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Comparison of Outcomes in Patients with Non-Obstructive, Labile-Obstructive, and Chronically Obstructive Hypertrophic Cardiomyopathy

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Abstract

Non-obstructive hypertrophic cardiomyopathy (HC) patients are considered low-risk, generally not requiring aggressive intervention. However, non- and labile-obstructive HC have been traditionally classified together and it is unknown if these 2 sub-groups have distinct risk profiles. We compared cardiovascular outcomes in 293 HC patients (96 non-obstructive, 114 labile-obstructive and 83 obstructive) referred for exercise echocardiography and magnetic resonance imaging and followed for 3.3±3.6 years. A sub-group (34 non-obstructive, 28 labile-obstructive, 21 obstructive) underwent positron emission tomography (PET). The mean number of sudden cardiac death risk factors was similar among groups (non-obstructive: 1.4 vs. labile-obstructive: 1.2 vs. obstructive: 1.4 risk factors, p=0.2). Prevalence of late gadolinium enhancement (LGE) was similar across groups but more non-obstructive patients had LGE≥20% of myocardial mass [23(30%) vs. 19(18%) labile-obstructive and 8(11%) obstructive, p=0.01]. Fewer labile-obstructive patients had regional PET perfusion abnormalities [12(46%) vs. non-obstructive 30(81%) and obstructive 17(85%), p=0.003]. During follow-up, 60 events were recorded (36 VT/VF, including 30 defibrillator discharges, 12 heart failure worsening and 2 deaths). Non-obstructive patients were at higher risk of VT/VF at follow-up, when compared to labile-obstructive (HR 0.18, 95%CI 0.04–0.84, p=0.03) and the risk persisted after adjusting for age, gender, syncope, family history of sudden cardiac death, abnormal blood pressure response and septum≥3cm (p=0.04). Appropriate defibrillator discharges were more frequent in non-obstructive [8(18%)] compared to labile-obstructive [0(0%), p=0.02] patients. In conclusion, non-obstructive

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hemodynamics is associated with more pronounced fibrosis and ischemia than labile-obstructive and is an independent predictor of VT/VF in HC.

Keywords

hypertrophic cardiomyopathy; arrhythmia; defibrillation

Novel imaging technologies have indicated that characteristics unrelated to outflow hemodynamics but related to the primary myopathy, such as fibrosis by imaging,[1] microvascular ischemia[2, 3] and abnormal myocardial mechanics,[4, 5] are highly prevalent in Hypertrophic Cardiomyopathy (HC) and may be important arbiters of outcomes.[1, 6, 7] Therefore, non-obstructive hemodynamics alone may not always confer low risk, a viewpoint corroborated by several anecdotal examples in our large-volume practice. Moreover, previously published outcome studies did not separate non-obstructive (resting and provoked gradients <30 mmHg) and labile-obstructive (resting <30 mmHg; provoked ≥30 mmHg) variants,[8–10] as is the current clinical practice.[11] Therefore, it is additionally unclear if there are differences in outcomes between non-obstructive versus labile-obstructive HC phenotypes not evident in existing published literature since both these groups were combined.

METHODS

This study was approved by the Institutional Review Board. A total of 344 patients were recruited at their first visit to the Johns Hopkins Hypertrophic Cardiomyopathy Center from 2005 to 2013 if they fulfilled previously used diagnostic criteria for HC, which primarily was a maximal septal wall thickness ≥15mm in the absence of other cardiac or systemic disease that may produce a similar degree of left ventricular hypertrophy[8, 11, 12] and 293 of them were followed for a mean of 3.3±3.6 years. Patients with a previous myectomy or alcohol septal ablation were excluded. Clinical information was collected as previously described.[13] We compared clinical features and outcomes within the 3 HC sub-groups.

Sustained ventricular tachycardia (VT), ventricular fibrillation (VF), appropriate implantable cardioverter defibrillator (ICD) discharge, heart failure worsening (defined as NYHA class worsening to class III or IV) and death were recorded by reviewing Holter and exercise ECG tracings, ICD interrogation reports and clinical visit notes. Appropriate ICD discharges were defined as documented ventricular tachycardia or fibrillation events at heart rate ≥180bpm.[14, 15] Sudden cardiac death (SCD) risk was assessed by noting non-sustained ventricular tachycardia (NSVT), unexplained syncope of non-neurocardiogenic origin, previous VT/VF, family history of SCD, septum≥3cm and abnormal blood pressure response.[11]

Echocardiography was performed using a GE Vivid 7 ultrasound machine (*GE Ultrasound, Milwaukee, WI*) using a standard clinical protocol. Conventional measurements were performed as previously published.[16, 17] Systolic anterior movement of the mitral valve was defined as absent, incomplete (no contact with the septum) and complete (contact between leaflet and septum).[18] Left ventricular outflow tract (LVOT) gradients were measured pre

and immediately post a symptom-limited exercise test[19, 20] and patients were classified into non-obstructive (<30mmHg at rest and exercise), labile-obstructive (<30mmHg at rest and ≥30mmHg with exercise) and obstructive (≥30mmHg at rest).[11]

Cardiac magnetic resonance imaging (CMR) was performed on a 1.5-Tesla system (MAGNETOM Avanto, Siemens Healthcare, Erlangen, Germany), as described previously,[21] with contrast, gadopentetate dimeglumine at 0.2 mmol/kg (Magnevist; Bayer Schering, Berlin, Germany). Late gadolinium enhancement (LGE) images were assessed in short axis view with validated software (QMASS 7.4, Medis) by an experienced reader (C.C.V). Endocardial and epicardial borders were manually traced in each slice and the myocardium was divided into 16 segments starting from the anterior insertion point of the right ventricle. A region of interest was placed in an area of normal appearing nulled myocardium, typically the basal lateral wall. Pixels with signal intensity greater than 6 standard deviations higher than the mean of normal myocardium were considered abnormal.[22] The extent of LGE was expressed as a percentage of total left ventricular (LV) myocardial mass.

