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Circulating Biomarkers in Hypertrophic Cardiomyopathy

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ABSTRACT: Hypertrophic cardiomyopathy is the most common genetic heart disease. Biomarkers, molecules measurable in the blood, could inform the clinician by aiding in diagnosis, directing treatment, and predicting outcomes. We present an updated review of circulating biomarkers in hypertrophic cardiomyopathy representing key pathologic processes including wall stretch, myocardial necrosis, fibrosis, inflammation, hypertrophy, and endothelial dysfunction, in addition to their clinical significance.

Key Words: biomarker ■ cardiac imaging ■ hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease. The genetic defect results in diverse phenotypic expressions, but the "classic" phenotype involves asymmetric left ventricular (LV) hypertrophy in the absence of precipitating factors. Although originally considered a monogenically inherited disease,[1] it is now known that most cases of HCM are polygenic and multifactorial.[2,3] Prevalence early on was estimated to be 1 in 500,[4] but recent studies indicate HCM may be more common, approximating 1 in 200 patients.[5] Although most affected individuals experience a clinically benign course, subsets of patients develop complications including heart failure, LV outflow tract obstruction, atrial and ventricular arrhythmias, and sudden cardiac death.[6] In the HCMR (Hypertrophic Cardiomyopathy Registry), 2 populations of patients were identified, 1 positive for the genetic sarcomere mutation and 1 negative for the mutation.[2] The genotype positive and negative groups were very different regarding morphology of the hypertrophy, extent of fibrosis, and presence of obstruction on cardiac magnetic resonance (CMR) imaging, highlighting the importance of examining clinical and imaging aspects of HCM and their correlation to molecules measurable in the blood related to the disease process. Such molecules, termed biomarkers, could inform the clinician by aiding in diagnosis, directing treatment, and predicting outcomes. The last comprehensive review of this subject was published in 2009.[7] We present an updated review related to biomarkers in HCM with a special emphasis on their correlations to cardiac imaging findings and clinical outcomes.

METHODS

Search Strategy

We performed a comprehensive literature search using MEDLINE database, Embase, and Google Scholar. The following search terms were used: hypertrophic cardiomyopathy, hypertrophic obstructive cardiomyopathy, obstructive hypertrophic cardiomyopathy, idiopathic hypertrophic cardiomyopathy, asymmetric hypertrophic cardiomyopathy, apical hypertrophic cardiomyopathy, familial hypertrophic cardiomyopathy, biomarker, biological marker, and biochemical marker. All papers were reviewed for content (E.L.M. and E.C.K.). The literature search was limited to (1) human studies, (2) English language, (3) measurement of circulating blood biomarkers, and (4) published since the last comprehensive review in 2009.[7] There was no minimum size for inclusion. Citations of all appropriate

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Nonstandard Abbreviations and Acronyms

GDF	growth differentiation factor
HCM	hypertrophic cardiomyopathy
HCMR	Hypertrophic Cardiomyopathy Registry
LGE	late gadolinium enhancement
MMP	matrix metalloproteinase
NYHA	New York Heart Association
vWF	von Willebrand factor

articles were screened to find additional, relevant studies. For each category of biomarker, we review its source, its correlation with HCM phenotypic features and functional characteristics, and its relationship to therapy and clinical outcomes, if available.

Biomarkers of Myocardial Wall Stretch

This category includes members of the natriuretic peptide family (brain-type natriuretic peptide [BNP]), atrial natriuretic peptide, and NT-proBNP (N-terminal pro-B-type natriuretic peptide). Natriuretic peptides, hormones secreted by the heart in response to increased wall tension or stretch,[8] are elevated in HCM[7] and are associated with imaging findings (Table 1). BNP and atrial natriuretic peptide are both associated with LV fibrosis on CMR,[12,14,16,25] and BNP is associated with LV mass.[12] Elevated BNP is associated with an increased risk of adverse cardiovascular events[15] and is a predictor of New York Heart Association (NYHA) functional class and need for septal reduction therapy,[13] heart failure hospitalization,[10] ventricular tachycardia,[16] and death in those undergoing septal myectomy.[9] Elevated BNP is also associated with an increased risk of sudden cardiac death[11] and is predictive of silent myocardial ischemia in HCM.[17] NT-proBNP also correlates with LV mass, LV mass index, and late gadolinium enhancement (LGE) on CMR.[18] In HCMR, NT-proBNP levels were significantly higher in patients who were mutation positive and in those with reduced LV systolic function, and a resting LV outflow tract gradient ≥30 mm Hg.[2] Furthermore, NT-proBNP levels correlated with increasing maximal wall thickness, extent of LGE and extracellular volume on CMR in a graded fashion.[2] Others have reported elevated NT-proBNP levels in patients with overt HCM compared with mutation carriers without LV hypertrophy,[24] and positive correlation with left atrial volume,[22] signal intensity coefficient on echocardiography,[20] and advanced stages of the disease.[19] Lastly, NT-proBNP is a predictor of heart failure and heart transplant-related death[23] and an effective screening tool for first-degree relatives of patients with HCM.[21] Natriuretic peptides are readily available in most clinical settings and provide important information with respect to volume status. Because they have been shown to correlate with noninvasive imaging findings of LV mass, LV wall thickness, and the presence of myocardial fibrosis, they can serve as surrogate markers and, therefore, provide important information that could affect clinical decision-making in the population with HCM. Moreover, used as a biomarker in HCM, natriuretic peptides provide crucial prognostic information including the subsequent risk of heart failure, ventricular arrhythmias, and death.

