Adulthood
Clinical presentation	No typical symptoms	Heart failure symptoms; typical angina; palpitations	No typical symptoms; dyspnea/angina at exercise in case of LVOT; syncope	Mostly symptoms of heart failure (despite normal LV function)	Systemic disease (no typical cardiac symptoms)	Systemic disease (no typical cardiac symptoms)	No typical symptoms
ECG	Possible high voltage QRS; resting bradycardia; ST segment abnormalities	Possible high voltage QRS; ST segment abnormalities	High voltage QRS; ST segment abnormalities	Absence of high ECG voltages despite LVH; conduction abnormalities	Dependent on subtype: conduction abnormalities; AV block	Conduction abnormalities; AV block	Conduction abnormalities; AV block
Echocardiography	Concentric LVH	Concentric LVH	Concentric assymmetric LVH	Concentric LVH; "sparkly" pattern; restrictive LV filling pattern; atrial enlargement; thickened cardiac valves and papillary muscles	Dependent on subtype: hypertrophic, dilative, restrictive pattern	Concentric LVH; valvular thickening with dysfunction (mostly aortic and mitral valve)	Concentric LVH; focal hypokinesia and wall thinning basal inferolateral; thickened aortic and mitral leaflets

(continued)

Table 16.1 (continued)

	Athlete's heart	**Hypertensive heart disease**	**Hypertrophic cardiomyopathy**	**Cardiac amyloidosis**	**Mitochondrial myopathy**	**Mucopolysaccharidosis**	**Anderson-Fabry disease**
CMR	Ischemic as well as nonischemic patterns of LGE	No specific LGE pattern; rather patchy pattern	Patchy or confluent LGE at the insertion points of the right ventricle into the LV and in the septum	LGE in the entire subendocardial circumference	Intramural LGE basal inferolateral in CPEO/KSS; unique HCM-like LGE in MELAS	No data	Subepicardial LGE basal inferolateral
EMB	Myocyte hypertrophy; expansion of interstitial and perivascular fibrosis by progressive collagen accumulation	Myocyte hypertrophy; expansion of interstitial and perivascular fibrosis by progressive collagen accumulation	Myocyte hypertrophy with nuclear enlargement; myofiber disarray and interstitial/ replacement fibrosis; reduced arteriolar density	Green-appearing fibrils during Congo red staining under polarized microscopy; rodlike bundles in EM	Myocyte hypertrophy with vacuolated cardiomyocytes; proliferation of abnormal mitochondria; mosaic appearance of COX deficiency	Vacuolated myocytes with enlarged cytoplasm in LM; GAG laden cells (called "clear" cells)	Intramyocyte accumulation of glycosphingolipids; empty myocytes in LM; lamellar, dense bodies in EM
Extracardiac manifestations	None	Possible vascular complications	None	Nephrotic syndrome and renal insufficiency; cholestatic liver failure; malabsorption and gastrointestinal bleeding; peripheral or autonomic neuropathy; macroglossia or periorbital purpura	Dependent on subtype: ptosis, proximal myopathy, fatigue, exercise intolerance, encephalopathy, and ataxia	Growth retardation; skeletal deformities; CNS involvement; ocular and hearing impairment; respiratory difficulties; gastrointestinal disorders	Renal failure; corneal deposits; nervous, gastrointestinal, and cutaneous manifestations

Inheritance	–	–	Mostly autosomal dominant; rarely autosomal recessive, X linked or maternal	ATTR: autosomal recessive	Mostly maternal inheritance	Mostly autosomal recessive; only MPS II X linked	X linked: males diseased; females carriers
Specific treatment	–	Antihypertensive treatment strategies	–	Chemotherapy in AL	–	Stem cell transplantation; enzyme replacement therapy	Enzyme replacement therapy

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AL acquired monoclonal immunoglobulin light chain amyloidosis, *ATTR* hereditary transthyretin-related form of amyloidosis, *AV* atrioventricular, *CMR* cardiac magnetic resonance, *CNS* central nervous system, *COX* cyclooxygenase, *CPEO* chronic progressive external ophthalmoplegia, *EM* electron microscopy, *EMB* endomyocardial biopsy, *GAG* glycosaminoglycans, *HCM* hypertrophic cardiomyopathy, *KSS* Kearns-Sayre syndrome, *LGE* late gadolinium enhancement, *LM* light microscopy, *LV* left ventricular, *LVH* left ventricular hypertrophy, *LVOT* left ventricular outflow tract, *MELAS* mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes, *MPS* mucopolysaccharidosis

causally involved in the development of LVH. However, β-myosin heavy chain may simply be marker of LVH rather than a causative signal, because it was found in similar quantities both in hypertrophied and non-hypertrophied myocytes of hypertrophied rodent hearts [6]. Cellular myocyte hypertrophy involves both recruitment of contractile elements and myocyte proteins, but increases in myocardial mass also stem from an increase in cells that make up the connective tissue: fibroblasts, vascular smooth muscle cells, and endothelial cells. These changes of the extracellular matrix are key in the development of cardiac dysfunction and the clinical phenotype of the cardiomyopathy. There is a complex interplay between mechanical (hemodynamic) and neurohumoral stress inducing hypertrophic gene expression in hypertensive heart disease [7]. Abnormalities of the myocardial microvasculature cause an imbalance between oxygen delivery and the increased metabolic demands of the hypertrophied myocardium—functional ischemia causing anginal symptoms and perpetuation of cell death and myocardial fibrosis. In hypertensive heart disease, several molecular mechanisms and a few genetic determinants of a hypertrophic response have been identified [8]. In contrast, in familial HCM, several (but not all) genetic causes have been identified, and our understanding of the molecular mechanisms remains incomplete [9–11].

16.1.1.1 LVH in Hypertensive Heart Disease

Increased hemodynamic burden is a key stimulant for the development of LVH in hypertensive (and valvular) heart disease. LVH is an initially effective compensatory mechanism to overcome increased afterload to maintain constant wall stress [12]. While pressure overload invariably leads to concentric LVH, volume overload leads to eccentric hypertrophy with increases of left ventricular internal dimensions, which can also be seen in end-stage cardiomyopathy due to pressure overload [2, 13].

The anatomical classification proposed by Ganau et al. [14] is based on echocardiographic measurements of left ventricular geometry and left ventricular muscle mass. Left ventricular geometry is determined by *relative wall thickness* (*RWT*) calculated as doubling the width of the left ventricular inferolateral wall and divided by the left ventricular end-diastolic internal diameter in end diastole. A RWT $\geq$0.44 is diagnostic for concentric LVH, while a RWT <0.44 with increased left ventricular mass is indicative of eccentric remodeling. This category can be further distinguished from physiologic hypertrophy, which is characterized by mild increases of left ventricular mass and a RWT between 0.32 and 0.44 [12]. For the determination of left ventricular mass in this classification, the following formula is most commonly used:

$$\text{Left ventricular mass} = 0.8 \times \left(1.04 \times \left[\left(\text{LVIDd} + \text{PWTd} + \text{SWTd}\right)^3 - \left(\text{LVIDd}\right)^3\right]\right) + 0.6 \text{ g}$$

Left ventricular mass is usually indexed to body surface area (Du Bois or Mosteller method) [15, 16]. LVIDd indicates left ventricular internal diameter in diastole,

PWTd posterior wall thickness in diastole, and SWTd septal wall thickness in diastole.

In clinical practice, echocardiography is widely available, has a reasonable cost, and is accurate in the clinical setting for the determination of left ventricular mass. While magnetic resonance imaging has greater precision than echocardiography, it has a higher cost, more limited availability, and limited tolerability [17, 18]. Thus, echocardiography is still the primary method to assess the presence, magnitude, and hemodynamic complications associated with LVH.