Patients with angina ≥3 months despite optimal medical therapy were referred for PET scanning and were imaged using a GE Discovery VCT PET/CT system. Regional myocardial perfusion was assessed using a same day rest/stress protocol as described previously.[3, 21, 23, 24] Attenuation-corrected PET images were reconstructed by an iterative algorithm with post-processing filtering and static datasets analyzed using CardIQ Physio (GE Healthcare). Regional myocardial perfusion was semi-quantitatively assessed from the re-oriented images on different cardiac planes (short, horizontal, and vertical long axes) using the standard 17 American Heart Association segmentation, 5-point visual score method.[3] The summed stress score (SSS) and summed rest score (SRS) consisted of the summation score of the 17 LV segments during vasodilator-stress and rest perfusion imaging. The summed difference score (SDS) consisted of the difference between SSS and SRS. An SDS ≥2 was considered abnormal in this study.

Data were analyzed using STATA software version 13 (StataCorp LP, College Station, Texas). Continuous variables are presented as mean ± standard deviation and categorical variables as the total number and percentage. Comparison of variables across groups was performed using ANOVA and Chi-square or Fisher's exact test as appropriate. Statistical significance was set at $p<0.05$. We used Kaplan-Meier procedure to estimate the survival function for each category of HC. We then used a log-rank test to determine whether there was a significant difference in the 3 survival functions. A Cox proportional multivariate hazard model was built to control for potential confounders.

RESULTS

Clinical and echocardiographic characteristics of the study population, which included 96 non-obstructive (33%), 114 labile-obstructive (39%) and 83 obstructive patients (28%), are summarized in Tables 1–2. Obstructive patients were older and had more dyspnea at presentation, while gender distribution, co-morbidity profiles and body mass index did not differ among groups. Family history of HC, history of VT/VF, NSVT and ICD in place were

more common in non-obstructive patients (Table 1). Maximum septal wall thickness and left ventricular ejection fraction were similar among groups. Obstructive patients had a higher E/e' ratio and a larger left atrial diameter (Table 2).

LGE images were available in 77 non-obstructive, 105 labile-obstructive and 72 obstructive patients (87% of the original sample), with clinical and echocardiographic characteristics comparable to those of the original groups. Presence of LGE was similar between groups [non-obstructive: 51(66%) vs. labile-obstructive: 64(61%) vs. obstructive: 49(68%), p=0.6]. However, extent of LGE was greater in non-obstructive (non-obstructive: 21±16 vs. labile-obstructive: 11±12 vs. obstructive: 12±10 %, p=0.002) and a larger proportion of non-obstructive patients carried a high LGE burden (≥20% myocardial mass) [non-obstructive: 23(30%) vs. labile-obstructive: 19(18%) vs. obstructive: 8(11%), p=0.01] (Figure 1).

A sub-set of 83 patients (34 non-obstructive, 28 labile-obstructive, and 21 obstructive) underwent ammonia PET scanning. Fewer labile-obstructive patients had SDS≥2, indicating a lower extent of regional perfusion abnormalities [non-obstructive: 28(82%) vs. labile-obstructive: 15(54%) vs. obstructive: 16(76%), p=0.04] (Figure 1).

We noted 60 events (36 VT/VF including 30 ICD discharges, 12 heart failure worsening and 2 deaths) in the 293 patients during follow-up. Follow-up time and the mean number of SCD risk factors did not differ among groups (Table 1).

Kaplan Meier (Figure 2) and univariable Cox regression analysis indicated non-obstructive patients were at significantly higher risk of VT/VF during follow-up when compared to labile-obstructive (p=0.03, Table 3). Adjusting for age, gender and the established SCD risk factors (syncope, family history of SCD, abnormal blood pressure response, septal thickness ≥3cm)[11], non-obstructive patients remained significantly at higher risk than labile-obstructive (p=0.04; Table 3). History of NSVT, family history of HC, NYHA functional class, presence or extent of LGE, CFR and SDS by PET, ejection fraction, left atrial diameter, septal thickness, E/e' ratio and LVOT gradients at rest or exercise were not associated with a higher risk of VT/VF in univariate analysis. A higher proportion of non-obstructive patients experienced a VT/VF at follow-up when compared to labile-obstructive (9.4% vs. 1.8%, p=0.01). A similar trend was noted when compared to the obstructive group (9.4% vs. 3.6%, p=0.1; Figure 3A).

There were no inter-group differences in the rates of heart failure worsening [non-obstructive: 6 (6.3%) vs. labile-obstructive: 2 (1.8%) vs. obstructive: 4 (4.8%), p=0.2) and death - 1 non-obstructive patient died of sepsis and 1 labile-obstructive patient of cardiac arrest (p=0.7).

