Left Ventricular Relaxation Half-Time as a Predictor of Cardiac Events in Idiopathic Dilated Cardiomyopathy and Hypertrophic Cardiomyopathy with Left Ventricular Systolic and /or Diastolic Dysfunction

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Running title: Prognostic value of $T_{1/2}$

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ABSTRACT

Purpose: Diastolic dysfunction preceding systolic dysfunction is considered an important interaction in cardiomyopathy with poor prognosis. The aim of this study was to compare left ventricular (LV) isovolumic relaxation with the other parameters as a potential prognostic marker for patients with idiopathic dilated cardiomyopathy (IDC) and hypertrophic cardiomyopathy (HC). Methods: A total of 145 patients with IDC and 116 with HC were evaluated for hemodynamic parameters; LV pressure was directly measured by a micromanometer catheter, and relaxation half-time ($T_{1/2}$) was used to determine LV isovolumic relaxation. The median follow-up period was 4.7 years. Results: The mean ages of the patients with IDC and HC were 52.0 ± 12.0 and 57.1 ± 12.4 years, respectively. Each patient group was further divided into 2 groups based on the median value of $T_{1/2}$: (1) <41.0 ms (D-L group) and ≥41.0 ms (D-H group) (2) <38.5 ms (H-L group) and ≥38.5 ms (H-H group). Kaplan–Meier analysis showed a significantly higher probability of cardiac events in the D-H group than in the D-L group ($P = 0.001$) and in the H-H group than in the H-L group ($P = 0.028$). Further, Cox proportional hazard regression analysis revealed that $T_{1/2}$ was an independent predictor of cardiac events for patients with IDC (hazard ratio, 1.109; $P = 0.007$) and HC (hazard ratio, 1.062; $P = 0.041$). In conclusion, regardless of the type of cardiomyopathy, $T_{1/2}$ as a measure of LV isovolumic relaxation function was found to be associated with the occurrence of cardiac events.

Key words; isovolumic relaxation, relaxation half-time, prognosis

INTRODUCTION

Several studies have suggested that left ventricular (LV) diastolic functional damage, especially LV relaxation, precedes the abnormalities in systolic ventricular performance. [1,2] Therefore, LV diastolic dysfunction is gaining increased recognition as a cardiac disorder and cause of heart failure (HF). [3-5] Conceptually, diastolic function can be separated into four components: LV isovolumic relaxation, filling, distensibility, and muscle stiffness. [6] Isovolumic relaxation is defined as the time from when the aortic valve closes to when the mitral valve opens (Fig. 1). Relaxation half-time ($T_{1/2}$) measured by cardiac catheterization is the time for the pressure at the beginning of isovolumic relaxation to decrease by one-half (Fig. 2); this parameter is considered a gold standard for evaluating the LV relaxation function. [7,8] LV relaxation appears to be independent of preload and afterload (end-diastolic pressure, peak LV pressure, stroke volume, and end-systolic fiber length). [9] Because relaxation is regarded as an active process, we hypothesized that LV relaxation reflects latent myocardial damage in patients with various type of cardiomyopathy.

METHODS

From April 2000 and March 2017, we enrolled 475 consecutive patients with cardiomyopathy at Nagoya University Hospital, Japan. All underwent cardiac catheterization to help assess their general

condition. IDC was defined by LV ejection fraction (EF) <50% and LV end-diastolic diameter >55 mm as determined by echocardiography, and HC was defined as LVEF >50% and maximal LV wall thickness >15 mm by echocardiography. After excluding secondary cardiomyopathy, ischemic cardiomyopathy, and valvular heart disease, 145 IDC patients and 116 HC patients were finally enrolled (Fig. 3). The study protocol complied with the Declaration of Helsinki and was approved by the appropriate institutional review committee, and all the subjects provided written consent to participate in the study after being informed in detail of its purpose and methods.

All patients underwent M-mode, 2-dimensional, pulsed, and color tissue Doppler echocardiography with a phased array electronic ultrasound system using a Vivid 7 system (GE Healthcare, WI, USA). [10] LVEF was measured using the modified Simpson's method. The peak flow velocities at the mitral level during rapid filling (E) and atrial contraction (A), the E/A ratio, and the deceleration time were calculated from the pulsed Doppler echocardiography data. We recorded the tissue Doppler imaging wave of the mitral annulus from the septal side of the apical four-chamber view and analyzed the early diastolic filling velocity (E'). The operators making the echocardiographic evaluations were blinded to the patients' clinical status.