The correlation between blood pressure measured in the physician's office and left ventricular mass is not linear [19]. There are at least four explanations for this finding: (1) office blood pressure is not a reliable surrogate for overall hemodynamic burden, while 24-h ambulatory blood pressure is a much better surrogate and indeed correlates much closer with left ventricular mass [20]. (2) Both office and 24-h ambulatory blood pressure monitoring provide estimates of hemodynamic stress at one point in time, while the amount of lifetime hemodynamic stress clearly will determine the development of LVH to a much greater degree. Hypertensive heart disease is a chronic condition that develops over many years. (3) Neurohumoral stimulation linked to the development of LVH may differ between individuals with hypertension. (4) A genetic propensity for the development of LVH may exist both in hypertension and valvular disease. Racial/ethnic differences in the probability of developing LVH strongly suggest a genetic component [21–23].

16.1.1.2 Molecular Mechanisms of Hypertensive Heart Disease

(a) *Renin-angiotensin-aldosterone system* (*RAAS*): Angiotensin II released by the myocardium activates G proteins and Rho proteins, which in turn increase protein synthesis in myocardial cells and collagen synthesis in fibroblasts [24–27]. These effects have been found to be independent of afterload in a mouse model suggesting a direct involvement of angiotensin II in LVH [28]. In addition, angiotensin II stimulates fibrosis via endothelin release [29]. Angiotensin II AT_1 receptor blockers and angiotensin-converting enzyme (ACE) inhibitors effectively reduce LVH in hypertensive individuals corroborating the importance of the RAAS in the development of LVH [30] (Chap. 36). Aldosterone also seems to be involved in the development of hypertrophy. Mineralocorticoid receptors are abundantly expressed in cardiomyocytes [31], and aldosterone itself induces vascular [32] and myocardial inflammation [33], myocardial fibrosis [34], and LVH [35]. In a hypertensive model of endothelial dysfunction, eplerenone prevented cardiac inflammation and fibrosis [36]. The nonselective aldosterone antagonist spironolactone and the selective aldosterone receptor antagonist, eplerenone, provided clear clinical benefit in patients with systolic heart failure [37, 38], but the benefit is less clear in patients with diastolic heart failure, in whom LVH oftentimes was the common denominator [39, 40] (Chap. 38). Studies to better assess the clinical effectiveness of aldosterone blockers for the treatment of LVH are in process.

(b) *Endothelin-1*: Endothelin-1, one of three human isoforms of endothelin, is a potent vasoconstrictor produced by endothelial cell. Endothelin has been shown to induce hypertrophy in animal models, and this phenotype can be suppressed by a pharmacologic endothelin-1 receptor blocker, such as bosentan [29, 41, 42]. Direct evidence of endothelin-1 as a mechanism for LVH in humans, however, is lacking (Chap. 45).

(c) *Heat shock proteins are* intracellular proteins, which increase numerically in cells that are exposed to thermal or other forms of stress, and regulate nuclear transcription factors. These factors have been suppressed with gene therapy and antioxidant therapy producing an anti-hypertrophic effect even in the presence of pressure overload [43]. A proteasome inhibitor (PS-519) known to suppress heat shock proteins also prevented isoproterenol-induced LVH in animals with or without preexisting LVH [44].

(d) *G proteins*: Many substances involved in the hypertrophic response to pressure and stress, including phenylephrine, angiotensin II, and endothelin-1, bind to myocyte membrane receptors that activate G proteins and small G proteins (i.e., Rho proteins). These proteins regulate transcription and have been shown to be involved in phenylephrine-induced LVH [45].

(e) *Calcineurin* : *It* is a calcium-/calmodulin-dependent serine-threonine phosphatase that induces myocardial growth in response to different pathological stimulus. It dephosphorylates cytosolic factors (e.g., nuclear factor of activated T cell (NFAT)), enabling them to translocate to the nucleus to activate transcription. Transgenic mice that overexpress calcineurin or its transcription factor targets develop cardiac hypertrophy [46] (Chaps. 4 and 18).

16.1.2 Genetic Factors of Hypertensive Heart Disease

Heritability of left ventricular mass has been reported to be low in first-degree family members with the estimated heritability of adjusted left ventricular mass having values between 0.24 and 0.32 [47]. A markedly higher heritability of left ventricular mass of 0.59 was demonstrated in twins [22]. There can be a large variability of left ventricular mass in patients with similar office blood pressure. The high rates of LVH in certain race/ethnic populations [21] support a genetic predisposition for the development of LVH in response to pressure overload. There are now some genes that have been identified to correlate with LVH in hypertensive patients.

(a) *Corin*, a membrane-bound serine protease expressed in cardiomyocytes, converts atrial and brain natriuretic peptide (ANP, BNP) to their active form. Corin knockout mice develop hypertension and cardiac hypertrophy [47]. Mutations of the corin I555 (P568) gene were exclusive to African-Americans in multiethnic samples with an allelic prevalence of 6–12 % and a clear association with both hypertension and LVH. Thus, corin mutations may explain in part the high prevalence of HTN and LVH in African-Americans [48].

(b) ACE gene polymorphism is also associated with both greater tissue and plasma ACE levels, as well as greater probability for LVH [49, 50] (Chap. 36).
(c) *Protein C* overexpression causes progressive LVH and diastolic dysfunction in animals.
(d) Bradykinin 2 receptor gene polymorphism, specifically the 9 bp receptor gene deletion is associated with greater left ventricular mass in subjects undergoing physical training [51]. Unlike LVH associated with pressure overload, the pathogenesis of LVH in HCM is clearly genetically mediated. However, genetic determinants of LVH in hypertensive hypertrophic cardiomyopathy may be important. As HCM can be associated with elevated LV systolic pressures due to left ventricular outflow tract (LVOT) obstruction, hemodynamics may also be a cause for exaggerated hypertrophy, and thus, there may be overlap between those two disease entities.

16.1.2.1 LVH in Hypertrophic Cardiomyopathy

Originally described in 1869 based on pathologic examination [52], HCM is present in 1 in 500 of the general population and the most common genetically transmitted cardiomyopathy. HCM can be caused by more than 1,400 different mutations [53] and is usually transmitted in an autosomal dominant pattern. Familial HCM describe a phenotype of thickened myocardium ($\geq$15 mm) in the absence of increased afterload (such as hypertension or aortic stenosis) or other explanations for the thickened myocardium (see Table 16.1). A genetic abnormality in gene loci encoding sarcomere proteins is often present (Table 16.2), and over 1,400 gene variations have been linked to HCM. However, in more than 50 % of probands tested, a causative gene cannot be identified [54], underscoring the complexity and variability of the genetics in HCM. Figure 16.1 illustrates the structure of proteins involved in HCM-causing mutations. Mutations in two genes—*MYH7* and *MYBPC3*—account for as many as 75 % of HCM gene-positive individuals [11]. A small subgroup of gene-positive HCM patients has two or more sarcomere protein gene mutations, which may be associated with an earlier onset and/or more rapid disease progression [55, 56]. The utilization of genetic testing is increasing. We believe the most useful applications of genetic testing are twofold: (1) in patients with a clinical suspicion of HCM, the disease can be confirmed, and (2) in family members of an affected gene-positive HCM patient, the presence of the gene defect can be confirmed or excluded. The latter situation provides assurance to gene-negative family members preventing unnecessary serial testing of these individuals, reducing stress, anxiety, and health-care costs [54]. In contrast, patients who are diagnosed with HCM in childhood or adolescence will need to be followed closely for the development of LVH. Whatever the genetic constellation, the clinical phenotype is highly variable, even within families of the same gene mutation, ranging from an asymptomatic course without macroscopic evidence for disease to an individual who has severe and rapid progressive LVH and cardiomyopathy and possibly early sudden cardiac