Sensitivity analysis was performed to assess for the potential bias introduced by differences in ICD prevalence and history of VT/VF among groups. When considering only those patients with an ICD in place at baseline or implanted at follow up [45(47%) in non-obstructive vs. 33(29%) in labile-obstructive vs. 33(40%) in obstructive, p=0.03], we found that more non-obstructive patients had at least one ICD discharge (n=8, 14%) as compared to labile-obstructive (n=0, 0%; p=0.02) and obstructive (n=2, 6%; p=0.2) (Figure 3B). In addition, the total number of appropriate ICD discharges was significantly higher in the non-

obstructive (n=28) as compared to the labile-obstructive group (n=0, p=0.02) and similar in the non-obstructive and obstructive groups (n=2, p=0.2).

After excluding patients with a history of VT/VF, a similar trend was noticed, with more non-obstructive patients experiencing VT/VF at follow up (6.9%) compared to labile-obstructive (1.8%, p=0.065) and obstructive (2.5%, p=0.2). For those with an ICD but without a history of VT/VF, more non-obstructive patients had discharges (14%) compared to labile-obstructive (0%, p=0.03). A similar trend was noted when compared to obstructive patients (3%, p=0.1).

Finally, in order to examine whether patients with end-stage HC were contributing to the higher prevalence of adverse events in the non-obstructive group, we specifically examined patients with ejection fraction <50% (11 non-obstructive, 5 labile-obstructive, 4 obstructive patients). Mean EF was similar among sub-groups (non-obstructive: 44±5% vs. labile-obstructive: 44±6% vs. obstructive: 44±7%, p=0.99). None of these patients had a VT/VF episode and heart failure worsening from NYHA class II to III was recorded in 1 patient in the non-obstructive group.

DISCUSSION

Our study presents novel results with important clinical implications. 1) Non-obstructive HC is associated with significantly higher rates of ventricular arrhythmias compared to labile-HC, and similar to obstructive HC despite a similar mean number of currently used clinical SCD risk factors across the 3 HC sub-groups. These findings are in contrast with previously held concepts that non-obstructive HC patients experience a stable clinical course without significant symptoms or a high-risk profile. 2) Hemodynamic sub-types of HC have characteristic myopathic profiles. Non-obstructive patients have higher prevalence of large LGE burden on magnetic resonance and microvascular ischemia by PET. On the other hand, labile-obstructive HC is characterized by the least myopathic profile and the most favorable outcomes.

Previous clinical outcome studies[8, 10] classified HC into obstructive and non-obstructive groups, the latter including those with labile obstruction. Since the emergence of the concept of labile obstruction,[25] non-obstructive HC is currently parsed into the true non-obstructive (resting and provoked gradients <30 mmHg) and labile-obstructive (provoked gradients ≥30 mmHg).[11] Our experience and review of HC literature[8, 26–30] led us to question whether there were wider clinical differences between non-obstructive and the other HC groups. Our study confirmed that non-obstructive patients had higher rates of arrhythmias and more frequent ICD discharges. Higher rates of ventricular arrhythmias historically (Table 1) further support our prospective findings. After excluding those with previous VT/VF we found non-obstructive patients having 4 times the VT/VF episodes compared to labile-obstructive and 3 times that of obstructive. ICD discharges were also more frequent in this group.

Ventricular arrhythmias and ICD discharges were not related to systolic or diastolic function, or outflow tract gradients. In patients with EF<50% we found none with VT/VF.

Similarly, fewer arrhythmias were noted in labile-obstructive compared to non-obstructive HC in the only other study comparing arrhythmia events between these 2 HC groups.[26] A study that indicated worse outcomes in obstructive HC, also noted that the annual rate of SCD events was only marginally higher in obstructive compared to patients without obstruction at rest (1.5 vs. 0.9%).[8] Yet another study revealed that only 30% of HC-related deaths were associated with obstructive hemodynamics.[27] In HC patients with a benign presentation and without risk factors, only 29% with SCD had obstruction and the rates (4.2%) were similar to those in our study (3.6%).[28] A recent study examining the utility of extent of scar on SCD risk stratification found that most patients experiencing an arrhythmia had low outflow gradients.[29] Data presented in these studies is highly concordant with ours. Our current findings imply that the favorable outcomes in the labile-obstructive group may drive the overall positive prognosis in the combined non-obstructive/labile-obstructive group presented in previous publications. Furthermore, previous studies that have shown no association between LVOT gradient and ventricular arrhythmias[8, 11, 30] indirectly validate our results.

Additional characterization using novel imaging techniques helps validate our clinical outcomes results. Non-hemodynamic pathologic features of HC, which we for the purposes of this paper are labeling as the myopathic features, were more pronounced in the non-obstructive group. Conversely, the labile-obstructive patients were found to have the least myopathic profile and, interestingly, have the most favorable outcomes. Our data therefore demonstrate that the three hemodynamic subtypes of HC are associated with distinct myopathic profiles. Figure 4 summarizes the clinical and morphological characteristics of the 3 HC groups. Overall, we propose that there is a conglomeration of adverse factors in non-obstructive HC leading to unfavorable outcomes in this group. Notwithstanding these results, our data indicate that the relationship between these myopathic features and clinical outcomes, particularly ventricular arrhythmias, is not straightforward. This suggests the need for a wider examination of the relative importance of microvascular ischemia versus scar burden as a trigger for arrhythmias.[3, 21] Moreover, arrhythmias were noted in HC patients with neither LGE nor ischemia, thus other factors may be operative. Notwithstanding the statistical results, the significantly higher proportion of non-obstructive patients with high LGE burden and PET-based ischemia suggests a role for fibrosis and ischemia in driving this risk. In our study, non-obstructive patients experienced almost 3 times as many VT/VF episodes compared to obstructive and 5 times as many compared to labile-obstructive patients. Consequently, our finding that non-obstructive patients are at high risk for adverse events revises a long-held concept in HC management.

