Clinical Outcomes in Patients with Excessive Trabeculation-Phenotype Left Ventricle

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Abstract

Objective: Trabeculation shows highly various presentations while noncompaction (NC) is a specific disease entity based on arithmetically wall thickness. We aimed to evaluate the clinical implications of trabeculation and its relevance to outcomes. Methods: total of 296 patients (age 63 ± 12 years; 64% men) with trabeculation who underwent echocardiography were retrospectively identified between January 2011 and December 2012. Analyses were conducted on distinguished trabeculation which was divided into noncompaction (NC) (maximum noncompacted/compacted ratio [?] 2.0) or hypertrabeculation (HT) (ratio < 2.0). We evaluated features of trabeculation and explored cardiovascular (CV) outcome events (coronary revascularization, hospitalization for worsening heart failure (HF), stroke, nonsustained ventricular tachycardia (VT), implantation of an implantable cardioverter defibrillator (ICD), and CV death). Results: Over a mean of 4.2 years, CV outcome events occurred in 122 (41%) patients who were older and had a higher frequency of diabetes mellitus, HF, stroke, and implantation of ICD. The frequencies of NC or HT, the trabeculation ratio, and its manifestation were similar among patients with and without events. NC/HT with concomitant apical hypocontractility and worsening systolic function were univariable predictors of adverse events. On multivariable analysis, concomitant apical hypocontractility on NC/HT still remained significant (HR 15.8, 95% CI 3.8-39.4, p < 0.001), together with old age, HF, and increased E/e' ratio. Conclusions: NC/HT with concomitant apical hypocontractility provided clues about the current medical illness and aided in risk-stratification.

INTRODUCTION

Noncompaction (NC) is characterized with a more excessively trabeculated layer than the compacted layer in the left ventricle (LV) and it can be accompanied with or without decreased contractility of the trabeculated or remote wall.[1-3] Unlike the rare isolated NC cardiomyopathy, NC or even just hypertrabeculation (HT) not meeting NC criteria can be frequently observed in various cardiac diseases such as coronary artery diseases (CADs) or heart failure (HF) including dilated or hypertrophic cardiomyopathy; however, there is not enough consensus over a casual relationship between these manifestations because NC or HT can be seen even in normal healthy subjects, and the differentiation of isolated NC cardiomyopathy from NC/HT-phenotype LV remains difficult (for genetic or acquired disorders) in clinical practice.[4-9]

Considering the common findings of trabeculation between genetic cardiomyopathy and sporadic form without family history, there is the question of whether trabeculation *per se* or a relevant potential abnormality is crucial for clinical physicians to predict CV events.[9-12] Therefore, we aimed to demonstrate the clinical implication of NC and HT, and explore their associations with CV adverse outcomes using a cohort of NC/HT patients from a single tertiary university hospital center.

METHODS

Patients and Echocardiography

We retrospectively reviewed all consecutive patients with NC/HT-phenotype LV who underwent echocardiography at the Keimyung University Dongsan Cardiovascular Imaging Center (Daegu, South Korea) between January 2011 and December 2012. Comprehensive integrated echocardiography was performed in all study patients according to the current guidelines. LV chamber quantifications such as dimension and wall thickness were performed and LV ejection fraction (EF) was calculated using the modified biplane Simpson's method. LV systolic dysfunction was defined as an LVEF $< 50\%$. Mitral inflow and tissue Doppler velocity imaging of the mitral annulus were analyzed. The degree of each valvular insufficiency was assessed using semiquantitative methods such as 4 grades of regurgitation (1+ to 4+).