Table 16.2 HCM-associated genes

HCM gene	Protein defect	Estimated prevalence in HCM probands (%)	Strength of evidence for causality	Location
No gene identified	NA	50	NA	NA
MYBPC3	Cardiac myosin-binding protein C	15–25	++	Intermediate filament
MYH7	β-Myosin heavy chain	15–25	++	Thick filament
TNNT2	Cardiac troponin T	7	++	Thin filament
TNNI3	Cardiac troponin I	<5	++	Thin filament
TPM1	α-Tropomyosin	<5	++	Thin filament
MYL3	Myosin light chain 3	<1	++	Thick filament
MYL2	Cardiac regulatory myosin light chain	<2	++	Thick filament
MYH6	α-Myosin heavy chain	<1	+	Thick filament
TNNC1	Cardiac troponin C	<1	++	Thin filament
ACTC	a-Actin	<1	++	Thin filament
MYOZ2	Myozenin-2	<1	+	Z-disc
ACTN2	Alpha-actinin-2	<1	+	Z-disc
CSRP3	Cysteine and glycine-rich protein 3	<1	+	Z-disc
TCAP	Telethonin	<1	+	Z-disc
CASQ2	Calsequestrin	<1	+	Ca^{++} handling
JPH2	Junctophilin 2	<1	+	Ca^{++} handling

death [54]. Figure 16.2 shows necropsy specimens from the hearts of two patients with HCM: one who had asymmetric septal hypertrophy and one who had concentric LVH. Some studies have identified high-risk [57, 58] and low-risk [59] mutations; however, conflicting reports exist [60] regarding the prognostic capability for predicting SCD. At present there is a lack of consensus about the role of genetic testing in predicting the magnitude or progression of LVH or the development of LVOT gradients, mitral regurgitation, or the clinical course and status as well as the need for strategies to prevent sudden death such as an implantable cardiac defibrillator (ICDs) [54, 61]. The relatively high cost of genetic testing, the inability to detect a disease-causing mutation in phenotypically affected patients (up to 50 %), and genetic variations of uncertain significance remain a challenge when using genetic testing in clinical practice [54].

As seen in Fig. 16.3, HCM is associated with cardiomyocyte hypertrophy, myofiber and myofibrillar disarray with more or less pronounced interstitial fibrosis, and an abnormal microvasculature with intimal hyperplasia and medial thickening are characteristic of HCM. The magnitude of myofiber disarray in HCM is quantitatively increased in comparison with other conditions with LVH [62]. Animal models including the use of transgenic mice [63, 64], transgenic rabbit [65], Maine coon

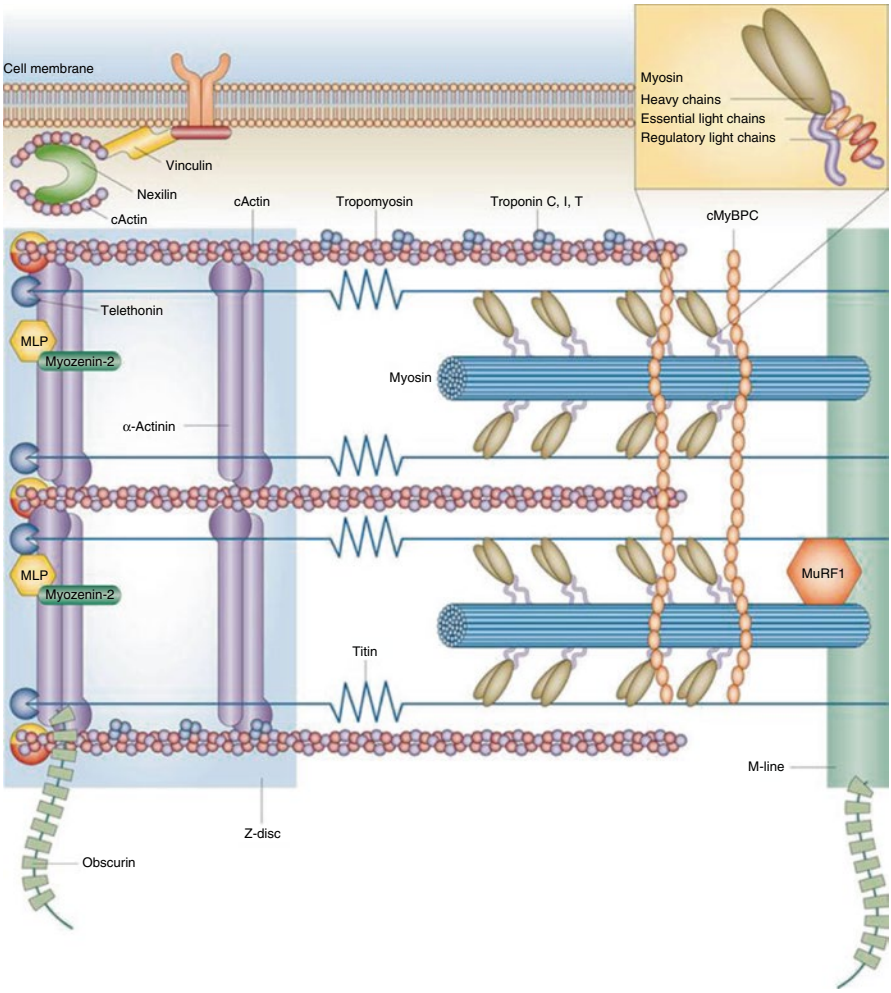

Fig. 16.1 Structure of proteins involved in HCM-causing mutations. *cActin* α-cardiac muscle actin 1, *cMyBPC* cardiac myosin-binding protein C, *MLP* cysteine and glycine-rich protein 3 (muscle LIM protein), *MuRF1* E3 ubiquitin-protein ligase TRIM63 (muscle-specific RING finger protein 1) (Adapted with permission from Frey et al. [11])

cats [66], and zebrafish [67] are being used to study the molecular mechanisms that translate a genetic defect into the hypertrophic phenotype. Several of these mechanisms have been proposed as being responsible for the clinical phenotype of HCM patients, and it is thought to be likely that HCM is a multifactorial disease:

(a) *Depressed contractile function*: One mechanistic hypothesis attributes myocardial contractile dysfunction from myocyte disarray and changes of the connective tissue (i.e., fibrosis) as the cause for progressive hypertrophy in the form of a compensatory mechanism [68–72]. There are several factors that cannot be

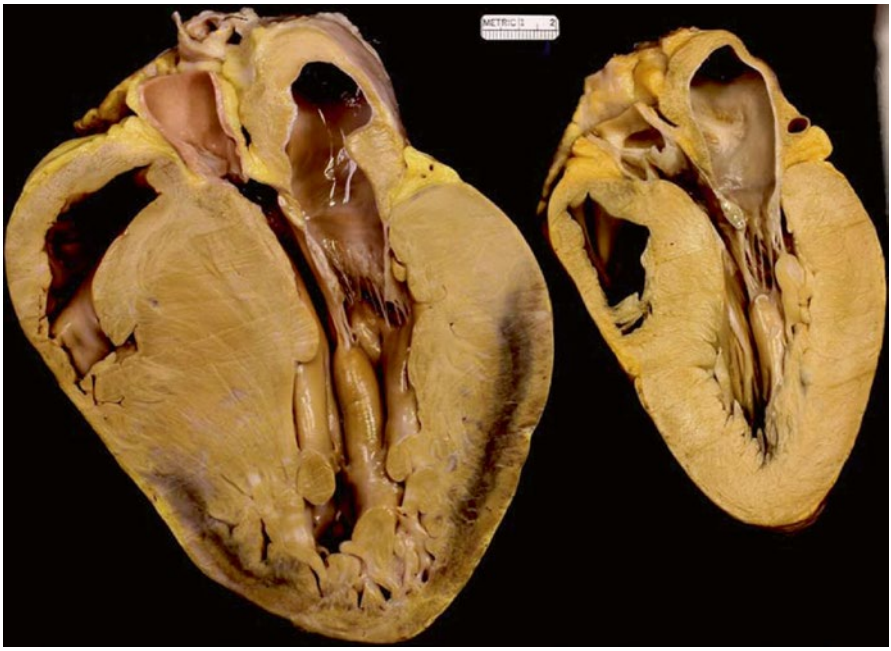

Fig. 16.2 Two heart necropsy specimens from teenagers with hypertrophic cardiomyopathy who had sudden death. Both specimens demonstrate left ventricular hypertrophy; *left*, asymmetric septal hypertrophy in the specimen; *right*, concentric hypertrophy in the specimen (Adapted with permission from Roberts [154])

explained by this compensatory hypothesis: (1) Hypertrophy often develops or progresses during the physiologic growth phase with and after puberty with no or slow progression thereafter even if diastolic and sometimes systolic function worsens. The protein defect on the other hand is present since heart development; thus, a purely compensatory mechanism seems unlikely. (2) Hypertrophy usually is asymmetric (but not always), while compensatory LVH is generally concentric (but not always). (3) A gain in function of the affected myocardium has been observed more recently with an increased energetic cost of cardiac contraction rather than left ventricular dysfunction as discussed next [73].