Biomarkers of Myocardial Necrosis

Cardiac troponin T and I, components of striated muscle sarcomeres, are highly sensitive for acute myocardial necrosis.[26] Since the prior review,[7] a substantial amount of new data has emerged in this category (Table 2). Troponin T and I are both elevated in HCM, and are associated with LGE on CMR,[14,18,24,27,32] and global myocardial strain and maximal LV thickness on echocardiography.[28] Elevated troponin T and I levels have also been associated with LV mass on CMR.[29–31,33–35,37] In one study of subjects with HCM and preserved LV function, elevated hs-cTnT (high-sensitivity cardiac troponin T) level was an independent predictor of subsequent LV dysfunction and progression to end-stage HCM over a mean follow-up of 6.3±2.8 years.[38] In another study, postexercise hs-cTnT levels rose in ~20% of patients with overt HCM compared with only 4% in mutation carriers without LV hypertrophy (P=0.01), and high signal intensity on T2-weighted CMR was an independent predictor of the rise of hs-cTnT.[39] In HCMR, levels of hs-cTnT were similar in participants who were mutation positive and negative and increased in a stepwise fashion with maximal wall thickness and extent of LGE on CMR in both men and women and with extracellular volume in men.[2] Elevated hs-cTnT levels correlate with NYHA class, outflow obstruction, systolic dysfunction, abnormal blood pressure response, presence of LGE on CMR, and disease severity in HCM[37] and are an independent predictor adverse events.[36,40] Several studies have investigated the predictive value of using a combination of elevated BNP and hs-cTnT levels: In one the combination was predictive of myocardial fibrosis on CMR,[14] and in another it was associated with ~12% increased risk of cardiovascular events.[15] Like the natriuretic peptides, troponin T and I levels, especially high-sensitivity forms, are readily available to measure in most clinical settings. In addition to correlation with noninvasive imaging findings such as increased LV mass, wall thickness, and fibrosis, biomarkers of myocardial necrosis also provide prognostic information including worsening LV function, lower exercise capacity, and increased major adverse events. Long-term follow-up of HCMR

Table 1. Biomarkers of Myocardial Wall Stretch in Hypertrophic Cardiomyopathy

Biomarker	# Subjects	Findings	Ref #
Brain natriuretic peptide	758 HCM No controls	Preoperative levels predicted 2-year mortality following myomectomy	[9]
	98 HCM No controls	Predictor for hospitalization for congestive heart failure	[10]
	346 HCM No controls	Risk of sudden cardiac death higher with levels >312 pg/mL	[11]
	109 HCM No controls	Positive correlation with clinical outcomes, LV fibrosis, and LV mass on CMR	[12]
	772 HCM No controls	Predictor of New York Heart Association functional class and future need for septal reduction therapy	[13]
	53 HCM (33 with fibrosis on CMR)	Associated with myocardial fibrosis	[14]
	167 HCM No controls	Elevated levels associated with 11.7% increased risk of cardiovascular events	[15]
	26 HCM (6 with ventricular tachycardia)	Elevated levels associated with ventricular tachycardia and LGE on CMR	[16]
	31 HCM 10 healthy controls	Levels measured during rest predicted silent myocardial ischemia	[17]
NT-proBNP	2755 HCM No controls	NT-proBNP higher in patients with resting LV outflow tract ≥30 mm Hg, reduced LV ejection fraction, baseline arrhythmia, sarcomere mutation+ Increased with increasing maximal wall thickness and LGE on CMR	[2]
	60 HCM No controls	Positive correlation with LV mass and maximal wall thickness on CMR	[18]
	61 HCM (20 obstructive, 41 nonobstructive) No controls	Higher levels in advanced stages Negative correlation with coronary flow reserve Positive correlation with septal ratio quotient of mitral inflow *E* (by pulsed Doppler), and septal *e′* measured by tissue Doppler	[19]
	36 HCM 10 healthy controls	Significant correlation with signal intensity coefficient on echocardiography	[20]
	106 first-degree relatives of patients with HCM No controls	Levels >70 pg/mL was an effective screening tool for high-risk first-degree relatives	[21]
	75 HCM No controls	Associated with left atrial volume	[22]
	847 HCM No controls	Predictor of heart failure and transplant-related death	[23]
	76 HCM 50 mutation+ LV hypertrophy-41 genotype-negative related controls	Elevated in HCM Exaggerated increase with exercise	[24]
Midregional proatrial natriuretic peptide	40 HCM No controls	Predictor of myocardial fibrosis by LGE on CMR	[25]

CMR indicates cardiac magnetic resonance; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricular; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

should provide additional information regarding the prognostic value of NT-proBNP and hs-cTnT alone and in combination.

Biomarkers of Fibrosis

Myocardial fibrosis is a key pathologic process in HCM and can lead to LV stiffness, manifesting clinically as diastolic dysfunction.[41] Replacement fibrosis (detected by LGE) and diffuse interstitial fibrosis (detected by T1 mapping and measurement of extracellular volume) are important findings on CMR in patients with HCM. Biomarkers in this category are summarized in Table 3. Plasma levels of procollagen type I carboxy-terminal (cleaved from procollagen during collagen I synthesis) are elevated in patients with HCM compared with controls[50,53] and is associated with extracellular volume on CMR, and collagen volume fraction measured in septal myectomy samples.[42] Procollagen type III amino-terminal propeptide (byproduct of type III collagen synthesis) was increased in overt HCM but not in mutation carriers only in one study,[50] whereas in another, there was no correlation between blood levels and myocardial fibrosis on CMR.[51] The ratio of N-terminal