All the patients underwent biventricular cardiac catheterization analysis. Right heart catheterization was performed at rest using a 7F triple-lumen Swan–Ganz thermodilution pulmonary artery catheter (Edwards Life Science Co., Irvine, CA, USA). After collecting the baseline hemodynamic data, LV

pressure was measured by advancing a 6F fluid-filled pigtail catheter with a high-fidelity micromanometer (CA-61000-PLB Pressure-tip Catheter, CD Leycom, Zoetermeer, The Netherlands) into the LV cavity through either the right or the left upper limb artery. Micromanometer pressure signals and standard electrocardiograms were recorded online using a multichannel recorder. LV pressure signals were digitized at 3-ms intervals and analyzed using a 32-bit microcomputer system equipped with software developed in-house. LV pressure and heart rate (HR) were determined as the average values for at least 13 consecutive beats. To evaluate LV isovolumic relaxation, we computed $T_{1/2}$, defined as the time required for the cavity pressure at LV dP/dt_{min} to be reduced by one-half, according to the method of Mirsky (Fig. 2). [2,7] After the measurement of LV pressure, left ventriculography was performed and the LV volume was calculated by the area–length method.

We followed up all the patients for the occurrence of primary events, defined as sudden cardiac death, ventricular tachycardia, or admission because of deteriorating HF.

Normally distributed data are presented as means ± SD and non-normally distributed variables as medians with interquartile ranges. For the baseline characteristics and hemodynamic variables, Student's *t*-test was used to evaluate comparisons of normally distributed continuous variables and the Mann–Whitney *U*-test for non-normally distributed continuous variables. Categorical variables were compared by using either the chi-square or Fisher's exact test. In addition to comparisons between the IDC and HC patient groups, each of these groups was subdivided into two subgroups

according to the median $T_{1/2}$ for the group. Cox proportional hazard regression analysis was performed to identify the independent predictors of cardiac events. A stepwise forward selection procedure was applied. Cumulative cardiac event estimates were calculated by the Kaplan–Meier method, with differences between the survival curves assessed by the log-rank test. All analyses were performed with JMP pro 13. A *P*-value of <0.05 was considered statistically significant.

RESULTS

The median value of $T_{1/2}$ was 41.0 ms for the IDC patients and 38.5 ms for the HC patients. Each patient group was divided into two subgroups (High; H and Low; L) on the basis of these median values of $T_{1/2}$: D-L group ($T_{1/2}$ < 41.0 ms; n = 72), D-H group ($T_{1/2} \geq$ 41.0 ms; n = 73), H-L group ($T_{1/2}$ < 38.5 ms; n = 58), and H-H group ($T_{1/2} \geq$ 38.5 ms; n = 58). Table 1 summarizes the comparisons between the subgroups. There were no significant differences in age and sex between the two subgroups for either the IDC or the HC patients. At the time of enrollment into the study, the prevalence of beta blockers treatment was significantly lower in the D-L group than in the D-H group. However, there were no significant differences between the D-L group and D-H group in HR, LVEF, E/A ratio, E/E' ratio, deceleration time, cardiac index, or mean pulmonary artery pressure, although the pulmonary capillary wedge pressure (PCWP) was significantly higher and LV dP/dt_{max} was significantly lower in the D-H subgroup compared with the D-L subgroup. There were no

significant differences between the H-L group and H-H subgroups in LVEF, E/E' ratio, or deceleration time. However, HR was lower and the E/A ratio, PCWP, and mean pulmonary artery pressure were significantly higher in the H-H subgroup than in the H-L subgroup, whereas the cardiac index and LV dP/dt_{max} were significantly lower.

Table 2 summarizes the incidence of cardiac events. Of the 145 patients with IDC, 32 (22.1%) experienced cardiac events, including 3 (2.1%) sudden cardiac deaths, 4 (2.8%) patients with ventricular tachycardia, and 25 (17.2%) hospitalized because of worsening HF. Of the 116 patients with HC, 10 (8.6%) experienced cardiac events, including 3 (2.6%) sudden cardiac deaths, 5 (4.3%) patients with ventricular tachycardia, and 2 (1.7%) hospitalized because of worsening HF.

The cumulative probability event survival curves for the two patient groups and four subgroups are shown in Fig. 4. The median follow-up periods were the same for the IDC and HC patients, 4.7 years in both cases. The Kaplan–Meier survival curves demonstrated a significantly higher probability of cardiac events in the D-H subgroup than in the D-L subgroup ($P = 0.001$), and in the H-H subgroup than in the H-L subgroup ($P = 0.028$).

Table 3 summarizes the univariate analyses of factors possibly associated with cardiac events. The univariate analysis for the patients with IDC revealed that age, serum creatinine, serum hemoglobin, log B-type natriuretic peptide (BNP), LVEF, E/A ratio, PCWP, and $T_{1/2}$ were significant predictors

of cardiac events. For the patients with HC, E/A ratio, PCWP, mean pulmonary artery pressure, and $T_{1/2}$ were significant predictors of cardiac events. These variables were then subjected to stepwise multivariate analysis. This showed that high $T_{1/2}$ was a significant independent predictor of cardiac events in both patient groups (IDC: hazard ratio, 1.109; 95% confidence interval, 1.032–1.232; HC: hazard ratio, 1.062; 95% confidence interval, 1.002–1.122).