(b) *Abnormal calcium handling*: Several animal studies suggested that hypertrophic myocytes exhibit an increased sensitivity and affinity to Ca^{2+} of the mutated proteins causing increased cross-bridge turnover and actin-activated ATPase activity [73–75]. This gain of function creates a greater energetic cost of each contraction, and energy depletion subsequently leads to cell death [73]. The enhanced calcium sensitivity has also been shown to increase susceptibility to ventricular arrhythmia by shortening the effective refractory period, increasing the heterogeneities in ventricular conduction and delayed after depolarization [74, 76] (Chap. 4).

(c) *Myocardial fibrosis*: Myocardial fibrosis appears to be the result of premature cell death and expansion of interstitial cells and proteins. Premature myocyte

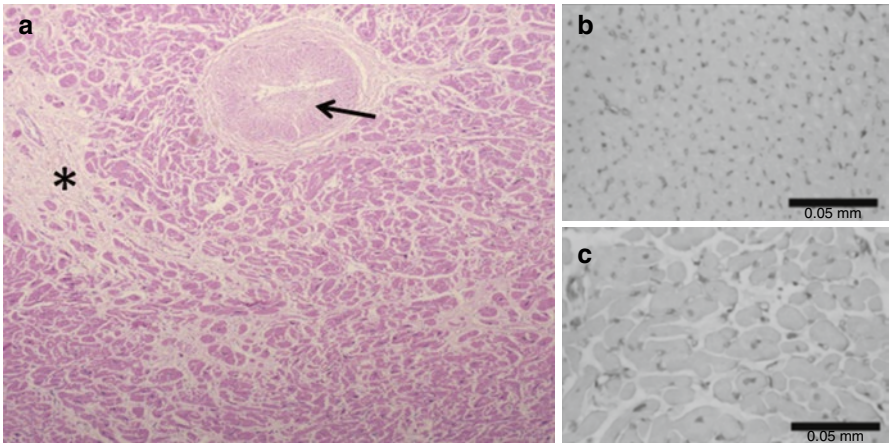

Fig. 16.3 Myocyte disarray, interstitial fibrosis (*), and vascular remodeling with intimal hyperplasia and medial thickening are typical for HCM but also other forms of LVH (panel **a**). Myocardial capillary density (panel **c**) is markedly decreased in HCM compared to a normal heart (panel **b**) (Sources: Panel **a**: Robert J Siegel, MD. Panels **b** and **c**: Adapted with permission from Kofflard et al. [155])

demise is thought to be related to changes in the microvascular architecture in conjunction with the aforementioned abnormal energy homeostasis. One key signal for fibroblast stimulation is the transforming growth factor-β (TGF-β). Indeed suppression of TGF-β [64] with the angiotensin II AT_1 receptor antagonist losartan [77] decreased fibrosis in animal models. The Valsartan for Attenuating Disease Evolution in Early Sarcomeric HCM [VANISH] trial [78] is testing whether angiotensin II AT_1 receptor blockers can reduce myocardial fibrosis in HCM patients. Late gadolinium enhancement on cardiac magnetic resonance imaging (MRI) identifies the extent of myocardial fibrosis and scarring and is associated with an increased risk of sudden death [54, 79]. Serum by-products of fibroblast-secreted collagen are elevated in HCM patients with hypertrophy, in gene-positive probands without hypertrophy and in HCM patients without MRI evidence of scarring. These findings suggest that myocardial fibrosis could be an early causative pathophysiologic mechanism in the development of hypertrophy, rather than a result of hypertrophy [80].

(d) *Abnormal biomechanical sensing*: Some of the HCM mutations involve proteins linked to the Z-disc and the M-band as shown in Table 16.2. These regions have been described to exert hypertrophic signaling from stretch-sensitive transcriptional modifiers in response to biomechanical stress [81]. Alterations in these regions may be involved in stimulating local hypertrophy. This hypothesis, however, is largely speculative at this time [11].

(e) *Abnormal energy production*: Several observations suggest an abnormal supply and demand of cardiac sarcomere adenosine triphosphate [ATP] which is central to contraction and relaxation (myosin ATP) and calcium homeostasis (sarcoplasmic reticulum). ^{31}Phosphorus-NMR demonstrates abnormal cardiac

energetics in both HCM patients and gene-positive probands when compared to healthy controls; this finding suggests that altered ATP production and use could be a causative factor in the development of the HCM phenotype [75]. Furthermore, mitochondrial abnormalities can be observed in gene-positive individuals without a hypertrophic phenotype, which suggests that these altered energetics in HCM and are a cause, but not the result, of hypertrophy [82]. As discussed in Table 16.1, the same mechanism is found to cause myocardial hypertrophy in genetic diseases, which also causes mitochondrial dysfunction. Abnormal cardiac energetics cause diastolic dysfunction from deficient calcium reuptake in the sarcoplasmic reticulum and a state of calcium overload in systolic and diastolic heart failure [83]. These findings are consistent with the clinical presentation of many HCM patients [73].

(f) *Abnormal microvasculature*: Scar burden (by cardiac MRI) and microvascular dysfunction appear to be closely related in HCM patients, and they have more pronounced gene-positive than gene-negative probands [84]. Histologically, intramyocardial microvessels demonstrate a completely abnormal architecture. Figure 16.3 shows histological findings of intimal hyperplasia ("onion skin appearance"), media hypertrophy, and decreased capillary density, all of which leads to reduced microvascular blood flow. In this combination with increased metabolic demands of the hypertrophied myocardium this causes microvascular ischemia and cell death. Therefore, this microvascular ischemia perpetuates fibrosis and as a consequence compensatory hypertrophy and contributes to the pro-arrhythmic substrate. In addition, the presence of microvascular ischemia indicates a worse prognosis in HCM [85]. Ongoing clinical trials are investigating improvements in microvascular ischemia and related arrhythmias from the use of late-current sodium channel blockers [86, 87].

16.1.2.2 Diagnosis of Hypertrophic Cardiomyopathy

Echocardiography is the standard method to screen for HCM because it has a good sensitivity for detecting global or focal hypertrophy. Therefore it is also the test of choice to follow affected individuals, who carry a diagnosis of HCM as well as screening their family members who are at risk for the development of HCM. Furthermore, Doppler echocardiography provides essential hemodynamic data identifying abnormal LV filling, LVOT gradients at rest and during exercise, and mitral regurgitation, which is associated with LVOT gradients and systolic anterior motion of the mitral valve (SAM). Echocardiography is also an essential method to monitor the mechanisms of symptoms, the risk of sudden death, as well as the effects of treatment, and the changes in resting and exertional LVOT gradients, mitral regurgitation, diastolic function, and pulmonary artery systolic pressure. Because of its better resolution and lower inter-study-variability than echocardiography [17, 18], MRI is increasingly being used to evaluate HCM patients; in addition, MRI has better spatial resolution, is less operator dependent, and is not affected by chest wall configuration or body habitus. Furthermore, late gadolinium

enhancement (LGE) can detect the presence, the pattern of distribution, and the extent of myocardial fibrosis, which is a marker for potential ventricular arrhythmias [88]. However, the importance of quantification of cardiac fibrosis as an indication for primary prevention of sudden death with implantable defibrillators is controversial and focus of ongoing research. While MRI has greater sensitivity to detect abnormal wall thickness and provide precise quantification, its high cost and poor tolerability in some patients limit its use for longitudinal follow-up. In addition, echocardiography is superior to MRI for the assessment of mitral regurgitation, quantification of LV outflow tracts, pulmonary artery systolic pressure, and left ventricular filling pressures.