Our results urge a re-consideration of several key management decisions in HC: 1) Non-obstructive HC patients may need to be monitored more closely and sudden cardiac death risk adjudication be performed more thoughtfully. 2) Estimation of scar burden via LGE and microvascular ischemia by PET may need to be considered as part of this risk adjudication. 3) Given the relatively benign clinical outcome profile, labile-obstructive HC may warrant a more conservative treatment strategy.

There may be other factors not examined or clearly evident in our analysis that may contribute to these inter-group differences. We did not see differences in deaths or heart

failure. This could be a reflection of our follow-up period, sample size and/or cohort case-mix. It is likely that longer follow-up periods may reveal that obstructive patients have higher rates of heart failure (as reported previously), which makes sense given the afterload burden in this group. Nonetheless, our arrhythmia data are convincing and relevant. We did not include genotyping data. At the current time, diagnosis, treatment and prognostication of HC is clinically adjudicated without use of genetic information. Moreover, eliminating gene-negative individuals would exclude about 50–60% of the population at-risk.

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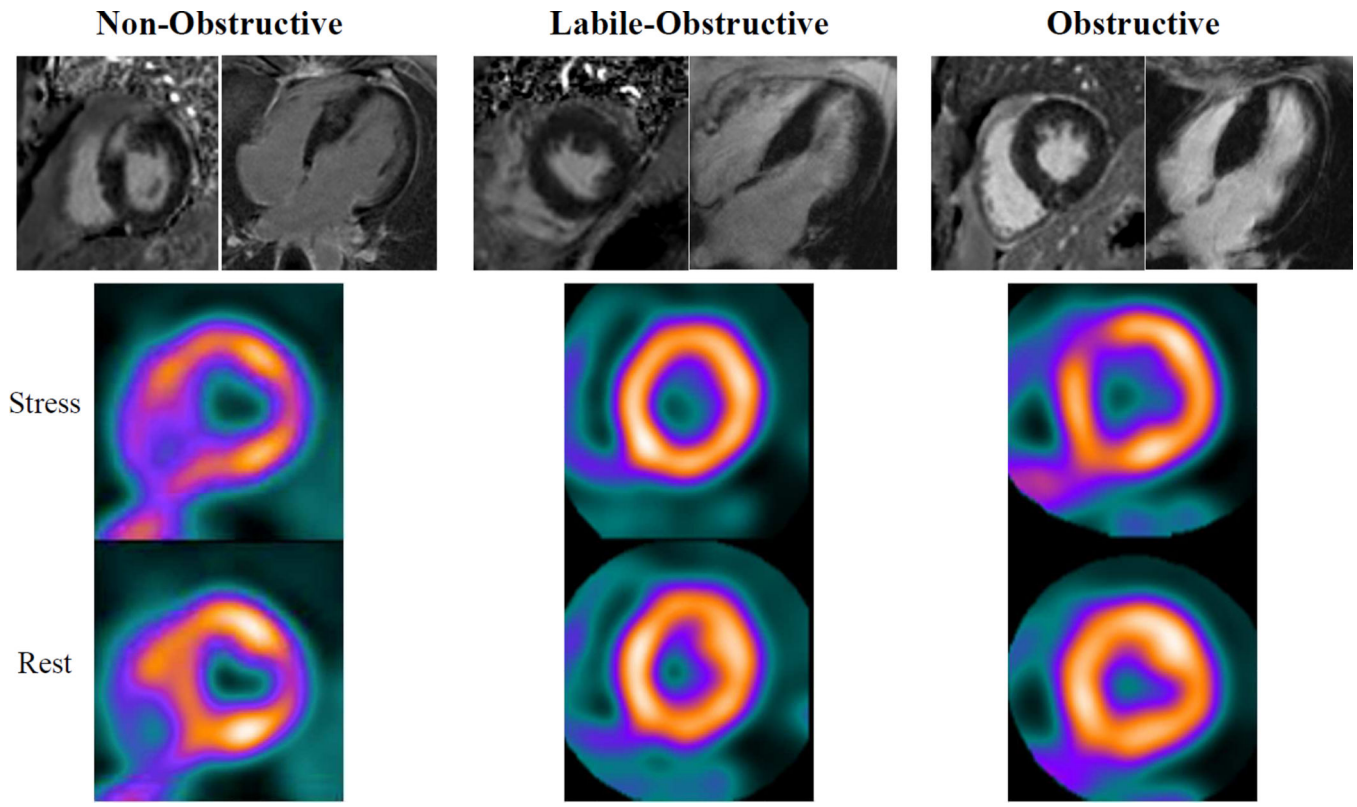


Figure 1. Representative magnetic resonance and PET images of the 3 HC groups

Patients without obstruction demonstrate higher late gadolinium enhancement (arrows) in magnetic resonance images. Non-obstructive and obstructive patients demonstrate perfusion abnormalities in PET images (arrows) compared to labile-obstructive, who demonstrate no clear perfusion abnormalities.