Noncompaction and Hypertrabeculation

The noncompacted and compacted layers on echocardiography were reviewed by two experienced physicians (H.K. and I-C.K.) blinded to the patients' clinical data and each other's results. A binary dichotomous classification was applied to characterize trabeculation manifestation: NC vs. HT. The layer thickness was measured during systole with the trabeculation maximally thickened in the parasternal short-axis or apical 2-/3-/4-chambver view (Figure 1). The maximal ratio of the noncompacted to compacted layer was determined and NC was defined as a ratio [?] 2.0 at end-systole in the parasternal short-axis or apical view, as was based on adopted criteria from Jenni et al.[1] On the other hand, HT was defined if the criteria of NC were not met: i.e., if the maximal ratio was less than 2.0, but more than 0.5, which was based on the study of normal healthy LV trabeculation by Dawson et al. because of a lack of data for normal LV trabeculation.[13] Trabeculation was identified in 16 segments and the sum of each trabeculation segment was calculated. Regional wall motion abnormality (RWMA) was also evaluated. The exclusion criteria were patients who showed poor echocardiographic imaging, patients who had a malignancy, patients with chronic renal failure with renal replacement therapy, patients with a poor life expectancy, patients with an active infection, or patients who did not have baseline characteristics or follow-up data.

Clinical Outcomes

A thorough review of the medical records was conducted for the baseline characteristics of all study subjects, and the clinical outcomes were evaluated. CV events were defined as a primary composite of the occurrence of coronary revascularization, hospitalization for worsening HF, stroke, arrhythmia of nonsustained ventricular tachycardia (VT), implantation of an implantable cardioverter defibrillator (ICD), and CV death. CV death was confirmed by a review of the patient's medical record or death certificate or phone calls with the next of kin. Follow-ups were censored for non-CV-related death or when the patient's follow-up records were no longer available. This study conforms to the ethical guidelines of the Declaration of Helsinki and was approved by the institutional review board at Keimyung University Dongsan Medical Center. Written informed consent was waived because of the retrospective nature of the study.

Statistical Analysis

For continuous variables, the means $\pm$ standard deviations are presented, and Student's t-test and Pearson's correlation were used to compare between the groups. For discrete variables, the frequency (or percentage) is presented and a chi-square test was used for comparisons. A Kaplan-Meier survival curve was constructed with the log-rank test. Univariable predictors were incorporated into multivariable Cox hazard regression analysis to determine the significant independent factors associated with adverse clinical outcomes. Inter- and intra-observer variability for the ratio of noncompacted to compacted layers was evaluated using the intraclass correlation coefficient (ICC) on 21 randomly selected trabeculation images. For intra-observer variability, the same observer evaluated the same image > 2 weeks later and for interobserver variability, the other observer, blinded to the results of the first observer, evaluated the trabeculation images. A p-value < 0.05 was considered significant, and all analyses were performed using the Statistical Package for Social Science version 13.0 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

Out of the 329 patients, 33 were excluded due to poor echocardiographic imaging and lack of follow-up

data. Finally, 296 patients (mean age: 62.5 ± 12.2 years, 63.5% men) were analyzed with a mean follow-up duration of 4.2 ± 2.5 years in the present study. Follow-up completeness was 93.2%, which was obtained by the index devised by Clark et al.[14] During follow-up, 122 patients experienced the specified composite endpoint: 14 coronary revascularization, 56 worsening HF, 17 stroke, 13 nonsustained VT, 9 implantations of ICD, and 13 CV death.

Baseline Findings

As shown in Table 1, patients who reached the composite endpoint were older and had more comorbid illnesses (a higher frequency of diabetes mellitus, HF, stroke, and ICD implantation) than those without events. Consistent with comorbidities, antiplatelets, anticoagulation, and diuretics were more frequently used in the event group. However, there was no difference regarding the frequency of atrial fibrillation, hypertension, and CAD between the two groups.

Echocardiographic Features

Regarding the baseline echocardiographic findings, the events group exhibited a dilated LV cavity, reduced LVEF, and increased left atrial dimension, resulting in an elevated E/e' ratio and worse valvular insufficiency findings compared with the no event group (Table 2). Trabeculation manifestations of both NC and HT were similar in terms of regional distribution and trabeculation thickness (Jenni's ratio). On the other hand, the hypocontractility was associated with a high event rate. Also associated with event occurrence were many hypocontractile segments manifested in NC or HT region. The inter- and intra-observer ICCs were 0.97 and 0.98 for noncompacted layers, and 0.95 and 0.97 for compacted layers, respectively.

