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Histologic characterization of hypertrophic cardiomyopathy with and without myofilament mutations

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Abstract

Background—Between 30% and 60% of clinical cases of hypertrophic cardiomyopathy (HC) can be attributed to mutations in the genes encoding cardiac myofilament proteins. Interestingly, it appears that the likelihood of an underlying myofilament mutation can be predicted by echocardiographic assessment of left ventricular morphology. However, it is not known whether genotypically characterized HC exists as a separate entity with discrete phenotypic morphology and histology or to what extent recognized polymorphisms of the renin-angiotensin-aldosterone system (RAAS) influence this relationship. The presence of cardiac myofilament and mutations and RAAS polymorphisms will have a strong association with the severity of histologic features of HC and characteristic septal shape.

Methods—We conducted a retrospective review of histology specimens, obtained at septal myectomy among 181 patients with medically refractory symptomatic HC. All patients underwent comprehensive genetic analysis for mutations in 8 myofilament-encoding genes; a subset was genotyped for 6 known RAAS-polymorphisms. Patients underwent comprehensive echocardiography by an expert blinded to genotype and microscopic status.

Results—Microscopically, severity of myocyte hypertrophy appears to be associated with the presence of recognized HC cardiac myofilament mutations ($P = .03$). Other histologic features characteristic of HC were not consistently associated with myofilament mutation status. A higher burden of pro-LVH RAAS polymorphisms also appeared to predict only myocyte hypertrophy ($P = .01$). The presence of RAAS polymorphisms was not associated with the development of a specific septal morphology ($P = .6$).

Conclusion—Myofilament-positive HC does not appear to represent a distinct clinical phenotypic entity as evidenced by specific histologic characteristics and septal shape.

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Hypertrophic cardiomyopathy (HC) is an inherited disorder often caused by mutations in genes that encode proteins of the cardiac sarcomeric myofilaments. It is characterized by a marked hypertrophy of the left ventricular wall without inciting factors such as aortic stenosis or hypertension, and microscopically by cardiomyocyte hypertrophy, myofibrillar disarray, and fibrosis.[1] Although most patients with HC have normal or near-normal life expectancy, it remains the most common cause of sudden cardiac death in those younger than 35 years, especially among young athletes.[2] Although it does appear that patients with any identified myofilament mutation have a worse prognosis,[3] the reports attributing risk to specific mutations are controversial.[4-6]

Recent studies have demonstrated that the presence or absence of an HC-associated myofilament mutation is closely related to ventricular and septal morphology,[7] leading us to hypothesize that there may also be differences in histology based on the underlying genetics. The expression, however, of certain mutations occurs across a vast spectrum of clinical phenotypes,[8,9] and further identification of risk factors and (genetic) modifiers continue to be a subject of intense interest.

A group of such modifiers may include polymorphisms in genes encoding proteins of the rennin-angiotensin-aldosterone system (RAAS).[10,11] Patients who are homozygous for the deletion alleles (DD) for the angiotensin-converting enzyme gene have increased tissue levels of ACE and in turn may be exposed to higher levels of angiotensin II with resultant increased hypertrophy and fibrosis.[10-12] Five additional polymorphisms in the RAAS have also been implicated as potential modifiers of ventricular hypertrophy.[13-18]

Histologic findings, although not part of the routine clinical diagnosis of HC, have been well characterized[19] and have not previously been analyzed with respect to cardiac myofilament mutations or associations with RAAS polymorphisms. In an effort to further study genotype-phenotype relationships in HC, we sought to determine with a microscopic and histologic approach (i) whether myofilament mutation–positive patients exist as a discrete phenotypic entity, with the distinct histology and septal morphology, (ii) and whether polymorphisms contributed in a synergistic or additional way toward a composite burden of gene-specific effects in patients with HC.