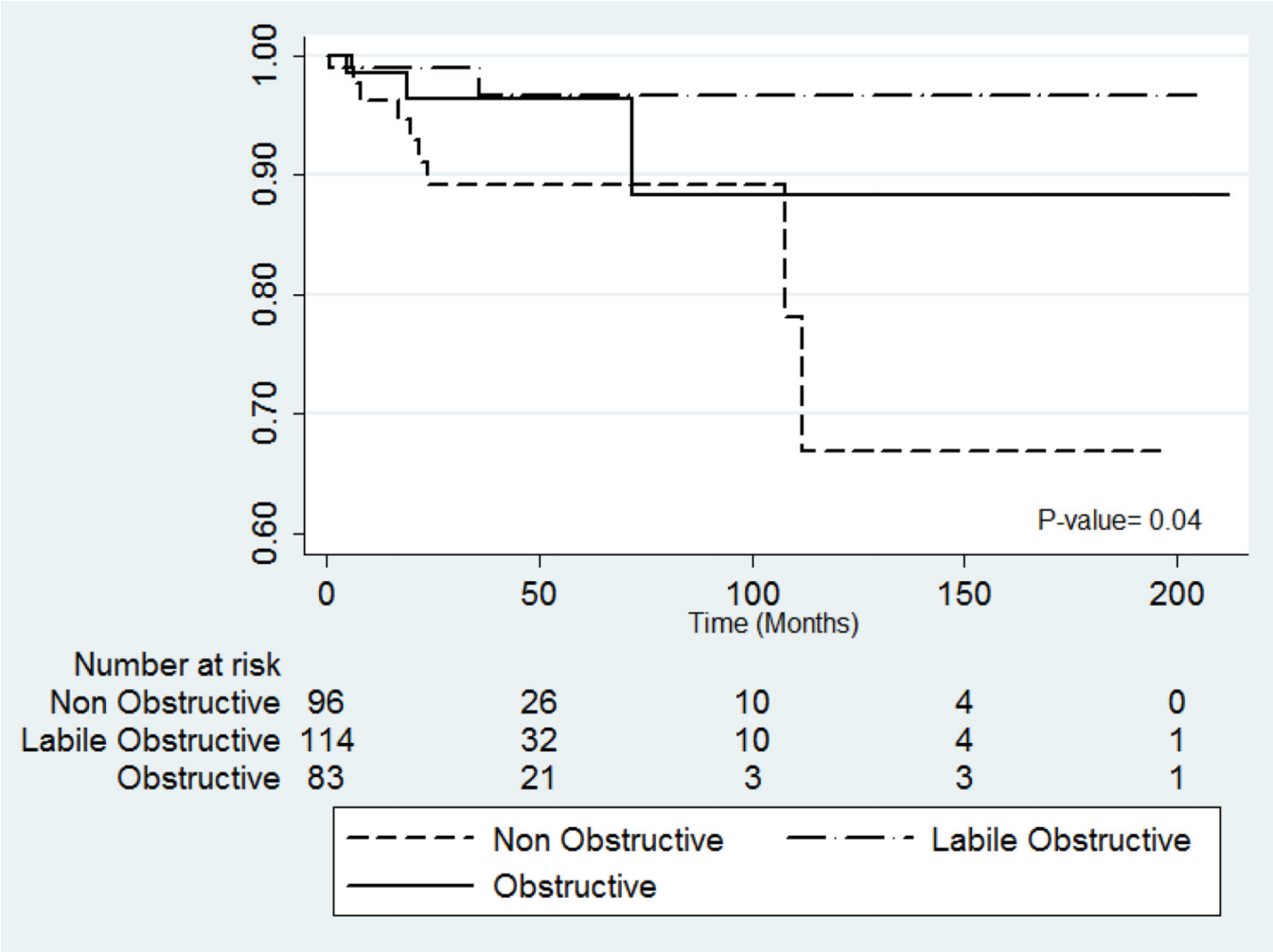
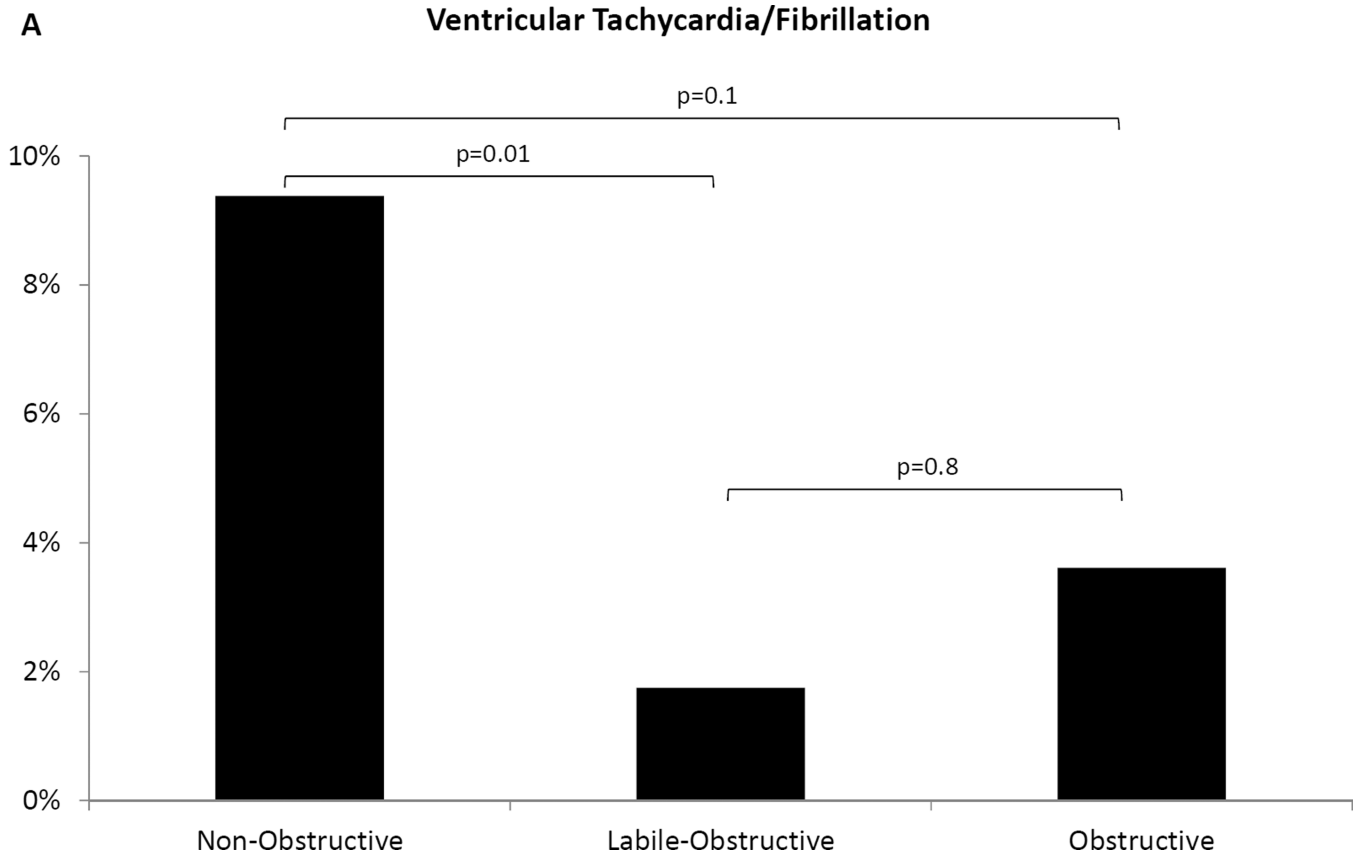