Table 2. Biomarkers of Myocardial Necrosis in Hypertrophic Cardiomyopathy

Biomarker	# Subjects	Findings	Ref #
Cardiac troponin I	116 HCM No controls	Positively correlated with LGE on CMR	[27]
	167 HCM No controls	Positive correlation with global longitudinal strain and maximum LV thickness on echocardiography	[28]
	149 HCM No controls	Correlated with maximum wall thickness, LV end-diastolic and end-systolic volume index, and LV mass index	[29]
	162 HCM No controls	Associated with maximum LV thickness and E/Ea, and male sex	[30]
High-sensitivity cardiac troponin I	107 subjects screened for HCM 24 borderline HCM (MWT 13–14 mm) 19 definitive HCM (MWT ≥15 mm)	Graded, positive association with LV mass in HCM and in those at risk of HCM	[31]
	76 HCM 50 mutation+ LVH- 41 genotype-negative related controls	Elevated in HCM	[24]
High-sensitivity cardiac troponin T	2755 HCM No controls	Higher in racial and ethnic minority groups, patients with hypertension, LV outflow tract ≥30 mm Hg, increased wall thickness, reduced LV ejection fraction Increased with increasing maximal wall thickness and LGE on CMR	[2]
	60 HCM No controls	Positive correlation with LV mass, maximal wall thickness, and LGE on CMR	[18]
	98 HCM No controls	Associated with LGE on CMR	[32]
	91 HCM No controls	Associated with maximum wall thickness, myocardial fibrosis, and lower exercise capacity	[33]
	98 HCM No controls	Associated with maximum LV thickness≥30 mm, LA area index and E/Ea septal	[34]
	62 HCM No controls	Associated with LV mass	[35]
	53 HCM	Associated with myocardial fibrosis by LGE on CMR	[14]
	183 HCM No controls	Associated with increased risk of adverse cardiovascular events	[36]
	95 HCM 45 healthy controls	Associated with maximum LV wall thickness and LA diameter Correlated with NYHA class, outflow obstruction, systolic dysfunction, abnormal blood pressure response, LGE, and disease severity	[37]
	157 HCM No controls	Elevated levels were associated with worsening LV systolic function	[38]
	127 HCM 53 mutation+ LV hypertrophy-	Postexercise increases in 20% of HCM High T2 on CMR was independent predictor of troponin rise	[39]
	135 HCM No controls	Elevated levels at baseline were associated with >4-fold risk of major adverse events at 5-year follow-up	[40]

CMR indicates cardiac magnetic resonance; HCM, hypertrophic cardiomyopathy; LA, left atrial; LGE, late gadolinium enhancement; LV, left ventricular; and MWT, maximal wall thickness.

propeptide of type I procollagen (measure of collagen I synthesis) to collagen type I pyridinoline cross-linked C-terminal telopeptide (measure of collagen I degradation) was higher in HCM compared with controls and associated with more severe diastolic dysfunction as measured by echocardiography.[52]

An imbalance of matrix metalloproteinases (MMPs) and tissue inhibitor metalloproteinases may contribute to a profibrotic state in HCM.[71] Several investigators have reported increased levels of MMPs and tissue inhibitor metalloproteinases in HCM[43] and correlations with fibrosis on CMR,[42,49] LV remodeling,[46,47] left atrial volume,[22] ventricular tachycardia,[45] and atrial fibrillation.[48] In 1 study, MMP-9 was associated with adverse clinical events in women, and MMP-3 was a predictor of adverse events independent of sex and extent of LGE on CMR.[49]

Galectin-3, a protein that modulates fibrosis,[72] is elevated in patients with heart failure with preserved ejection fraction.[73] This biomarker is also elevated in patients with HCM compared with controls[55,57] and has been associated with septal thickness and LV mass index on echocardiography,[57] NYHA functional

Table 3. Biomarkers of Fibrosis in Hypertrophic Cardiomyopathy

Biomarker	# Subjects	Findings	Ref #
MMP, TIMP	52 HCM No controls	MMP-2 associated with ECV on CMR	[42]
	23 HCM 16 offspring of patients with HCM who are phenotype negative 66 healthy controls	Significantly higher levels of MMP-1 and TIMP-1 in HCM compared with other groups	[43]
	17 HCM 17 healthy controls	Significantly higher levels of TIMP-2 in HCM compared with controls	[44]
	45 HCM No controls	MMP-3 positively associated with VT	[45]
	16 HCM No controls	MMP-2 correlated with worsening LV systolic function on echocardiography MMP-9 correlated with maximum LV wall thickness on echocardiography	[46]
	41 HCM No controls	MMP-2 and TIMP-1 directly correlated with LV end-systolic dimension and LA dimension, and indirectly with LV ejection fraction MMP-9 showed no correlation MMP-2 associated with severe symptoms and worse outcomes MMP-2 and TIMP-1 correlated indirectly with LV function	[47]
	43 HCM No controls	MMP-2 correlated with higher LA volume	[22]
	55 obstructive HCM No controls	MMP-2/TIMP-1 ratio correlated with microvascular density MMP-2/TIMP-1 ratio predicted development of atrial fibrillation	[48]
	54 HCM No controls	Increased MMP-9 associated with LGE on CMR and adverse events in women. MMP-3 associated with higher event rate independent of sex and extent of LGE	[49]
	40 HCM No controls	MMP-9 and TIMP-1 were not associated with the extent of LGE on CMR	[25]
Collagen turnover	55 obstructive HCM No controls	PICP/ICTP ratio predicted development of atrial fibrillation	[48]
	38 HCM mutation+ LVH+ 39 HCM mutation+ LVH- 30 healthy, mutation-negative relative controls	PICP levels elevated in HCM PIIINP levels and PICP/CITP ratio increased in clinical HCM but not in mutation carriers only	[50]
	50 HCM 25 healthy controls	CITP had measurable myocardial concentration gradient, but not measurable in peripheral blood No correlation between PINP and PIIINP levels and CMR or echocardiographic findings of fibrosis	[51]
	36 HCM 21 controls with normal LV thickness	Higher PINP/ICTP ratio in HCM associated with resting diastolic dysfunction on echocardiography	[52]
	23 HCM 16 offspring of patients with HCM who are phenotype negative 66 healthy controls	Patients HCM with *E/e'*>8 had significantly higher ICTP levels compared with the other groups	[43]
	52 HCM No controls	PICP associated with ECV on CMR Plasma PICP correlated with myocardial PICP Calcium channel blocker treatment associated with lower serum and myocardial PICP levels, and less fibrosis measured by ECV on CMR	[42]
	37 mutation+ LVH+ 29 mutation+ LVH- 11 healthy controls	PICP elevated in HCM	[53]