Endomyocardial biopsy with histologic evaluation of myocyte appearance and myofiber orientation is useful for excluding other infiltrative cardiomyopathies which can mimic HCM as detailed in Table 16.1. As previously discussed, genetic testing is helpful to confirm clinical suspicion of HCM and to exclude a known gene defect in family members of an affected individual, which obviates the need for serial long-term follow-up. At present, genetic testing is not a reliable method to predict future development of the disease in phenotypically normal but gene-positive individuals or for the prediction of disease progression and severity in HCM patients [54].

16.1.2.3 Amyloidosis as a Cause of Cardiac Hypertrophy

Cardiac amyloidosis causes a progressive increase in heart wall thickness that is not due to myocardial hypertrophy but rather to extracellular amyloid deposition [89]. This extracellular deposition of amyloid fibrils is composed of an autologous protein which has a beta sheet fibrillar confirmation. While the two main forms of amyloidosis, light chain (AL) and TTR amyloidosis, are the most common, there are more than 30 related amyloidosis proteins capable of forming amyloid fibrils [90, 91]. Cardiac involvement in amyloidosis can be rapidly progressive, and it is the most common cause of death in AL amyloidosis and a major determinant of prognosis. AL amyloid frequently involves the heart, liver, kidney, peripheral and autonomic nervous system, as well as the GI tract [89, 90]. Most patients are diagnosed in the fifth decade of life, and about 50 % have cardiac involvement. CHF augurs a poor prognosis with a survival of only 6 months in untreated patients. Death is usually due to progressive CHF or sudden death due to asystole or electromechanical dissociation.

For TTR amyloidosis, there is a hereditary and nonhereditary form, the latter of which is known as senile amyloid (SA). The hereditary form is autosomal dominant with a 50 % likelihood that the offspring will inherit the disease. TTR generally manifests in the third to fifth decades as cardiac amyloid, neuropathy, or both, depending on the specific molecular abnormality. Senile amyloidosis is related to the breakdown of abnormal TTR. SA generally affects the heart in men in their seventh or eighth decade of life [92]. CHF is often the first manifestation of SA.

Amyloidosis has protean manifestations due to organ infiltration, and symptoms are often nonspecific. Amyloid may present as CHF, progressive wasting, or as a peripheral neuropathy. The finding of low voltage in the electrocardiogram and thick LV walls in the echocardiogram known as voltage-mass discordance is a useful clue to the diagnosis of amyloid in a CHF patient [89]. Cardiac MRI with abnormal gadolinium uptake may also be indicative of cardiac amyloid [93]. Technetium pyrophosphate radionuclide scans may show homogenous uptake of the heart in cases of TTR and SA due to the binding of the P component of the amyloid fibrils [89]. Once there is clinical suspicion of amyloid, a tissue diagnosis should be made. This can be done with a needle biopsy of the abdominal fat or biopsy of another involved tissue. However, in cases with suspected cardiac amyloid, an endomyocardial biopsy may be needed [93]. For AL, amyloid blood and urine are also assessed with immunofixation to detect abnormal proteins which can be quantified by a free light chain assay. In the presence of these abnormal proteins, a bone marrow biopsy should be done to assess the severity of plasma cell dyscrasia [90]. In the absence of AL amyloid, blood testing can be done for a mutation of TTR. If this is negative, SA is the most likely diagnosis. In ambiguous cases, special staining of the biopsy specimens can elucidate the type of amyloid.

Cardiac amyloidosis can be clinically distinguished from HCM by the progressive nature of LVH secondary to progressive amyloid deposition. In HCM the ECG demonstrates LVH, whereas in amyloid, the ECG voltage is low and progressively decreases with amyloid infiltration as wall thickness increases due to the amyloid infiltration [93]. The clinical presentation of cardiac amyloid reflects myocardial infiltration. Initially there is impaired diastolic dysfunction and which generally progresses to systolic dysfunction [89]. Patients often develop right- and left-sided heart failure as well as atrial and ventricular arrhythmias [94, 95]. When CHF is seen in association with other organ involvement suggesting amyloid infiltration such as macroglossia, carpal tunnel syndrome, easy bruising and bleeding, autonomic neuropathy, nephrotic syndrome, and cachexia, amyloid should strongly be considered.

On echocardiography, amyloid may mimic HCM by the presence of asymmetric septal hypertrophy. Cardinal echocardiographic findings in amyloid to suggest the diagnosis are a sparkling appearance of the myocardium, progressive diastolic dysfunction, increased wall thickness of the LV, RV septum in the absence of systemic or pulmonary hypertension, and the intra-atrial septum and bi-atrial dilation. Strain and strain rate imaging show impaired myocardial function which progresses over time [93].

Treatment which is similar for all amyloidosis involving the heart requires management of the cardiac-related complications. Most patients develop CHF with volume overload and thus should be on a low-sodium diet (1–2 G of sodium per day). Patients should monitor their weights daily as well as their edema and ascites. Diuretics are the mainstay of therapy for CHF due to amyloid [89]. In addition certain cardiac drugs such as digoxin and calcium channel blockers are generally contraindicated as they might bind to the P component of the amyloid fibrils which can result in digoxin toxicity and in the case of calcium channel blockers severe and even fatal hypotension. Beta blockers are generally not useful in amyloid as they promote bradycardia as well as hypotension. Afterload reduction is often problematic due to

autonomic dysfunction and systemic or orthostatic hypotension [89]. Chronic oral anticoagulation is warranted in patients with atrial fibrillation to reduce the risk of systemic embolization and stroke. TTR has a proclivity for cardiac conduction disturbances and bradycardia so that pacemaker therapy is useful in this setting. It is unclear if defibrillators are effective in preventing sudden death in these patients as sudden death may be due to asystole or electromechanical dissociation [94, 95].

The most common type of AL amyloid produced by plasma cells in the bone marrow may be treated by autologous bone marrow transplantation or chemotherapy with thalidomide, melphalan, dexamethasone, bortezomib, lenalidomide, and bendamustine or with a combination of these medications [90]. AL amyloid therapy is focused on reducing or eliminating plasma cell production of free light chains. Response to therapy can be in part assessed by reduction in the cardiac biomarker for CHF (BNP). A 30 % reduction in levels is indicative of a positive response; however, progressive renal failure can cause increases in BNP and limit the utility of the BNP level for assessing the response to therapy [91].

Melphalan-dexamethasone is a standard regimen which is generally well-tolerated [96], but its effectiveness in patients with advanced cardiac disease is limited [91], with median survivals being between 10 and 18 months. Recently, bendamustine, an alkylating agent with a unique mechanism of action, has shown potential promise as a therapeutic agent. However, the data is limited on improving survival.

Combination therapy with immunomodulating drug thalidomide with dexamethasone and cyclophosphamide has shown benefits on end-organ responsiveness in 33 % of patients; however, toxicity occurs in up to 60 % of patients. The second-generation drug lenalidomide and third-generation agent pomalidomide in combination with dexamethasone are being assessed [90]. In small studies, 40–50 % of patients appear to be responders. The addition of alkylating agents increases the response rate but also the drug toxicity [91].

Protease inhibitor drugs such as bortezomib, ixazomib, and carfilzomib are being tested [97]. These drugs have been shown to be effective in reducing the production of free fibrillar light chains [98]. The newer protease inhibitors ixazomib and carfilzomib appear to have a greater protease inhibitor effect and less toxicity. These drugs are currently being evaluated in clinical trials [97].

In some patients with AL amyloid combined bone marrow and heart transplant or in patients with TTR, amyloid combined liver and heart transplantation may be effective in eliminating the source of amyloid production and restoring normal cardiac function [89, 93, 99]. A recent study has shown preliminary promising results using a therapeutic approach of RNA interference which reduced the production of transthyretin [92].