Methods

Study group and design

Between April 1990 and May 2002, 1532 patients with HC were seen at our institution. Four hundred forty-five individuals from this group underwent myectomy for drug-refractory symptoms, and the septal tissue was sent for anatomical pathology review. Of these, 181 patients consented to genetic mutational analysis for multiple research studies. All individuals provided informed written consent in accordance with study protocols approved by the Mayo Foundation Institutional Review Board. All patients met clinical HC diagnostic criteria: left ventricular wall thickness greater than the normal range for age and body surface area in the absence of another confounding diagnosis or hypertrophy inciting factors, such as aortic stenosis or hypertension. This group of patients was further defined by a comprehensive preoperative echocardiographic examination, and all patients underwent subsequent surgical septal myectomy for relief of symptoms refractory to maximal medical therapy. All patients provided blood samples for comprehensive genetic testing and genotyping of polymorphisms. This work was supported by the Mayo Clinic Windland Smith Rice Comprehensive Sudden Cardiac Death program (MJA), and the authors are solely responsible for the design and conduct of this study, all study analyses, and the drafting and editing of the paper and its final contents.

Microscopic evaluation

Histologic examination of the septal muscle was reviewed by a single expert cardiac pathologist (WDE) who was blinded to all other features of the patient's clinical and genetic background. All slides had been stained with hematoxylin-eosin, and a sulfated Alcian blue stain for the detection of amyloid had been prepared in patients >30 years old. All cases were evaluated for the presence or absence of the following myocardial features: cardiomyocyte hypertrophy, myofibrillar disarray, interstitial fibrosis, and endocardial fibrosis. Hypertrophy was diagnosed if myocytes consistently had enlarged and hyperchromatic nuclei, and cell diameters >20 μm, or greater than the diameters of 3 red blood cells (RBCs). Myofibrillar disarray included cellular interlacing, whirling, or herringbone patterns.[20] Endocardium was evaluated for the presence or absence of fibrosis and amyloidosis. If amyloid was detected, these patients were excluded from the study (3 patients).

In nondilated hearts, myocyte diameter is directly proportional to the extent of hypertrophy. Therefore, hypertrophy was considered mild if myocyte diameters overall were 21 to 29 μm (3-4 RBCs), moderate if 30 to 38 μm (4-5 RBCs), and severe if >38 μm (>5 RBCs). Myocyte disarray was graded as mild if its extent was 1% to 25% of the myocardial area on the microscopic slide, moderate if 26% to 50%, and severe if >50%. Interstitial fibrosis was determined to be absent if the extent of collagen was <5% of the myocardial area, mild if 6% to 15%, moderate if 16% to 25%, and severe if >25%. Endocardial fibrosis was deemed to be absent if endocardial thickness was <30 μm, mild if 30 to 75 μm, moderate if 76 to 150 μm, and severe if >150 μm.

Genetic analysis

After extraction of DNA from the blood samples,[11] comprehensive mutational analysis of the 8 most common myofilament-encoding HC-associated genes was pursued, as described previously by our group.[4,21-24] This analysis was set up to address mutations in all translated exons of myosin binding protein C (MYBPC3), β-myosin heavy chain (MYH7), essential and regulatory myosin light chains (MYL2, MYL3), cardiac troponin T (TNNT2), cardiac troponin I (TNNI3), α-tropomyosin (TPM1), and cardiac actin (ACTC). Akin to previous studies, all mutations—independent of the underlying gene—were pooled to designate patients as myofilament-positive or myofilament-negative to study the role of mutation status on histology and septal shape as well as to include smaller genetic subgroups into the analysis. Furthermore, a subset of 157 patients were genotyped for 6 RAAS polymorphisms according to previously described methods.[11] The polymorphisms are (i) a deletion/insertion (D/I) polymorphism in the angiotensin-converting enzyme (ACE); (ii) an A/C substitution at position 1666 of the angiotensin II receptor Type 1 gene (*AGTR1*); (iii) an A/G exchange at position –1903 of the cardiac chymase A gene (*CMA*); 2 nucleotide substitutions resulting in amino acid changes at codons (iv) 174 (Thr/Met) and (v) 235 (Met/Thr) of the gene encoding angiotensinogen (*AGT*); and (vi) a C/T exchange at position –344 in the aldolase synthase gene (*CYP11B2*).[11,25] Pro-LVH polymorphisms were defined as DD-*ACE*, CC-*AGTR1*, AA-*CMA*, T174M- and M235T-*AGT*, and CC-*CYP11B2*.[10]