Clinical Adverse Outcomes

Table 3 shows the results of univariable and multivariable Cox regression analysis. Old age, elevated E/e' ratio, low LVEF ($< 50\%$), and history of HF and CAD were related to event occurrence in univariable analysis. However, the manifestation of both NC (as a categorical variable) and Jenni's ratio (as a continuous variable) was not associated with an event. Similarly, the number of NC or HT segments was not associated with CV events, as was also true for apical manifestations of NC or HT. When analyzed in terms of RWMA over NC or HT, we found significantly strong effects of RWMA on CV events, and NC or HT with specifically concomitant apical, mid, and basal hypocontractility was related to the composite endpoint.

After adjusting for trabeculation parameters and other univariable predictors, old age, E/e' ratio, past history of HF, and NC or HT with concomitant apical wall motion abnormalities were independently related to the composite endpoint, whereas history of CAD and mid or basal RWMA associated with NC or HT were no longer significant. The Kaplan-Meier survival curve showed higher event rates in those who had NC or HT with concomitant hypokinesia than those without, as was more prominently noticeable in apical region (Figure 2).

DISCUSSIOIN

Manifestation of Trabeculation in Ventricular Cavity

An NC/HT-phenotype LV can be frequently encountered in clinical practice, whereas isolated NC cardiomyopathy is a rare disease entity.[6-8] According to recent studies on a large population cohort, the incidence of NC may reach up to 39-43%, irrespective of the etiology of trabeculation.[5,6]However, the manifestation of trabeculation is highly variable in terms of its distribution and it is difficult for clinical physicians to estimate to what extent trabeculation may contribute to LV dysfunction or CV events.[9,10,15]

Although the cut-off values of 2.0 such as Jenni's criteria is suggested to define NC, the grade or severity of NC thickness appears less important in the present study to predict clinical outcomes than expected; CV events may develop even in patients who do not meet the NC criteria. Unfortunately, none of the existing NC criteria based on echocardiography or cardiac magnetic resonance (CMR) imaging was associated with adverse outcomes.[5,7,8,16] Moreover, it is difficult to recognize whether NC/HT-phenotype LV dysfunction is due to the natural course of trabeculation or secondary to other concomitant cardiac disorders. Thus, we

could not confirm whether clinical outcomes and LV dysfunction were related to trabeculation severity, and whether the current definition of trabeculation ratio or thickness has clinical implications remains a basic unanswered question.

Association of Trabeculation with Medical Comorbidity

When encountered with excessive trabeculation, it is not easy to determine whether the thickness severity or extent of trabeculation is related to a certain underlying medical illness. We observed that CAD frequently prevailed among medical comorbidities, particularly in patients who had both apical trabeculation and abnormal contractility, although the prevalence of CAD has been reported to be relatively low in other studies.[17,18] This may be explained by the fact that coronary microcirculatory dysfunction or reduced flow reserve in noncompacted segments has been observed in radionuclide or echocardiographic studies, and the decreased thickness of compacted layers in the trabeculated wall fails to maintain coronary perfusion, leading to aggravation of LV thrombus formation and remodeling.[19-21] Furthermore, it is noteworthy that an impairment of coronary flow was not only restricted to noncompacted segments, but also extended to remote compacted segments; these coronary flow dysfunctions were evidenced by the detection of myocardial fibrosis using CMR imaging.[16,22] Thus, the underlying myocardial dysfunction in noncompacted as well as compacted walls may be a contributing risk factor for future CV events, and CAD can be frequently observed in patients with both noncompaction and hypocontractility.[2,19,20]