(*Continued*)

Table 3. Continued

Biomarker	# Subjects	Findings	Ref #
Galectin-3	53 HCM No controls	Correlated with increased risk of sudden cardiac death	[54]
	60 HCM No controls	No correlation with LV wall thickness, mass	[18]
	57 HCM 18 healthy controls	Higher levels in HCM and associated with NYHA class	[55]
	76 HCM 50 mutation+ LVH- 41 genotype-negative related controls	No different difference across groups	[24]
	107 HCM 85 DCM	Addition of galectin-3 to LGE improved prognostic value than LGE alone	[56]
	40 HCM 35 healthy controls	Levels increased in HCM	[57]
Soluble suppressor of tumorigenicity 2	60 HCM No controls	Correlated with LV wall thickness and mass	[18]
	57 HCM 18 healthy controls	Levels higher in HCM and associated with NYHA class and nonsustained VT	[55]
	76 HCM 50 mutation+ LVH- 41 genotype-negative related controls	No different difference across groups	[24]
Adiponectin	26 HCM No controls	Elevated levels associated with diastolic dysfunction	[58]
	106 HCM No controls	Associated with LV systolic dysfunction	[59]
Aldosterone	8 HCM undergoing septal myectomy 12 heart-beating organ donor controls	Similar cardiac and serum aldosterone levels in HCM as normal hearts	[60]
	53 HCM No controls	Aldosterone inhibitors had no significant impact on clinical or imaging outcomes at 1-year follow-up	[61]
Copeptin	40 HCM No controls	No relationship to fibrosis on CMR	[25]
	24 obstructive HCM 36 nonobstructive HCM 36 healthy controls	Elevated in HCM Correlated with IV septal thickness, LA diameter, and LV outflow tract gradient Correlated with adverse cardiac events	[62]
Transforming growth factor-beta	49 HCM 40 healthy controls	Levels increased in HCM Associated with higher NYHA class and adverse events	[63]
	109 HCM No controls	Elevated levels predicted atrial fibrillation postmyectomy	[64]
Urotensin II	40 HCM 30 healthy controls	Elevated levels inversely associated left ventricular ejection fraction	[65]
Scleraxis	46 HCM 20 healthy controls	Higher in HCM No correlation with LV thickness, LGE, or disease severity	[66]
Osteopontin	43 HCM 64 DCM 75 healthy controls	Higher in DCM No different in HCM compared with controls	[67]
Cathepsin	23 HCM 16 offspring of patients with HCM who are phenotype negative 66 healthy controls	Higher in HCM Correlated with LV mass index and *E/e′* on echocardiography	[43]
Endostatin	23 HCM 16 offspring of patients with HCM who are phenotype negative 66 healthy controls	Higher in HCM Inversely correlated to adenosine perfusion by CMR Correlated with LV mass index and *E/e′* on echocardiography	[43]
Myostatin	23 HCM 16 offspring of patients with HCM who are phenotype negative 66 healthy controls	Levels were lower in the HCM-risk group compared with the other groups	[43]

(*Continued*)

Table 3. Continued

Biomarker	# Subjects	Findings	Ref #
Fibronectin	17 HCM 17 healthy controls	Fibronectin levels were significantly lower in HCM	[44]
Apelin	116 HCM No controls	Apelin negatively correlated with LGE on CMR	[27]
Omentin-1	87 HCM 50 healthy controls	Low levels in HCM compared with controls Correlated with elevated IV septal thickness, and LA diameter Low levels associated with adverse cardiac events	[68]
Tenascin-C	36 HCM No controls	Elevated levels in HCM Associated with heart failure events	[69]
Midregional-proadrenomedullin	40 HCM No controls	Levels showed no relationship to fibrosis on CMR	[25]
Cardiotrophin	124 HCM 29 healthy controls	Increased in HCM Correlated with maximal LV thickness on echocardiogram	[70]

CITP indicates C-telopeptide for type I collagen; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; ECV, extracellular volume; *E/e′*, septal ratio quotient of mitral inflow *E* (by pulsed Doppler) and septal *e′* measured by tissue Doppler; HCM, hypertrophic cardiomyopathy; ICTP, carboxyterminal telopeptide of type I collagen; IV, intraventricular; LA, left atrium; LV, left ventricular; LVH, left ventricular hypertrophy; MMP, matrix metalloproteinase; NYHA, New York Heart Association; PICP, C-terminal propeptide of procollagen type I; PIIINP, N-terminal propeptide of procollagen type III; PINP, amino-terminal propeptide of type I collagen; TIMP, tissue inhibitor of metalloproteinase; and VT, ventricular tachycardia.

class,[55] and the risk of sudden death.[54] In at least 1 study, the combination of galectin-3 levels and extent of LGE on CMR may improve prognostic value compared with LGE alone.[56]