Echocardiography

The shape of the septum was evaluated in the long axis view at end-diastole. Sigmoid septal morphology was defined as a generally ovoid left ventricular (LV) cavity with the septum being concave toward the LV with a pronounced basal septal bulge. Reverse curve septal morphology was defined as a predominant midseptal convexity toward the left ventricular cavity with the cavity itself having an overall crescent shape. Apical variant HC was defined as a predominant apical distribution of hypertrophy. Neutral septal contour was defined by an overall straight or variable convexity that was neither predominantly convex nor concave

toward the LV cavity. These echocardiographic parameters were assessed by independent reviewers who were blinded to all other patient characteristics.

Statistical analysis

The primary interest was to identify any relationship between the histologic phenotype associated with myofilament mutations and ACE polymorphism status among patients with HC. Analysis of variance and contingency analysis testing using Pearson likelihood ratio method were used to assess for associations across the groups. RAAS gene status was analyzed as a pooled, 6-gene "pro-LVH score."[10] For all statistical tests, two-sided analysis was performed, and a P value <.05 was considered statistically significant.

Results

Patient demographics and genetic analyses

Baseline characteristics are summarized in Table I. Of the patients, 52.5% were female, with most patients (~90%) of white ethnicity. The most common septal shape was sigmoid (48%), with a reverse septal contour prevalent in 29% of patients. Neutral and apical septal shape accounted for 17% and 6% of patients, respectively.

Only 23% of patients did not harbor any of the studied RAAS polymorphisms, with the majority (66%) possessing only one of these elements. The occurrence of more than one of these disease modifiers tapered predictably in prevalence, as shown in Table I. Table II reflects the frequency of homozygous mutations withinthe 6pro-LVH polymorphisms. The frequency within this HC cohort is similar to those reported in other study populations.[10,11,14,15,18,26]

Histologic findings

As evidenced in Table III, myocyte hypertrophy of moderate and severe was were found in 46.1% and 53.8% of the myofilament-negative patients, respectively—contrasted with 30.2% and 69.7%, respectively, in the myofilament-positive group. Myofibrillar disarray was predominantly of a mild grade in both the myofilament-negative and myofilament-positive groups, whereas interstitial fibrosis was also principally of a mild grade. Endocardial fibrosis was of a moderate degree in both groups.

Predictors of histologic pattern

With respect to cardiac myofilament mutations, only the severity of cardiomyocyte hypertrophy was associated with the presence of a myofilament mutation such that a significantly higher proportion of patients with a mutation demonstrated severe hypertrophy (P = .03, Figure 1). Other characteristic histologic patterns typical for HC were not consistently associated with the presence or absence of a myofilament mutation: myofibrillar disarray (P = .2), interstitial fibrosis (P = .4), and endocardial fibrosis (P = .9) (Table III). No differences were seen for the larger genetic subgroups (ie, MYH7- or MYBPC3-HC); the other genetic subgroups were too small to perform individual analyses.

The presence of any single RAAS polymorphism—defined as pro-LVH score—was also linked with cardiomyocyte hypertrophy (P = .01) (Table IV, but not the other histologic features. Individually, the specific RAAS polymorphisms did not confer a greater likelihood of the presence of gross histologic or morphologic manifestations of disease; however, the number or burden of pro-LVH polymorphisms showed a positive correlation with cardiomyocyte hypertrophy (P = .01, Table V. There was no effect seen in the presence of non–LVH-associated heterozygote or homozygote RAAS polymorphisms, and no potential additive or synergistic associations between HC mutations and RAAS polymorphisms on

histology. Septal shape appeared to be significantly associated with myocyte hypertrophy ($P < .01$) and endocardial fibrosis ($P < .01$) (Table IV).