Regarding the cause-and-effect between trabeculation and high frequency of CV comorbidities, it is not easy to fully evaluate the relevant etiologies or to identify CV risk stratification. In other words, it remains unclear whether trabeculation-phenotype LV is an epiphenomenon in response to pressure-/volume-loading or ischemic stress; the reason for that is most ischemic LVs usually show thin, hypocontractile, or further dyskinetic aneurysm rather than an excessively trabeculated wall.[9] Overall, we can expect that trabeculation may indeed play a key role for a fingerprint of an underlying CAD or a risk factor for CV events because of following some issues considered: first, it is difficult to distinguish healthy normal variants from isolated NC cardiomyopathy which has a low prevalence. Second, the manifestation NC/HT-phenotype LV are similarly equivocal, both of which are frequently observed in clinical practice. Third, the growing advanced imaging modalities allow an increased detection of NC/HT-phenotype LV, which would shed new light on risk factor and further a CV prognosis, irrespective of etiologies.

In the current study, hypocontractility was revealed as an important factor of clinical outcomes. In cases of hypocontractility in deep recess/trabeculations segment, microemboli or thrombi embedded in an involved segment would have the chance for systemic embolization. It should be also emphasized that apical trabeculation with concomitant hypokinesia may not sufficiently obliterate the LV apex. This failure of apical obliteration would raise the chance of embolization more crucially than in other segments. This is because the apical segment has just two muscle fibers, the longitudinal and circumferential layers, which lack radial force.

Limitations

However, there are some limitations that should be addressed and considered. First, this study was conducted by retrospectively reviewing medical records. Therefore, a clear causal relationship between trabeculation and clinical outcomes could not be explored completely. But the association of medical illness with NC or HT might be considered for the risk-stratification of CV events. Second, pathologic or genetic studies were not obtained. Thus, more research is required in the near future.

COCLUSIONS

Patients with HT revealed similar clinical outcomes compared to those with NC. Among these NC and HT groups, the echocardiographic findings regarding the severity of trabeculation did not contribute to adverse outcomes. However, more importantly, the involved regions of trabeculation, including the LV apex, were significantly related to clinical outcomes and could better aid in risk-stratification for CV events compared to the severity of trabeculation *per se* . In the present study addressing nonspecific patients referred for echo-

cardiography, NC/HT-phenotype LV discovered to have concomitant apical hypocontractility is becoming a useful indicator of CV events.

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Funding and conflicts of interest

None

Ethics approval

This study was approved by the Institutional Review Board of the Keimyung University Dongsan Medical Center (IRB FILE No.: 2020-01-039).

Author contributions

Hyungseop Kim: Concept/design, Interpretation, Drafting, Methodology, Writing-Original Draft, Writing-Review & Editing, Approval.

In-Chol Kim: Data analysis/Interpretation, Validation, Investigation, Writing-Review & Editing.

Jin-Wook Chung: Drafting, Statistics, Data Collection. Critical revision of article.

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Table 1 Baseline characteristics of study patients according to events

Variable	Events (-) (n = 174)	Events (+) (n = 122)	p Value
Age (years)	60.6 ± 13.0	65.2 ± 10.4	0.001
Male	103 (59)	85 (70)	0.07
Height (cm)	162.3 ± 9.5	162.3 ± 9.1	0.95
Weight (kg)	62.3 ± 11.4	60.7 ± 11.2	0.24
Systolic BP (mmHg)	125.8 ± 17.2	124.1 ± 21.5	0.44
Diastolic BP (mmHg)	74.3 ± 13.5	74.5 ± 12.5	0.91
Heart rate (bpm)	76.0 ± 12.5	77.4 ± 15.0	0.39
Co-morbidity			
Atrial fibrillation	15 (9)	12 (10)	0.84
Hypertension	75 (43)	64 (53)	0.13
Diabetes mellitus	41 (24)	49 (40)	0.003
Coronary artery disease	52 (30)	43 (35)	0.38
Heart failure	25 (14)	56 (46)	< 0.001
Stroke	14 (8)	25 (21)	0.002
Implantation of ICD	0 (0)	7 (6)	0.002
Medications			
Antiplatelets	81 (47)	76 (62)	0.01