16.2 Part II: Management of Hypertrophic Cardiomyopathy

Many individuals affected by HCM are undiagnosed, most will not experience lethal events, and many will not have symptoms. However, those who develop symptoms such as dyspnea, angina, and lightheadedness can experience functional

disability secondary to heart failure and stroke as well as to sudden cardiac death (SCD). The development of atrial fibrillation puts these patients at substantial risk of stroke. Of note, the association of sleep apnea and HCM carries a high risk of atrial fibrillation [100], and thus HCM patients with sleep apnea should be treated for it in an attempt to reduce the risk of developing atrial fibrillation or its recurrence. Therapy of patients with HCM can be classified into medical, interventional/device, and surgical treatments (Chaps. 7 and 53).

16.2.1 Medical Treatment

Most of HCM patients are either asymptomatic or present with only minimal symptoms rendering them to a lower risk of SCD than patients who are symptomatic [101–104]. The majority of HCM patients are treated medically with the initial aim of reducing symptoms along with reducing the risk for SCD.

Currently there is no consensus on the ideal marker for identifying when to initiate therapy and how to appropriately adjust therapeutic goals. Some advocate the use of the LVOT pressure gradient to monitor and tailor therapy; however, these measurements can be quite variable on a daily basis [105]. Moreover, the association between the resting LVOT gradient, symptoms, and the risk of SCD is somewhat inconsistent [106]. BNP may be a useful biomarker to monitor (Chap. 12) and correlate with patients' symptoms and change in therapy.

Pharmacological therapy is the initial approach to treat symptoms related to HCM and can be subclassified into three categories: (1) symptom relief, including exercise intolerance, angina, or syncope; (2) arrhythmia management and prevention of SCD; and (3) prevention of disease progression. Table 16.3 details the different medications available for treatment of patients with HCM. Additional adjunct therapies such as initiation of anticoagulation once atrial fibrillation appears [107], as well as aggressive treatment for obstructive sleep apnea to prevent new onset or recurrence of atrial fibrillation are also recommended and are beyond the scope of this chapter (discussed in Chap. 50). As randomized clinical trials on therapeutic interventions in patients with HCM are scarce, most clinicians rely on their own experience as well as on expert consensus guidelines [107].

16.2.1.1 Medical Therapy for Symptomatic Relief

(a) *Beta-Adrenergic Receptor Blockers* (β-*Blockers*) (*Atenolol*, *Metoprolol*, *Bisoprolol*, *Propranolol*, and *Nadolol*)

β-Blockers are the most studied therapeutic class in patients with HCM and are regarded as the first-line therapy in patients with HCM for symptom relief. Their effectiveness is due to the negative chronotropic and inotropic effects: increase in diastolic filling time and attenuation of adrenergic-induced tachycardia, improving myocardial oxygen supply-demand and reducing myocardial

Table 16.3 Medical therapies for patients with hypertrophic cardiomyopathy

	Main use	Mechanism of action	Prevention of sudden cardiac death	Side effects	Comments
β-Blockers (atenolol; metoprolol; bisoprolol; propranolol; nadolol)	First-line therapy for symptomatic relief	Negative inotropic and chronotropic effect: Heart rate reduction Increase in diastolic filling time Improvement of myocardial oxygen supply-demand and reduction of myocardial ischemia	No (might be if started at younger age [107])	Bradycardia (especially if given in combination with CCBs) Hypotension Fatigue Depression Alopecia Impotence	Can reduce resting LVOT gradients as well as increase exercise-induced LVOT gradients β-Blockers with vasodilatory effects (i.e., carvedilol) should be avoided
Calcium channel blockers (CCBs) (verapamil; diltiazem)	An alternative in those who cannot tolerate β-blockers	Negative inotropic and AV nodal blocking effect Increased LV relaxation Small decrease in LVOT gradient Might reduce myocardial ischemia through coronary artery dilatory effect	No	Bradycardia (especially if given in combination with β-blockers) Hypotension	Should be used with caution in those with elevated PCWP as the can worsen heart failure Vasodilation can cause elevation of the LVOT gradient

(continued)

Table 16.3 (continued)

	Main use	Mechanism of action	Prevention of sudden cardiac death	Side effects	Comments
Disopyramide	Reduction of LVOT gradient and mitral regurgitation related to SAM of the mitral valve	Blunting of the sodium-calcium exchange system, decreasing myocardial inotropy Decrease of heart rate and slowing of conduction through the bundle of his Reduction of the LVOT gradient and mitral regurgitation (when related to systolic anterior motion) Reduction of LV wall stress Improves diastolic dysfunction	A trend toward reduction	Cardiac arrhythmias QT prolongation Urinary retention Dry mouth Exacerbation of glaucoma Side effects can be managed by concomitant use of pyridostigmine	A combination of disopyramide and a β-blocker is most effective for reduction of LVOT gradients Should not be used as monotherapy in patients with AF as it can enhance AV conduction
Amiodarone	Both rate and rhythm control of atrial fibrillation episodes in HCM patients	Class III antiarrhythmic also with β-blocking effects and negative inotropic effects	Controversial—data does not support the administration of amiodarone for reduction of SCD	QT prolongation Pulmonary fibrosis Thyroid dysfunction Liver toxicity Corneal deposits Skin discoloration	Must be stopped prior to initiation of disopyramide due to QT prolongation effect
Angiotensin receptor blockers (losartan; valsartan)	Reversal of interstitial fibrosis	Blockade of the AT_1 receptor, prevents cells form undergoing angiotensin II-induced changes Decrease in LV mass Decreases rest and exercise gradient	No	Growth retardation in children Hypotension	Decrease in blood pressure may increase LVOT gradients

ischemia [107]. β-Blockers can reduce or abolish both resting LVOT gradients as well as the increase in the LVOT gradient that occurs with exertion. This is also attributable to the negative inotropic and chronotropic actions of β-blockers. Slowing of the heart rate causes an increase in the diastolic filling time and thus an increase in LV end-diastolic volume along with a decrease in the end-diastolic pressure [108]. This results in more efficient inactivation of myocardial contractile proteins and improvement in diastolic filling time [107, 109]. β-Blockers also improve isovolumic relaxation in patients with HCM to <50 ms when adequately treated [110], suggesting that β-blockers increase LV compliance and improve diastolic dysfunction [52]. Reduction in heart rate also reduces myocardial scarring and fibrosis [111], which further decreases the substrate for arrhythmia [88, 112]. There is limited evidence suggesting improved survival with β-blocker therapy (when therapy is initiated in young patients) [113] (Chaps. 5 and 8).

Initial studies in HCM patients used propranolol. This drug has largely been replaced by longer-acting drugs (e.g., metoprolol and atenolol) with better tolerance and greater β-1 receptor selectivity. However, carvedilol and other β-blockers, which have vasodilatory effects, should not be used in patients with HCM due to their vasodilatory effects potentially causing an increase in the LVOT gradients, as well as worsening of mitral regurgitation secondary to systolic anterior motion of the mitral valve. β-Blocker therapy, especially when given in high doses, may lead to unwanted effects such as bradycardia, fatigue, hypotension, depression, alopecia, and impotence.

(b) *Calcium Channel Blockers* (*CCBs*) (*Verapamil* and *Diltiazem*)

Non-dihydropyridine CCBs mainly provide an alternative to patients who are unable to tolerate β-blocker therapy such as those with severe chronic obstructive lung disease or asthma. Although, as shown in Table 16.3, there is a difference in their mechanism of action, CCBs possess negative inotropic effects, as well as AV nodal blocking effects, producing a similar clinical effect as that of β-blockers. However, the effect of CCBS on diastolic dysfunction is controversial [107]. Verapamil has been the most commonly used and studied CCB in patients with HCM. CCBs increase LV relaxation through negative inotropic effect and can cause a small decrease in the LVOT gradient, an increase in the cardiac index, and an increase in exercise capacity [114]. Verapamil has also been shown to "normalize" LV diastolic filling and thus prevent hemodynamic compensation associated with the onset of atrial fibrillation in patients with HCM [115] (Chap. 37).