Figure 2. Kaplan-Meier curve for ventricular tachycardia/fibrillation events

Non-obstructive patients had a higher rate for ventricular tachycardia/fibrillation events.



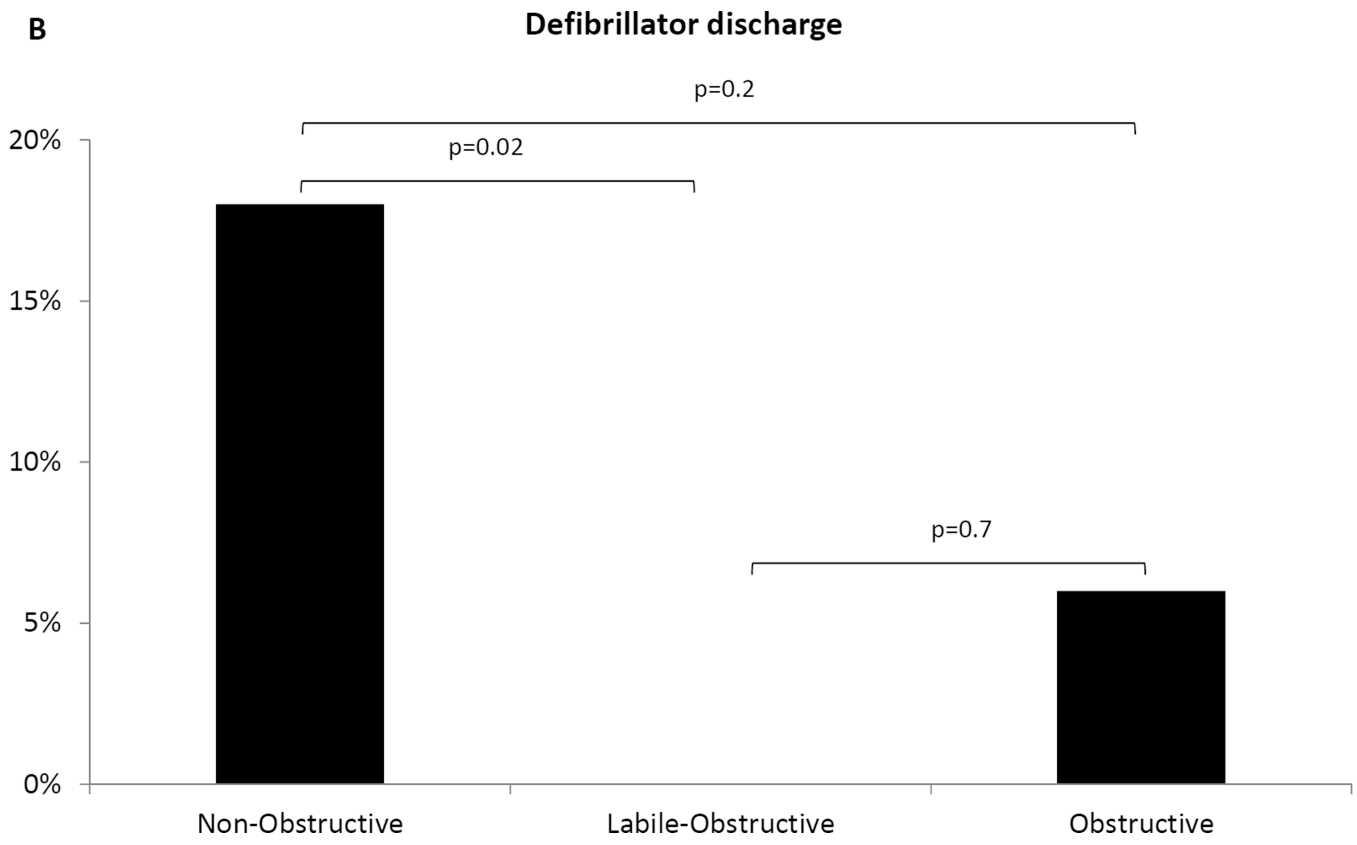


Figure 3. Ventricular tachycardia events and ICD discharges at follow-up

(A) Non-obstructive patients had the highest prevalence of ventricular