Variable	Events (-) (n = 174)	Events (+) (n = 122)	p Value
Anticoagulations	13 (8)	17 (14)	0.08
Beta-blockers	70 (40)	60 (49)	0.15
Calcium-blockers	39 (22)	18 (15)	0.13
ACEi or ARBs	78 (45)	66 (54)	0.13
Statin	89 (51)	63 (52)	1.00
Diuretics	36 (21)	64 (53)	< 0.001

BP, blood pressure; PM, pacemaker; ICD, implantable cardioverter defibrillator; ACEi, angiotensin converting enzyme inhibitor; ARBs, angiotensin receptor blockers.

Data are expressed as mean ± SD or as percentages.

Table 2 Echocardiographic findings according to events

Variable	Events (-) (n = 174)	Events (+) (n = 122)	p Value
LVEDd (cm)	5.23 ± 0.59	5.86 ± 0.95	< 0.001
LVESd (cm)	3.67 ± 0.93	4.57 ± 1.31	< 0.001
IVST (cm)	0.96 ± 0.16	0.95 ± 0.38	0.79
PWT (cm)	0.92 ± 0.17	0.93 ± 0.18	0.82
LVEF (%)	53.8 ± 15.0	39.3 ± 16.5	< 0.001
LAD (cm)	3.98 ± 0.76	4.53 ± 0.77	< 0.001
Mitral inflow study			
Mitral E (m/s)	0.72 ± 0.26	0.76 ± 0.32	0.23
TDI-s' (cm/s)	6.22 ± 1.57	5.16 ± 1.69	< 0.001
TDI-e' (cm/s)	5.69 ± 1.99	4.76 ± 1.90	< 0.001
E/e' ratio	13.2 ± 5.4	16.8 ± 7.2	< 0.001
PASP (mmHg)	25.7 ± 10.7	32.0 ± 15.8	< 0.001
Valvular insufficiency			
MR grade	2.48 ± 0.68	2.85 ± 0.82	< 0.001
AR grade	1.59 ± 0.89	1.89 ± 0.94	0.01
TR grade	2.24 ± 0.77	2.48 ± 0.80	0.01
NC	97 (56)	76 (62)	0.28
No. of NC segment	3.43 ± 3.83	3.70 ± 3.71	0.54
No. of HT segment	4.14 ± 2.90	4.16 ± 3.17	0.96
Jenni's ratio	2.21 ± 0.98	2.31 ± 0.87	0.36
Manifestation of HT			
Apical HT	144 (83)	93 (76)	0.19
Mid HT	86 (49)	68 (56)	0.29
Basal HT	15 (9)	17 (14)	0.18
Manifestation of NC			
Apical NC	96 (55)	76 (62)	0.23
Mid NC	57 (33)	44 (36)	0.62
Basal NC	4 (2)	4 (3)	0.72
Hypocontractility			
With HT	38 (22)	44 (36)	0.008
No. of HT segment	1.08 ± 2.47	1.96 ± 3.24	0.012
With NC	58 (33)	72 (59)	< 0.001
No. of NC segment	1.78 ± 3.11	3.06 ± 3.43	0.001
Concomitant hypocontractility			

Variable	Events (-) (n = 174)	Events (+) (n = 122)	p Value
Apical NC/HT	90 (52)	119 (98)	< 0.001
Mid NC/HT	72 (41)	87 (71)	< 0.001
Basal NC/HT	34 (20)	47 (39)	0.001

LVEDd, left ventricular end-diastolic dimension; LVESd, left ventricular end-systolic dimension; IVST, interventricular septal thickness; PWT, posterior wall thickness; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; TDI-s', systolic tissue Doppler imaging of septal mitral annulus; TDI-e', early diastolic tissue Doppler imaging of septal mitral annulus; PASP, pulmonary arterial systolic pressure; MR, mitral regurgitation; AR, aortic regurgitation; TR, tricuspid regurgitation; HT, hypertrabeculation; NC, noncompaction.