Septal shape

Prior observations (overlapping with this study)[7] regarding the presence of myofilament mutations and septal shape were confirmed such that patients with an identified HC-causing mutation are more likely to have a particular septal shape—reverse contour ($P < .001$). Yet the presence of RAAS polymorphisms does not appear to be linked to the development of a certain septal morphology ($P = .6$). There does appear to be a trend toward an association between septal shape and extent of myocyte disarray ($P = .06$, Table IV). To this effect, the apical-shaped septum was found to have a greater proportion of moderate to severe degrees of disarray, whereas the sigmoid-shaped septum exhibited the mildest degrees of disarray. With regard to interobserver variability, the overall agreement assigning patients to the 4 groups (sigmoid septum, reverse curvature, apical, or neutral) was 83%.

Discussion

Conceptually, HC is viewed as a genetic disease of the cardiac sarcomere, associated with distinctive alterations in myocardial morphology and histology. Importantly, there are a substantial number of patients with clinically diagnosed HC who do not have identifiable myofilament mutations leading to questions as to whether mutation status defines ≥2 different diseases rather than just one entity. Initially described by Teare[27] half a century ago, the histologic examination of myocardium in young adults with asymmetric hypertrophy revealed bizarre arrangements of the muscle-fiber bundles. Subsequent investigators have described myocyte hypertrophy, myocyte disarray, and endocardial and interstitial fibrosis as the most commonly observed microscopic features,[28] and these features remain the “gold standard” for pathologic confirmation of the diagnosis. Interestingly, none of these histologic features are pathognomonic of HC, and can be found in a variety of cardiac disease states,[19] hallmarking the importance of experienced pathologic interpretation for diagnosis.

Microscopic features

This current report identifies that microscopic myocyte hypertrophy, present in moderate to severe degrees in all of surgical specimens, consistent with prior reports,[28-30] is the only histologic feature that is consistently more severe in mutation-positive patients. Histologic findings thought to be more specific for HC including myofibrillar disarray and fibrosis were not related to the presence or absence of a mutation. This result supports the notion that among patients with a clinical diagnosis of HC, the underlying histopathology is not substantially impacted by genotype.

Although cardiac myocyte hypertrophy is not specific to HC, myofibrillar disarray is typically absent in other conditions that may mimic HC, such as hypertensive heart disease and aortic stenosis. The extent of disarray does appear to be associated with a more malignant course in younger patients, as does severe myocardial fibrosis appears to promote premature deaths from heart failure and an increased risk of primary ventricular arrhythmias.[31] Nevertheless, disarray and fibrosis are also not pathognomonic of HC.[32]

This initial and hypothesis-generating study simply addresses whether distinctive HC phenotypes observed in other descriptive reports[3,7] have correlative and distinguishing histology findings. Although not exact, the 4-point grading system used in this report has been previously used to identify gross trends in HC pathology reports[33-36] and is the norm for clinical histopathology identification of the disease entity. Several studies have

addressed pathologic findings in HC and other cardiomyopathies by using percentage of disarray, fibrosis, and hypertrophy as the unit of comparison between autopsied/whole hearts.[32,37-40] All samples in our study are derived from myectomy specimens, and hence this method is not applicable. It does also allude to a potential limitation with regard to the amount of inference that can be made from a limited sample size. To this effect the most consistent changes in histology appear to be found in the ventricular septum,[41,42] from where samples were excised to obviate outflow tract obstruction.