HCM patients show reversible ischemia secondary to an increased demand in the hypertrophied myocardium, intramural coronary artery medial thickening, or endothelial dysfunction [52]. Verapamil reduces and even eliminates perfusion deficits in some patients with HCM, as well as exercise-induced perfusion deficits [116–118]. Diltiazem has also been shown to improve measures of diastolic performance [119] and reduce myocardial ischemia [120] in HCM patients.

Major adverse events of CCBs include bradycardia and hypotension. CCBs should be used cautiously in HCM patients with elevated pulmonary capillary

wedge pressures as they have been associated with an increased risk of worsening CHF and even death in this setting. In patients with borderline blood pressure (systolic blood pressure <90 mmHg), CCBs can cause vasodilation and afterload reduction which can increase the LVOT gradient causing worsening mitral regurgitation and leading to potential hypotension. Administration of both β-blockers and CCBs should be done cautiously as this combination may cause severe bradycardia with or without high degree atrioventricular block. The dihydropyridine class CCBs should not be used in obstructive HCM patients as they cause afterload reduction which can aggravate LVOT gradients, mitral regurgitation, and hypotension [107].

(c) *Disopyramide*

Disopyramide is a class IA antiarrhythmic drug initially used to treat arrhythmias; it acts by blunting the sodium-calcium exchange system, decreasing myocardial inotropy. Its effects are somewhat similar to that of CCBs only without the effect of a lowered systemic blood pressure [121]. Disopyramide reduces the LVOT gradient and mitral regurgitation and may thus also increase forward stroke volume and blood pressure. Since the initial report of its clinical benefit in patients with HCM by Pollick [122], disopyramide has been shown to effectively reduce LVOT gradients, LV wall stress, and MR severity (when related to systolic anterior motion of the mitral valve), along with improving diastolic function in HCM patients. Despite its negative inotropic effects, disopyramide produces favorable hemodynamic effects, maintaining cardiac output, which might reflect a decrease in systolic anterior motion (SAM) and consequently a decrease the severity of resulting mitral regurgitation [123]. Invasive and noninvasive studies have shown that disopyramide improves LV pressure-volume curves and consequently diastolic dysfunction [124, 125] (Chap. 52).

Owing to its negative inotropic effect, disopyramide alone is more effective than β-blockers or CCBs in patients with dynamic LVOT gradients for reducing LVOT gradients [126]. The combination of disopyramide and a β-blocker had the greatest effect on reducing LVOT gradients as well as on improving clinical status [127]. In a large multicenter study evaluating 491 patients with LVOT gradients >30 mmHg, patients who received disopyramide had amelioration of symptoms in about 66 % of cases and a 50 % reduction in the outflow gradient over a period of ≥3 years. Despite initial concerns, disopyramide has not been found to be proarrhythmic in patients with a normal QT interval on ECG nor does it cause an increase in cardiac and sudden cardiac death. Treatment with disopyramide has shown a trend toward reducing SCD as well as all-cause mortality when compared to standard monotherapy [128]. In patients resistant to initial pharmacological therapy with β-blockers or CCBs, substantial symptom relief can be achieved along with low mortality through a stepped management that includes adding disopyramide to selected patients [129]. Thus, disopyramide treatment should be tried in obstructive HCM prior to proceeding to surgical or percutaneous interventions.

Disopyramide also reduces myocardial ischemia in patients with HCM. In patients who were treated with disopyramide, although there was no change in blood flow with the drug, the peak LV pressure and external work markedly decreased, leading to less oxygen demand and reduction in ischemia [130].

Disopyramide can cause QT interval prolongation. As with any antiarrhythmic medication, when initiating disopyramide therapy, monitoring for cardiac arrhythmias is needed as well as monitoring for QT prolongation. Caution should be used in patients receiving other QT prolonging medications, and the drug should not be used in those with a prolonged QTc as well as in patients with sinus node dysfunction (in the absence of a pacemaker) (Chaps. 46 and 49). Disopyramide should not be used as monotherapy in HCM patients without concomitant β-blocker or CCBs that block AV node conduction. If the patient develops atrial fibrillation, disopyramide can enhance AV conduction and dangerously lead to an increase in the ventricular rate [107]. Other adverse events include anticholinergic effects such as urinary retention, dry mouth, and membranes and exacerbation of closed-angle glaucoma. Anticholinergic side effects can be managed by dose reduction [107] or be reversed and prevented with the concomitant use of pyridostigmine [131]. Thus, the occurrence of anticholinergic side effects should not cause immediate cessation of disopyramide but rather initiation of therapy with pyridostigmine.

16.2.1.2 Medical Therapy for Prevention and Treatment of Arrhythmias in Patients with HCM

Amiodarone

Atrial fibrillation can complicate the clinical course of patients with HCM and is frequent when left atrial enlargement is present. The presence of AF generally leads to clinical deterioration of patients with HCM. The loss of atrial contribution to left ventricular filling and the increase in heart rate associated with AF cause a substantial increase in the risk for thromboembolic events. Amiodarone, a class III antiarrhythmic drug which also possesses β-adrenergic receptor antagonist effects and negative inotropic effects, is the only medication for which there is efficacy and safety data regarding treatment of AF in patients with HCM [132]. Amiodarone can control both rate and rhythm in HCM patients effectively by reducing embolic episodes as well as the need for cardioversion [133]. Amiodarone with or without β-blocker therapy is advocated for the treatment of AF and maintenance of rhythm control by the current AHA/ACC guidelines for the management of AF [134] (Chaps. 50 and 52).

While beneficial in the setting of AF, the role of amiodarone in preventing SCD, the most dreaded complication of HCM, is controversial. Amiodarone use for SCD is now less relevant with the advent of use of the automatic implanted cardioverter defibrillator (AICD). Initial reports suggested a protective effect of amiodarone in patients with HCM [135, 136]. However, subsequent studies have shown that amiodarone may actually increase the risk of lethal arrhythmias [137, 138]. In one study, 20 % of patients treated with amiodarone developed delayed conduction in the Hessian and Purkinje systems; of these, 50 % had a lower threshold for inducible ventricular tachycardia upon electrophysiologic testing [138]. Additional studies

have shown that despite therapy with amiodarone, the rate of SCD [139] or appropriate implantable cardioverter defibrillator (ICD) discharge [140] was high. Current data does not support the use of amiodarone to prevent SCD in most HCM patients.

The long-term use of amiodarone can be offset by its numerous side effects which include pulmonary fibrosis, thyroid function abnormalities, liver toxicity, corneal deposits, and skin discoloration. These, along with the potential for QT prolongation, limit the widespread utilization of amiodarone. In addition, because of potential QT prolongation, amiodarone cannot be used in conjunction with disopyramide. When initiating disopyramide therapy, patients need to be off amiodarone for several weeks, due to the long half-life of amiodarone. The QT interval needs to be checked before starting disopyramide and subsequent to its initiation in case the amiodarone effect on the QT interval is still present [128].

16.2.1.3 Medical Therapy for Prevention of Disease Progression

Angiotensin II AT_1 Receptor Blockers (ARBs) (Losartan and Valsartan)

Angiotensin II acts as a growth factor, which can cause hypertrophy of cardiac myocytes and mitogenesis of cardiac fibroblasts. These effects, resembling load-induced hypertrophy, are mediated mainly through the AT_1-R receptor. They may initiate a positive feedback regulation of this hypertrophy by inducing the angiotensin gene and transforming growth factor-beta 1 (TGFβ1) gene [141]. In vitro treatment of myocytes in cell cultures with losartan, an AT_1-R receptor blocker, prevented the cells form undergoing angiotensin II-induced changes. However, treatment with an investigational drug PD 123319, an angiotensin II AT_2 receptor (AT_2-R) blocker, did not have the same protective effect [141, 142]. As opposed to AT_1-R, the AT_2-R is expressed in low levels in the normal heart; however, it is upregulated in pathophysiological conditions including left ventricular hypertrophy (LVH) and plays a functional role in counterbalancing AT_1-R-mediated growth effects [142, 143]. Several studies show that stimulation of AT_2-R exerts an antigrowth effect in various cell types including cardiomyocytes [144], and AT_2-R blockade amplifies cardiac protein synthesis in hypertrophied hearts ex vivo [145]. Others have shown that pressure overload failed to induce LVH in AT_2-R knockout mice, suggesting that AT_2-R is obligatory for a hypertrophic response [146]. The ratio of AT_2-R to AT_1-R increases in failing hearts, suggesting that AT_2-R-related benefits can be further enhanced by drugs with combined AT_1-R blockade and AT_2-R agonist properties.