tachycardia/ fibrillation events among the three groups. (B) More non-obstructive patients experienced appropriate ICD discharges compared to the other groups, while no events were recorded in the labile-obstructive group.

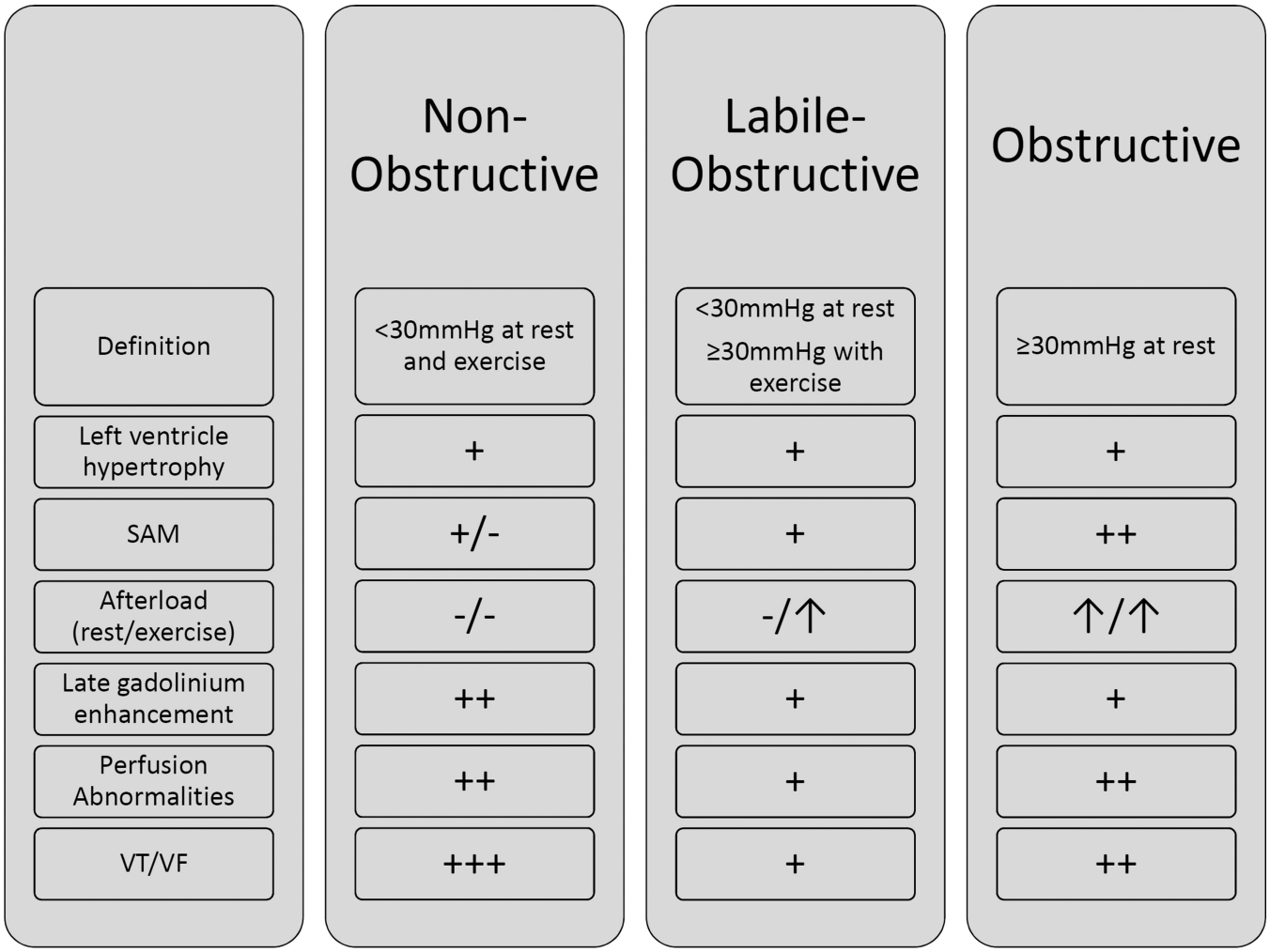


Figure 4. Summary of anatomic and clinical characteristics of the 3 HC hemodynamic subtypes