Genetic features

The diverse phenotypic expression observed between unrelated families or even among affected individuals from the same family continues to raise intriguing questions about genetic penetrance and the impact of additional factors.[43] Polymorphisms of the angiotensin-converting enzyme system present an attractive hypothesis as potential disease modifiers. Hypertrophic cardiomyopathy families with a high incidence of sudden cardiac death have been shown to more frequently retain the ACE gene polymorphism, DD.[44] This particular genotype is associated with higher plasma concentrations of ACE, and perhaps through its subsequent interaction with certain oncogenic pathways has also been shown to be related to more severe degrees of cardiac hypertrophy.[45] Accordingly, several other polymorphisms within RAAS are suggested to influence hypertrophy in HC,[10] resulting not only in increased pathway protein concentrations but also more sensitive receptor activation.[25,46,47] Further clarification of the influence on this pathway suggests that RAAS genotypes may modify the clinical phenotype of HC in a disease gene-specific fashion rather than indiscriminately.[11] In addition, the small sample size and particularly the low numbers of patients with specific HC mutations may have impacted these results—evidenced by the previously shown interaction between MYBP3 and RAAS polymorphisms—not identified in this study.[10,11]

Interestingly, we find that there is a pooled effect of 6 RAAS polymorphisms on the risk of developing more severe degrees of myocyte hypertrophy, regardless of myofilament mutation status. The presence of these polymorphisms, however, does not appear to correlate with any particular septal morphology or other histologic features.

An important consideration with regard to the study is the great variability in the distribution of the histology within each heart that we noted. In mitigation of this limitation, all of our specimens were obtained from septal myectomy of the hypertrophied region compared with the bulk of prior data that have been chiefly derived from autopsy studies. All of these patients were symptomatic and referred for septal myectomy (representing only 12% of the HC patients evaluated and ~ 40% of patients undergoing myectomy during this period)—potentially introducing bias into the analysis. A further caveat to the interpretation of these results exists with regard to the progressive nature of HC. Parallel progressive changes in the histology therefore could be obscured when one analyzes a cross-section of ages—as in this study.[48,49] It is also pertinent to consider that this analysis of gene-positive patients may be incomplete in that we specifically genotyped for only 8 myofilament-encoding genes, although currently, 20 HC-associated genes have been identified.[50,51] Furthermore, it must be noted that only 181 of a total of 1,532 patients were genotyped. Because patients were assembled from different cohorts, only 157 of 181 patients were genotyped for the described RAAS polymorphisms.

Conclusions

The concept that HC with identifiable cardiac myofilament mutations exists as a distinct clinical and pathogenetic entity from HC without such mutations is challenged by this analysis. The nonspecific finding of myocyte hypertrophy appears to be the only

microscopic feature that occurs more severely in this group with an associated reverse septal contour. Independent of myofilament mutation status, the RAAS phenotype contributes toward the development of myocyte hypertrophy in this group.

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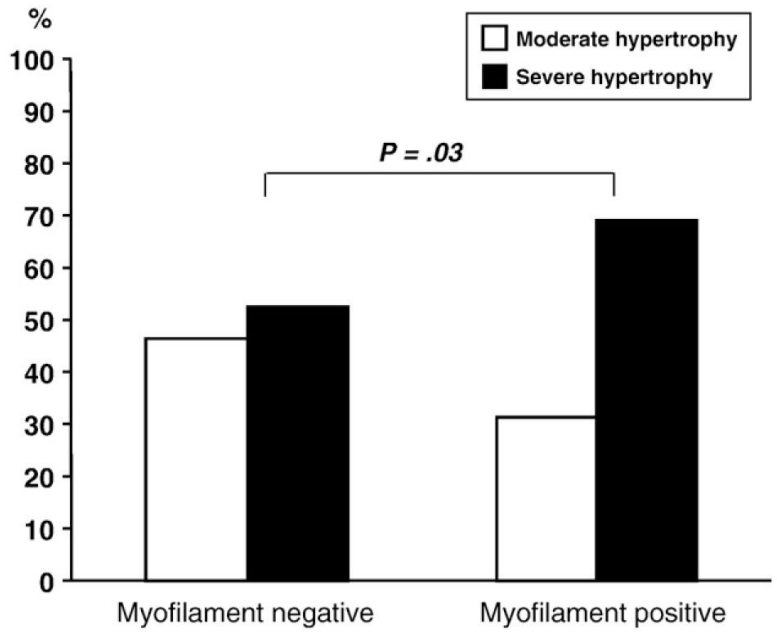