The suppression of tumorigenicity (ST)-2/IL-33 (interleukin-33) system is induced with myocardial stretch and overload.[74] The ligand for ST-2, IL-33, binds to activate cardioprotective effects that are anti-inflammatory and antifibrotic.[74] Soluble sST-2 (soluble suppressor of tumorigenicity-2) is a plasma protein that counteracts the protective effects of ST-2/IL-33 by binding with IL-33 and competing for ST-2 as a decoy receptor. In HCM, sST-2 is associated with LV wall thickness,[18] NYHA functional class, and nonsustained ventricular tachycardia.[55] Other biomarkers including transforming growth factor-beta,[63,64] fibronectin,[44] tenascin-C,[69] apelin,[27] osteopontin,[67] scleraxis,[66] cardiotrophin-1,[70] cathepsin S, endostatin, and myostatin[43] have been studied in HCM with varying results. Although some reported higher[43,63,64,66,69,70] or lower[44] circulating levels in patients with HCM, few studies showed any correlation with cardiac imaging[43,67,70] or clinical outcomes,[63,64,69] limiting their use clinically. These studies are small, and findings need to be validated in larger cohorts.

Aldosterone, a hormone involved in the renin-angiotensin-aldosterone system, plays an important role in myocardial fibrosis[75] and has been studied in HCM. In patients with HCM undergoing septal myomectomy, aldosterone levels measured in myocardial tissue were the same as those measured in hearts of organ donors, and aldosterone levels measured in the plasma of patients with HCM were normal to low,[60] suggesting against increased aldosterone production in HCM. Moreover, a prospective, randomized, double-blinded, placebo-controlled trial of 53 patients with HCM randomized to the aldosterone antagonist, spironolactone, or placebo found no difference between circulating biomarkers of collagen formation and degradation, imaging findings, or clinical outcomes at 1-year follow-up.[61] Adiponectin,[58,59] omentin-1,[68] copeptin,[62] midregional proadrenomedullin,[25] and urotensin-II[65] have all been studied in HCM. Several of these biomarkers have been associated with structural findings such as diastolic dysfunction,[58] LV systolic dysfunction,[59,65] increased interventricular septal thickness, left atrial diameter, and septal ratio quotient of mitral inflow *E* (by pulsed Doppler) and septal *e′* measured by tissue Doppler ratio,[68] and increased adverse cardiac events.[62,68] In summary, galectin-3, sST-2, transforming growth factor-beta, MMP-2, MMP-3, urotensin-II, adiponectin, and tenascin-C have been shown to be predictive of adverse clinical outcomes including sudden death,[54] heart failure,[47,55,69] atrial fibrillation,[48,64] ventricular tachycardia,[45] and diastolic and systolic dysfunction[58,59,65] in HCM. In general, these biomarkers are mainly used in a research setting, not clinically. Galectin-3 has been studied in several small studies by different investigators with mixed results. When compared with healthy controls, however, galectin-3 levels were higher in patients with HCM in 2 separate studies.[55,57] More studies assessing the clinical utility, if any, of biomarkers of fibrosis in HCM need to be performed.

Biomarkers of Inflammation and Apoptosis

This category includes studies of uric acid (metabolite of purine degradation) and CRP (C-reactive protein) (Table 4). Elevated uric acid levels are an independent predictor of adverse events, including death, heart failure, and arrhythmia in HCM,[76–78] especially in women.[79] Mixed results have been reported for GDF-15 (growth

differentiation factor-15), a member of the transforming growth factor-beta cytokine family.[80,81] To date, no significant correlation of GDF-15 levels with cardiac imaging findings has been reported.[18,32] In a study measuring tumor necrosis factor-alpha levels in patients with HCM and a healthy control group, investigators reported significantly higher circulating levels of tumor necrosis factor-alpha in HCM.[84] CRP is elevated in HCM[82] and is associated with increased left atrial volume[22] and LGE on CMR.[82] In 1 large observational cohort study, patients with HCM and elevated levels of hs-CRP (>3.0 mg/dL) had increased risk of adverse cardiac events compared with those with lower levels (<1.0 mg/dL), including cardiac death (adjusted hazard ratio, 5.41 [95% CI, 1.96–14.93], *P*=0.024),[83] suggesting an association between chronic inflammation and progression of disease. CRP, hs-CRP, and uric acid are readily available in most clinical settings. Although studies evaluating uric acid[76–79] and hs-CRP[83] were large, no controls were enrolled limiting the applicability of the results. Future studies comparing uric acid and CRP levels in both HCM and control subjects are needed to determine their possible contribution more fully in this field.

Biomarkers of Endothelial Dysfunction and Hemostasis

Biomarkers reflecting endothelial dysfunction and hemostasis in HCM are summarized in Table 5. Both endothelin-1, a potent vasoconstrictor, and big-endothelin, its precursor, are elevated in HCM and are associated with LGE on CMR and adverse clinical outcomes including progression of NYHA functional class, death,[85] and atrial fibrillation.[86,87] Asymmetric dimethylarginine, a nitric oxide synthase inhibitor that competes for arginine, is a marker of endothelial dysfunction and is positively correlated with the extent of diastolic dysfunction in patients with HCM.[91] Increased sheer stress from the outflow tract gradient is thought to cleave high molecular weight multimers of von Willebrand's Factor (vWF) and result in acquired vWF syndrome in patients with HCM. From a clinical standpoint, this increases their risk of bleeding.[94] Several studies have reported that vWF levels correlate with LV outflow tract gradient, and adverse clinical outcomes.[88–90] In 1 prospective study of patients with obstructive HCM, vWF multimers that were abnormal at baseline partially normalized after septal ablation and completely normalized after