ARBs primarily act by blocking angiotensin 1 receptors (AT_1-R) which are present throughout the cardiovascular system. ARBs have been shown to be beneficial in patients with CHF, not only through reducing blood pressure but also through blocking the neurohormonal signaling in the heart [52, 147] (see Chap. 36 for discussion on ARBs and ACE-I). As opposed to angiotensin-converting enzyme inhibitors (ACE-I) that cause an overall decrease in the level of stimulating angiotensin II, thus reducing its activity at AT_1-R and AT_2-R sites, ARBs are more specific for blocking the AT_1-R subtype. Thus, it is contemplated that ARBs may have a more beneficial effect than ACE-I in HCM patients. Studies have shown that

the use of ARBs in HCM patients without LVOT gradients reduces symptoms and can also halt and cause reverse remodeling of the left atrium, improvement in LV diastolic function [148], and reduce LV mass [149, 150]. At the molecular level, procollagen alpha1, a precursor protein, which is converted into its active form in cardiac tissue, has been shown to increase cardiac fibrosis and correlate with early mortality through increased risk for SCD [151]. In HCM transgenic mice treated with losartan, significantly lower levels of procollagen alpha 1 and TGF-β1 were found, suggesting that this therapy can reverse interstitial fibrosis in HCM and have salutary effects in HCM patients [151].

16.2.1.4 Procedural/Interventional Treatment

Reduction of Symptoms

Other therapies aimed at reduction of the LVOT gradient, and thus reduction of symptoms includes surgical myectomy, catheter-based alcohol septal ablation, and dual-chamber pacing. Surgery and alcohol septal ablation should optimally be performed by experienced operators and only in patients with symptoms interfering with everyday activity despite optimal medical therapy, have a dynamic LVOT gradient of ≥50 mmHg which is associated with septal hypertrophy and systolic anterior motion of the mitral valve, and a septal thickness sufficient to perform the procedure [107]. Dual-chamber pacing has also been used to reduce LVOT pressure gradients in a small subset of mostly elderly patients. However, pacing has been less validated than septal reduction and should be reserved for those who are refractory to medical therapy and who cannot undergo either myectomy or alcohol septal ablation [107].

Prevention of SCD

Patients with HCM should undergo risk stratification for determination of risk for SCD. Therapy with an AICD has been shown to be effective in treatment of ventricular arrhythmias and preventing SCD in HCM patients [152]. Risk factors for sudden cardiac death are listed in Table 16.4. Absolute indications for defibrillator placement include history of SCD, ventricular fibrillation, or hemodynamically significant ventricular tachycardia, in those with a wall thickness of ≥3 cm and unexplained syncope episodes and in those with an abnormal response to exercise who have additional risk factors or modifiers for SCD [107] (also see Chap. 7).

Heart Transplantation

A recent analysis within a large US transplant cohort demonstrated that the prevalence of transplantation due to HCM was about 1 %/year, similar to patients with restrictive cardiomyopathy, but significantly less than ischemic or dilated

Table 16.4 Risk factors for sudden cardiac death (SCD) in patients with hypertrophic cardiomyopathy (HCM) [107]

Established risk markers for SCD
Personal history of an episode of either ventricular fibrillation, sustained ventricular tachycardia (VT), or an event of SCD, including appropriate therapy which terminated an episode of SCD
Family history of SCD, including appropriate therapy which terminated an episode of SCD
Unexplained syncope
Documented non-sustained VT: 3 or more beats at greater than or equal to 120 beats per minute
Left ventricular (LV) wall thickness of >3 cm
Inappropriate response to exercise testing: failure to increase the systolic blood pressure by 20 mmHg or a drop of at least 20 mmHg during effort
Other potential risk modifiers for SCD
Late gadolinium enhancement on MRI
Genetic mutations
Marked LVOT obstruction (>30 mmHg)
LV apical aneurysm

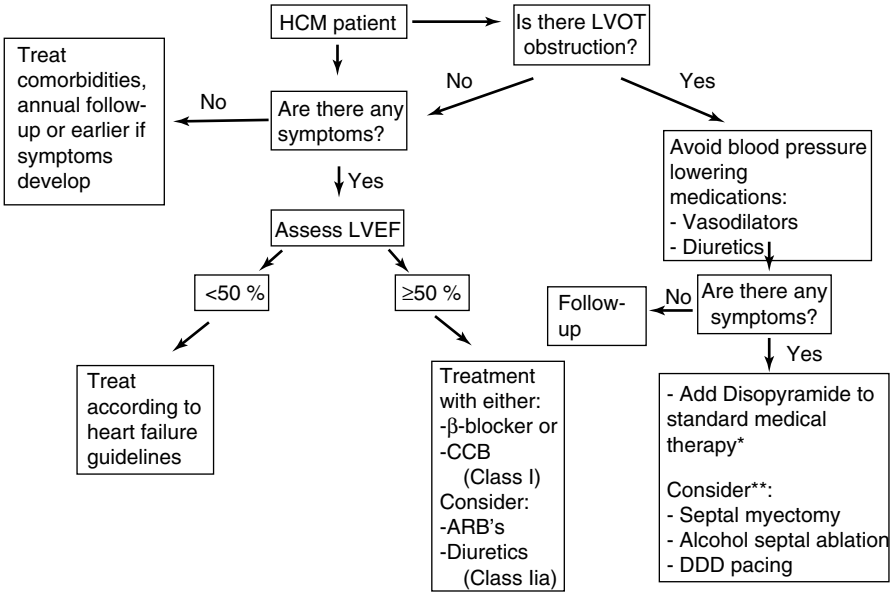

Fig. 16.4 Treatment scheme for patients with hypertrophic cardiomyopathy (HCM). *LVEF* left ventricular ejection fraction. *Maximal medical therapy should be used, including disopyramide, before proceeding with surgery/interventional therapy. Disopyramide should be used in conjunction with β-blocker therapy. **The ideal treatment option will be determined according to the patient's risk for surgery (Adapted with permission from Gersh et al. [107])

cardiomyopathy [153]. HCM patients who underwent transplantation had a 1-, 5-, and 10-year survival of 85 %, 75 %, and 61 %, respectively [153], comparable to other, non-HCM-related cardiac transplantation. Heart transplantation should be reserved as a practical therapeutic option in patients with HCM who develop

advanced CHF despite medical and/or septal reduction therapy (surgical or percutaneous); heart transplant may be the only viable therapeutic option [153].

16.3 Concluding Remarks

Myocardial hypertrophy is a phenotype that is secondary to multiple cardiac disease entities, but it is the primary manifestation of HCM, as it occurs in the absence of LV pressure overload. HCM is an inherited heart disease occurring in 1 in 500 people along with the occurrence of spontaneous variants. It presents with a diverse and complex clinical presentation, which can lead to marked morbidity and mortality if left untreated. As detailed in this chapter and outlined in Fig. 16.4, the current medical options primarily address reduction of symptoms. Patients with the obstructive form of this disease who are symptomatic might also benefit from procedural/interventional treatment. At present with current therapy, the disease-related mortality is <1 %/year. However, there is no evidence that gradient reduction therapy, which frequently improves symptoms, enhances longevity. Ongoing research is directed at developing a more complete understanding of this disease along with improved diagnostic and therapeutic capabilities, which should allow better patient management and improved quality of life.

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