Figure 1.
Association of severity of cardiac myocyte hypertrophy with myofilament status. In the setting of a myofilament mutation, a significantly greater portion of people shows severe cardiac myocyte hypertrophy.

Table I

Clinical characteristics of 181 patients with HC

Patient demographics	
Age at myectomy (y)	49 ± 19
Male gender (n [%])	86 (47.5)
Septal shape	n (%)
Sigmoid	83 (48)
Apical	10 (6)
Reverse	49 (29)
Neutral	30 (17)
Myofilament mutation	n (%)
None	105 (58)
MYH7	35 (19)
MYBPC3	30 (16)
TNNI3	3 (2)
MYL2	2 (1)
TPM1	1 (1)
Multiple	5 (3)
Presence of pro-LVH RAAS polymorphisms	n (%)
None	35 (22)
1	57 (36)
2	34 (22)
3	22 (14)
4	7 (5)
5	2 (1)
6	0 (0)

Table II

Frequency of homozygous RAAS polymorphisms

	ACE DD/II		AGT M235T		AGTR1 A1166C		CYP11B2 −344 C/T		CMA –1903 C/A		AGT T174M	
Homozygous alleles*	**DD**	II	**TT**	MM	**CC**	AA	**CC**	TT	**AA**	GG	**TT**	MM
No. of patients	58	28	27	67	16	87	34	47	38	54	138	4
Frequency (%)	32	17	15	37	9	48	19	26	21	30	76	2

*Previously reported pro-LVH alleles for each RAAS polymorphism are highlighted in bold.

Table III

Association of pathologic hallmarks of HC with the presence of a myofilament mutation

	Myofilament negative				Myofilament positive				
	None	**Mild**	**Moderate**	**Severe**	**None**	**Mild**	**Moderate**	**Severe**	***P***
Myocyte hypertrophy	0	0	48 (46.1)	56 (53.8)	0	0	23 (30.2)	53 (69.7)	.03
Myofiber disarray	17 (16.5)	64 (62.1)	20 (19.4)	2 (1.9)	5 (6.5)	52 (68.4)	16 (21.1)	3 (3.9)	.2
Interstitial fibrosis	21 (20.6)	52 (51.0)	23 (22.5)	6 (5.9)	10 (13.9)	34 (47.2)	23 (31.9)	5 (6.9)	.4
Endocardial fibrosis	7 (6.7)	22 (21.5)	48 (46.1)	27 (25.9)	4 (5.3)	16 (21.3)	33 (44.0)	22 (29.3)	.9

Mod, Moderate.

Table IV

Likelihood analyses of association of presence of mutation, RAAS polymorphisms, and septal shape with various histologic hallmarks of HC

	Presence of mutation (*P*)	RAAS polymorphism (6-gene) (*P*)	Septal shape (*P*)
Myocyte hypertrophy	.03	.01	<.01
Myofiber disarray	.19	.27	.06
Interstitial fibrosis	.44	.29	.40
Endocardial fibrosis	.94	.48	<.01

Table V

Association of presence of RAAS polymorphisms with severity of myocyte hypertrophy

	Presence of a RAAS polymorphisms							
Myocyte hypertrophy	**0**	**1**	**2**	**3**	**4**	**5**	**6**	***P***
Moderate	16 (10.2)	18 (11.5)	17 (10.9)	12 (7.6)	0	0	0	.01
Severe	19 (12.1)	39 (24.8)	17 (10.8)	10 (6.4)	7 (4.5)	2 (1.3)	0	.01

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