Table 4. Biomarkers of Inflammation and Apoptosis in Hypertrophic Cardiomyopathy

Biomarker	# Subjects	Findings	Ref #
Uric acid	317 obstructive HCM No controls	Independent predictor of cardiac death	[76]
	454 HCM No controls	Both high and low serum levels were associated with increased risk of all-cause mortality and HCM-related mortality	[77]
	588 HCM No controls	Independent predictor of major adverse cardiac events including death, heart failure, and arrhythmia	[78]
	161 obstructive HCM No controls	Independently associated with left ventricular mass index on CMR in women but not men	[79]
Growth differentiation factor-15	93 pts hypertensive LVH 28 HCM 28 healthy controls	Elevated in hypertensive LVH compared with HCM and controls Predictive of hypertensive LVH	[80]
	102 HCM No controls	Elevation associated with more severe disease Associated with dyspnea and NYHA class	[81]
	60 HCM No controls	No correlation with hypertrophy or fibrosis	[18]
	98 HCM No controls	No correlation with imaging findings on CMR	[32]
CRP	75 HCM No controls	Elevated levels associated with increased left atrial volume	[22]
	24 HCM 17 healthy controls	Increased CRP associated with histopathological myocardial fibrosis	[82]
hs-CRP	490 HCM No controls	Associated with increased risk for sudden cardiac death, cardiovascular death, heart failure-related death, and all-cause mortality	[83]
	24 HCM 17 healthy controls	hs-CRP was positively correlated with LGE on CMR	[82]
TNF-alpha	24 HCM 17 healthy controls	TNF-alpha was positively correlated with LGE on CMR	[82]
	50 HCM 20 healthy controls	Increased in HCM	[84]

CMR indicates cardiac magnetic resonance; CRP, C-reactive protein; GDF,; HCM, hypertrophic cardiomyopathy; hs, high sensitivity; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; and TNF, tumor necrosis factor.

Table 5. Biomarkers of Endothelial Dysfunction and Hemostasis in Hypertrophic Cardiomyopathy

Biomarker	# Subjects	Findings	Ref #
Big endothelin-1	252 HCM No controls	Increased level associated with worse clinical outcomes and late gadolinium enhancement on CMR	[85]
	118 obstructive HCM No controls	Increased level associated with postmyectomy atrial fibrillation	[86]
	375 HCM (90 with atrial fibrillation, 285 without atrial fibrillation) No controls	Increased level associated with atrial fibrillation	[87]
vWF	62 obstructive HCM 28 nonobstructive HCM 10 healthy controls	Abnormal in obstructive compared with nonobstructive HCM Correlated with left ventricular outflow tract gradient Normalized after surgical myomectomy	[88]
	62 HCM (28 obstructive, 33 nonobstructive) No controls	Lower ratio of vWF-collagen-binding to antigen in obstructive HCM Correlated with degree of outflow tract obstruction	[89]
	124 HCM 59 healthy controls 20 ischemic heart disease	Increased level correlated with obstruction, worse New York Heart Association class, atrial fibrillation and non-sustained ventricular tachycardia	[90]
ADMA Symmetric dimethylarginine	215 HCM (143 with diastolic dysfunction, 61 without diastolic dysfunction) No controls	Both elevated in HCM with diastolic dysfunction ADMA most strongly associated with increasing diastolic dysfunction	[91]
Haptoglobin	20 HCM 20 healthy controls	Decreased in HCM	[92]
Erythrocyte creatinine	92 HCM (12 with outflow tract obstruction, 4 with midventricular obstruction, 76 nonobstructive) No controls	Higher levels associated with greater intraventricular gradient	[93]
Vascular cell adhesion molecule/ICAM	23 HCM 16 HCM risk 66 healthy controls	Both increased in HCM ICAM correlated with perfusion by adenosine CMR	[43]

ADMA indicates asymmetric dimethylarginine; CMR, cardiac magnetic resonance; HCM, hypertrophic cardiomyopathy; ICAM, intracellular adhesion molecule; and vWF, von Willebrand factor.

surgical myectomy.[88] In addition, erythrocyte creatine levels have been associated with intraventricular pressure gradients[93] and haptoglobin levels with subaortic gradients.[92] Lastly, in a small study, both vascular and intracellular cell adhesion molecules that facilitate migration of inflammatory cells correlated with myocardial perfusion by CMR.[43] Although the studies measuring big-endothelin were large with respect to the number of HCM subjects evaluated and showed promise with respect to correlation with atrial fibrillation and worse clinical outcomes, no controls were included, which is a limitation.

Autoantibodies as Biomarkers

Antibodies against self-antigens (autoantibodies) have been proposed as a potential biomarker in HCM. The concentration of autoantibodies against the muscarinic-2 and B1-adrenergic receptors were higher in women and in patients with prior history of syncope and correlated with resting LV outflow tract gradient, maximal wall thickness, and interventricular septum thickness in 1 study.[95] Additional investigation regarding the role of autoantibodies as potential biomarkers in HCM is needed.

Genomic, Proteomic, Metabolomic Biomarkers

These areas of research are beyond the scope of the present review and the reader is referred to recently published reviews on this topic. A multitude of microRNAs have been shown to be up- or downregulated in HCM and associated with the extent of LV hypertrophy, fibrosis, and cardiomyocyte apoptosis.[96] However, none of the microRNAs studied thus far have been shown to predict clinical outcomes. Proteomics and metabolomics[97] are also exciting areas of active investigation in HCM that may inform novel treatment in the future.