SAM: systolic anterior motion of mitral valve, VF: ventricular fibrillation, VT: ventricular tachycardia

Table 1

Baseline characteristics

Variable		Non-Obstructive (n=96)	Labile-Obstructive (n=114)	Obstructive (n=83)	Total (n=293)	p-value
Length of follow-up (years)		3.5±3.8	3.2±3.5	2.8±3.2	3.3±3.6	0.5
Age (years)		49±15	50±15	55±13	51±15	0.01
Male		60 (63%)	83 (73%)	51 (61%)	194 (66%)	0.2
Body Mass Index (kg/m^2)		29.4±5.7	29.7±5.3	30.4±6.0	29.8±5.7	0.5
NYHA	I	64 (67%)	71 (62%)	30 (36%)	165 (56%)	
	II	24 (25%)	24 (21%)	37 (45%)	85 (29%)	<0.001
	III	8 (8%)	19 (17%)	16 (19%)	43 (15%)	
Angina pectoris		33 (34%)	46 (40.4)	37 (44.6)	116 (39.6)	0.4
Syncope		17 (18%)	25 (21.9)	14 (17.1)	56 (19.2)	0.6
Ventricular tachycardia/fibrillation		10 (10%)	0 (0%)	1 (1%)	11 (4%)	<0.001
Non-sustained ventricular tachycardia		18 (19%)	9 (8%)	8 (10%)	35 (12%)	0.047
Atrial Fibrillation		17 (18%)	9 (8%)	8 (10%)	34 (12%)	0.08
Implantable Cardioverter Defibrillator		18 (19%)	6 (5%)	9 (11%)	33 (11%)	0.009
Family History						
Hypertrophic Cardiomyopathy		29 (31%)	16 (15%)	10 (12%)	55 (19%)	0.003
Sudden cardiac death		26 (27%)	28 (26%)	19 (23%)	73 (25%)	0.8
Sudden cardiac death risk factors		1.4±1.1	1.2±1.0	1.4±1.0	1.3±1.0	0.2
Medications						
β-blocker		68 (71%)	77 (68%)	67 (81%)	212 (73%)	0.1
Disopyramide		0 (0%)	6 (5%)	5 (6%)	11 (4%)	0.06
Ca-blocker		13 (14%)	28 (25%)	25 (30%)	66 (23%)	0.02

Table 2

Exercise Echocardiography

Variables		Non-Obstructive	Labile-Obstructive	Obstructive	Total	p-value
Max wall thickness (cm)		2.0±0.5	2.0±0.5	2.2±0.5	2.1±0.5	0.1
Left atrium (cm)		4.0±0.7	4.1±0.7	4.5±0.7	4.2±0.7	<0.001
Ejection fraction (%)		63±10	64±8	65±9	64±9	0.2
E/A		1.4±0.8	1.3±0.5	1.3±0.7	1.3±0.6	0.4
E/e'		16±9	17±9	24±13	19±11	<0.001
Left ventricular outflow tract gradient at rest (mmHg)		8±4	15±7	58±25	25±26	<0.001
Left ventricular outflow tract gradient at stress (mmHg)		18±6	69±42	111±40	64±50	<0.001
Systolic anterior motion of mitral valve	no	41 (43%)	31 (27%)	2 (2%)	74 (25%)	<0.001
	incomplete	54 (57%)	68 (60%)	44 (53%)	166 (57%)	
	complete	0 (0%)	15 (13%)	37 (45%)	52 (18%)	
Exercise time (seconds)		552±195	573±224	486±184	545±206	0.04
Exercise capacity (METs)		10.7±3.6	10.6±4.4	8.0±3.5	9.9±4.1	<0.001
Heart rate at rest (beats/min)		66±13	63±14	65±12	65±13	0.2
Systolic blood pressure at rest (mmHg)		128±19	134±17	131±18	131±18	0.05
Diastolic blood pressure at rest (mmHg)		77±12	78±11	74±11	76±11	0.05
Heart rate at stress (beats/min)		147±27	147±28	135±26	143±27	0.004
Systolic blood pressure at stress (mmHg)		166±30	167±34	147±34	161±34	<0.001
Diastolic blood pressure at stress (mmHg)		82±17	84±17	75±17	81±18	0.002
Age-predicted heart rate (%)		86.1±14.5	86.7±14.3	81.2±14.1	84.9±14.5	0.02

Table 3

Cox proportional hazard ratios (95% confidence interval) for the prediction of ventricular tachycardia/ fibrillation

	Unadjusted Hazard Ratio (95% CI)	p-value	Adjusted Hazard Ratio* (95% CI)	p-value
HC group				
Non-Obstructive	1.0	-	1.0	-
Labile-Obstructive	0.18 (0.04–0.84)	0.03	0.2 (0.04–0.98)	0.04
Obstructive	0.45 (0.12–1.66)	0.23	0.5 (0.11–2.02)	0.31

*Adjusted for age, gender, syncope, family history of sudden cardiac death, max wall thickness ≥3cm and abnormal blood pressure response.