Data are presented as mean ± SD or n (%).

Table 3 Univariable and multivariable Cox regression for events

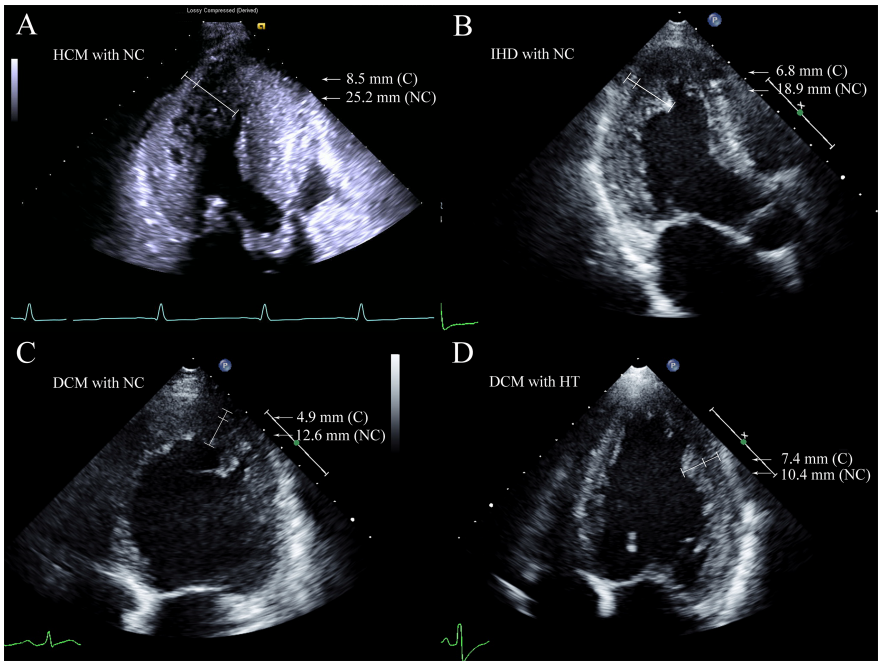
Variable	Univariable	Univariable	Univariable	Multivariable	Multivariable	Multivariable
	HR	95% CI	p Value	HR	95% CI	p Value
Age (years)	1.03	1.02-1.05	< 0.001	1.02	1.00-1.04	0.01
E/e' ratio	1.07	1.05-1.10	< 0.001	1.03	1.01-1.05	0.01
LVEF < 50%	3.43	2.07-5.67	< 0.001	0.65	0.33-1.28	0.22
NC (+)	1.20	0.83-1.75	0.34	-	-	-
Jenni's ratio	1.05	0.88-1.27	0.58	-	-	-
History of HF	3.19	2.21 - 4.59	< 0.001	1.65	1.09-2.48	0.02
History of CAD	1.54	1.21 – 1.50	0.03	1.07	0.67-1.25	0.31
Seg. of HT	1.01	0.95-1.08	0.71	-	-	-
Seg. of NC	1.05	0.99-1.11	0.98	-	-	-
Apical HT (+)	0.74	0.49-1.13	0.16	-	-	-
Apical NC (+)	1.27	0.87-1.84	0.21	-	-	-
NC-WMA (+)	2.10	1.46-3.02	< 0.001	1.35	0.48-3.79	0.57
HT-WMA (+)	1.53	1.05-2.23	0.03	1.15	0.39-3.40	0.79
NC/HT-Apical WMA	21.8	6.92-68.5	< 0.001	15.77	3.79-39.4	< 0.001
NC/HT-Mid WMA	2.87	1.93-4.27	< 0.001	1.15	0.67-1.97	0.63
NC/HT-Basal WMA	2.03	1.40-2.95	< 0.001	1.15	0.71-1.85	0.58

LVEF, left ventricular ejection fraction; NC, noncompaction; HF, heart failure; HT, hypertrabeculation; WMA, wall motion abnormality.