Biomarkers Associated With Left Ventricular Outflow Tract Obstruction

In HCMR 2 patient populations were identified by CMR findings, 1 positive for the genetic sarcomere mutation

Table 6. Biomarkers Associated With Left Ventricular Outflow Tract Obstruction in Hypertrophic Cardiomyopathy

Biomarker	# Subjects	Findings	Ref #
vWF	62 obstructive HCM 28 nonobstructive HCM 10 healthy controls	Abnormal in obstructive compared with nonobstructive HCM Correlated with LV outflow tract gradient Normalized after surgical myomectomy	[88]
	62 HCM (28 obstructive, 33 nonobstructive) No controls	Lower ratio of vWF-collagen-binding to antigen in obstructive HCM Correlated with degree of outflow tract obstruction	[89]
	124 HCM 59 healthy controls 20 ischemic heart disease	Increased level correlated with obstruction, worse NYHA class, atrial fibrillation and nonsustained ventricular tachycardia	[90]
High-sensitivity cardiac troponin T	2755 HCM No controls	Higher in racial and ethnic minority groups, patients with hypertension, LVOT ≥30 mm Hg, increased wall thickness, reduced LVEF Increased with increasing maximal wall thickness and LGE on CMR	[2]
	95 HCM 45 healthy controls	Associated with maximum LV wall thickness and LA diameter Correlated with NYHA class, outflow obstruction, systolic dysfunction, abnormal blood pressure response, LGE, and disease severity	[37]
NT-proBNP	2755 HCM No controls	NT-proBNP higher in patients with resting LVOT ≥30 mm Hg, reduced LVEF, baseline arrhythmia, sarcomere mutation+ Increased with increasing maximal wall thickness and LGE on CMR	[2]
Erythrocyte creatinine	92 HCM (12 with outflow tract obstruction, 4 with midventricular obstruction, 76 nonobstructive) No controls	Higher levels associated with greater intraventricular gradient	[93]
Copeptin	24 obstructive HCM 36 nonobstructive HCM 36 healthy controls	Elevated in HCM Correlated with intraventricular septal thickness, LA diameter, and LVOT gradient Correlated with adverse cardiac events	[62]

CMR indicates cardiac magnetic resonance; HCM, hypertrophic cardiomyopathy; LA, left atrium; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and vWF, von Willebrand factor.

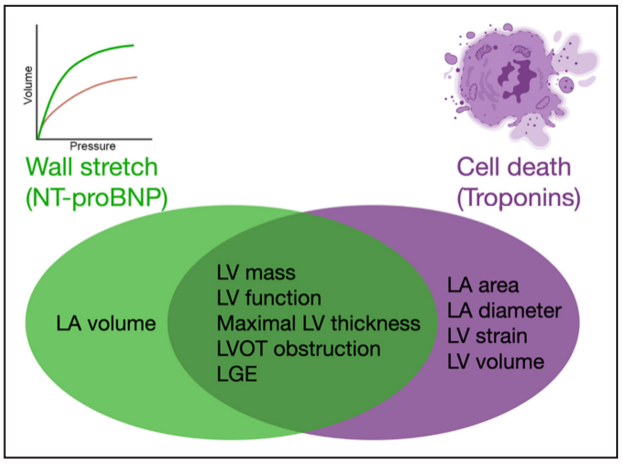

Figure 1. Circulating biomarkers in hypertrophic cardiomyopathy that correlate with noninvasive imaging include NT-proBNP (N-terminal pro-B-type natriuretic peptide), cTnI (cardiac troponin I), hs-cTnT (high-sensitivity cardiac troponin T), and hs-cTnI (high-sensitivity cardiac troponin I).
LA indicates left atrium; LGE, late gadolinium enhancement; LV, left ventricle; and LVOT, left ventricular outflow tract.

and 1 negative for the mutation.[2] The genotype positive group had more extensive LGE but less resting LV outflow tract obstruction whereas the genotype negative group had less LGE but more resting LV outflow tract obstruction (19% versus 26.8%, $P<0.001$).[2] Given the importance of LV outflow obstruction for prognosis, biomarkers that could identify the presence of this feature could be a valuable addition to HCM management. The biomarkers that have been associated with LV outflow tract obstruction in HCM include the following: vWF,[88–90] hs-cTnT,[2,37] NT-proBNP,[2] erythrocyte creatinine,[93] and copeptin[62] (Table 6). Several of these biomarkers were not only associated with LV outflow tract obstruction but were also predictive of adverse clinical outcomes including worsening NYHA class and atrial and ventricular arrhythmias.[2,37,62,90] In 1 study, elevated vWF levels could accurately discriminate between patients with obstructive (elevated levels) and nonobstructive HCM.[88] Moreover, following successful surgical myomectomy in those with obstructive HCM, vWF levels normalized.[88] This is an example of how circulating biomarkers could be used to track important aspects of this disease process and response to therapy.

Treatment Implications Using Biomarkers in HCM

One important question is whether circulating biomarkers can be used to assess response to therapy. There are some data to suggest they can. In