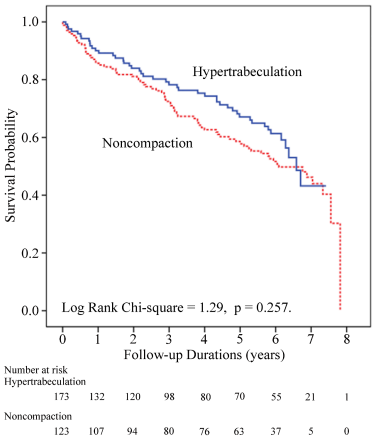
Figure legend

Figure 1. Determination of the maximal ratio of the noncompacted/compacted layer in different types of underlying heart diseases. Illustrative examples of noncompaction or hypertrabeculation are (A) Hypertrophic cardiomyopathy with noncompaction (ratio of 2.96), (B) ischemic heart disease with noncompaction (ratio of 2.78), (C) dilated cardiomyopathy with noncompaction (ratio of 2.57), and (D) dilated cardiomyopathy with hypertrabeculation (ratio of 1.41). C, compacted layer; NC, noncompacted layer.

Figure 2. Kaplan-Meier survival curve stratified by hypertrabeculation or noncompaction (A), trabeculation with or without apical (B), mid (C), and basal hypocontractility (D).



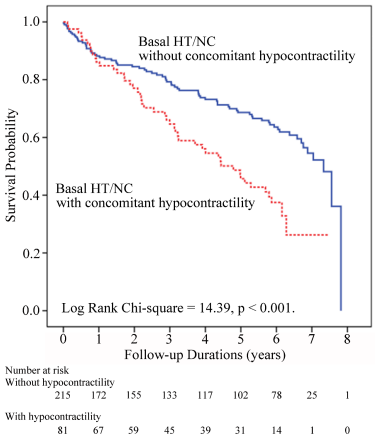
A



Number at risk

Hypertrabeculation	173	132	120	98	80	70	55	21	1
Noncompaction	123	107	94	80	76	63	37	5	0

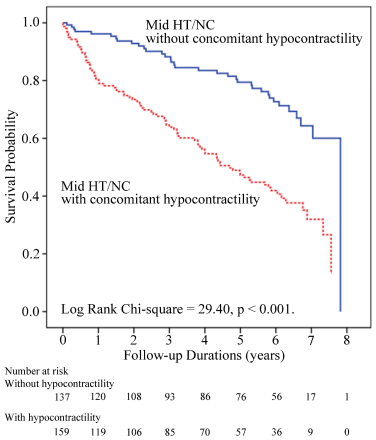
B



Number at risk

Without hypocontractility	215	172	155	133	117	102	78	25	1
With hypocontractility	81	67	59	45	39	31	14	1	0

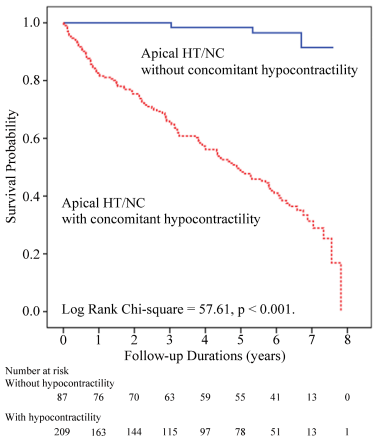
C



Number at risk

Without hypocontractility	137	120	108	93	86	76	56	17	1
With hypocontractility	159	119	106	85	70	57	36	9	0

D



Number at risk

Without hypocontractility	87	76	70	63	59	55	41	13	0
With hypocontractility	209	163	144	115	97	78	51	13	1