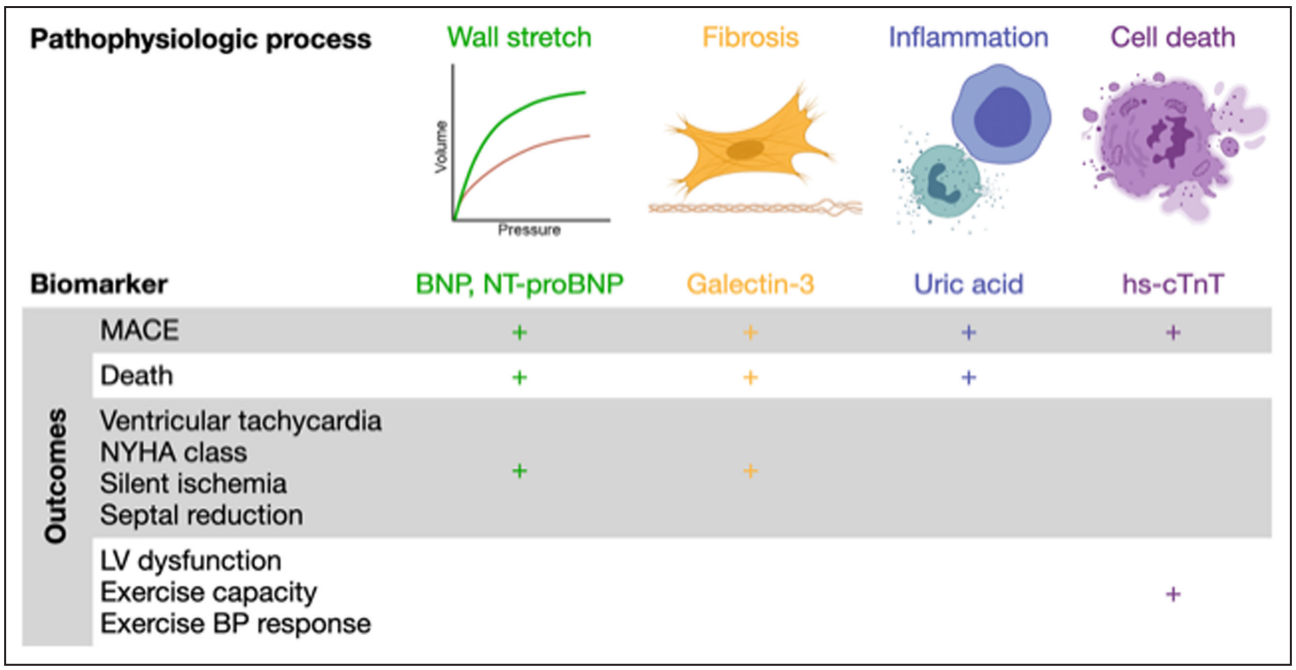

Figure 2. Circulating biomarkers in hypertrophic cardiomyopathy that correlate with clinical outcomes include brain natriuretic peptide (BNP), NT-proBNP (N-terminal pro-B-type natriuretic peptide), galectin-3, uric acid, and hs-cTnT (high-sensitivity cardiac troponin T).
MACE definitions: congestive heart failure, arrhythmia, death (references [56, 78]); congestive heart failure-related death, hospitalization, NYHA progression; arrhythmia-related sudden cardiac death, ventricular tachycardia, appropriate implantable cardioverter defibrillator discharge (reference [36]); sudden cardiac death; heart failure-related death, stroke-related death; heart failure hospitalization, stroke hospitalization, ventricular tachycardia, appropriate implantable cardioverter defibrillator discharge, worsening NYHA class (reference [40]). BP indicates blood pressure; LV, left ventricle; MACE, major adverse cardiac events; and NYHA, New York Heart Association.

addition to the data that correlate successful surgical myomectomy with normalization of vWF levels in patients with obstructive HCM,[88] there are examples that biomarkers can reflect response to medical therapy. In the CMR substudy of EXPLORER-HCM (Clinical Study to Evaluate Mavacamten [MYK-461] in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy) trial, subjects randomized to mavacamten had a 50% greater reduction in hs-cTnI (high-sensitivity cardiac troponin I) and 80% greater reduction in NT-proBNP compared with those randomized to placebo (P<0.01).[98] Moreover, change in LV mass index assessed by CMR directly correlated with change in hs-cTnI levels. Recent data from the VANISH (Valsartan for Attenuating Disease Evolution in Early Sarcomeric Hypertrophic Cardiomyopathy) trial[99] indicated that patients with early-stage HCM randomized to the angiotensin receptor blocker, valsartan, had improved primary composite outcome (cardiac structure/function and remodeling) and stable or lower levels of NT-proBNP at 2-year follow-up compared with those randomized to placebo. Lastly, in the randomized, double-blind VALOR-HCM (A Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive HCM Who Are Eligible for Septal Reduction Therapy) trial, subjects randomized to mavacamtem were less likely to meet guideline criteria for septal reduction therapy or chose to undergo it (primary end point) and had more improvement in NYHA functional class compared with those randomized to placebo.[100] Secondary end points included measuring changes in circulating levels of NT-proBNP and cTnI over the 16-week dosing period. These investigators found a statistically significant reduction in circulating levels of both NT-proBNP and cTnI in subjects randomized to mavacamten compared with placebo. These studies highlight the potential for circulating biomarkers to not only gauge response to therapy but also serve as surrogate end points or be included in composite end points in clinical trials.

CONCLUSIONS

Many studies have evaluated the utility of circulating biomarkers in HCM. The majority, however, are small and do not include a healthy control group. Nevertheless, several biomarkers representing different pathologic pathways are promising in HCM. Some of the strongest data to date come from studies correlating NT-proBNP and cardiac troponin (cTnI, hs-cTnI, and hs-cTnT) with noninvasive imaging findings (Figure 1). NT-proBNP and cardiac troponin are particularly useful because they are readily accessible in most clinical settings. Long-term follow-up data from HCMR will provide important information regarding the ability of NT-proBNP and hs-TnT to predict clinical outcomes. Currently available data regarding biomarkers and their correlation with clinical outcomes highlight the predictive value of BNP, NT-proBNP, hs-cTnT, galectin-3, and uric acid (Figure 2). Select biomarkers representing fibrosis, inflammation, and endothelial dysfunction also appear promising but need to be validated in larger cohorts. MicroRNA analysis, proteomics, metabolomics, and machine learning platforms, although beyond the scope of this review, all have the potential to uncover new pathways that could inform novel therapeutic targets in HCM.

ARTICLE INFORMATION

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