DISCUSSION

In the ventricular relaxation phase, there is dissociation of actin–myosin cross bridges and the recoil of elastic structures, and the reversal of tension requires energy to reduce the interaction between actin and myosin through the active uptake of Ca^{2+} in the sarcoplasmic reticulum. [11] Sarcoplasmic reticulum Ca^{2+}-ATPase 2a (SERCA2a) activity directly affects the speed of myocardial relaxation, because it determines the rate of Ca^{2+} sequestration from the cytoplasm into the sarcoplasmic reticulum. [12] It has also been reported that spontaneous diastolic Ca^{2+} release increased in the sarcoplasmic reticulum of failed hearts with diastolic dysfunction, triggering arrhythmias. Another related factor is β-adrenergic stimulation. This increases cytosolic cAMP and enhances the phosphorylation of phospholamban, a substrate within the myocyto that increases the Ca^{2+} sensitivity of SERCA2a and Ca^{2+} uptake into the sarcoplasmic reticulum, which consequently increases the rate

of relaxation.[13-15] On addition to SERCA2a function, recent research reveals that βarr2 (β-arrestin-2), which is one of the G protein-coupled receptor (GPCR) located in the membranes of all three major cardiac cell types (myocytes, fibroblasts and endotherial cells) enhance protein levels of SERCA2a. [16] In failing hearts, this series of myocardial functions may be damaged, and this may be associated with impairment of the isovolumic relaxation. Furthermore, an association has been reported between adrenergic sympathetic nerve function assessed by ^{123}I-MIBG scans and prolonged $T_{1/2}$ in IDC patients. [17] With regard to mitochondrial function, it has been reported that IDC patients with increased washout of ^{99m}Tc sestamibi showed reduced mRNA expression of proteins related to the mitochondrial electron transport chain, mitochondrial morphological abnormalities such as in shape and size, and degeneration of the cristae formation, and that this was associated with the impairment of isovolumic relaxation. [18] In addition, transient subendocardial ischemia in severe hypertrophy has been reported to affect ventricular relaxation. [19]

Traditionally, echocardiography with tissue Doppler imaging of mitral annulus motion has been used to assess diastolic function in patients with cardiomyopathy. This reflects the shortening and lengthening of the myocardial fibers in the long-axis dimension and shows a stronger correlation with LV relaxation than does conventional Doppler echocardiography. [20] In addition, the early diastolic velocity of the mitral annulus (E') acts as a relatively load-independent measure of LV relaxation. [21] Some reports have shown correlations with relaxation with both isovolumic relaxation

time measured by tissue Doppler imaging [22,23] and dp/dt_{min} measured from the Doppler spectrum of the mitral valve regurgitation jet in the apical 4-chamber view. [24] Speckle tracking echocardiography based on 2-dimensional echocardiography provides high accuracy for diagnosing diastolic dysfunction in HC, and the strain rate during the isovolumic relaxation period and the peak early diastolic strain rate show close correlation with the time constant of isovolumic pressure decay measured by cardiac catheterization. [25] Speckle tracking echocardiography can be used to estimate this time constant noninvasively and accurately, with results reported to correlate well with those obtained by cardiac catheterization ($r = 0.693$). [26] Although echocardiography is rapid and noninvasive and provides information at the bedside, it does not allow the direct estimation of diastolic ventricular function; this requires expertise and is contingent on the presence of adequate views. [27] It is therefore difficult to evaluate agreement between institutions and variability within and between observers. [20,21,28] Furthermore, these echogenic indexes are affected by preload, elastic recoil, lengthening load, and the duration of systole. In the diastolic phase, isovolumic relaxation starts at the time when LV ejection terminates with the closure of the aortic valve, and ends when the LV pressure decreases below the left atrial pressure and the mitral valve opens. During that time, the ventricle is a closed chamber with little change in volume, and it is not affected by ventricular ejection or filling. [7] Importantly, the impairment of isovolumic relaxation starts at the early stage of HF in patients with no or slight symptoms.

This study had some limitations. First, this was a single-center study with a small number of patients and only a small number of cardiac events. Second, $T_{1/2}$ requires catheterization, which is relatively invasive; it is therefore difficult to repeatedly assess changes over time in the dysfunction of isovolumic relaxation, particularly in asymptomatic patients. Third, a disadvantage of $T_{1/2}$ is that it is based on pressure measurements at only two points of LV pressure curve, which increases the error in its determination. To increase precision in this study, we calculated $T_{1/2}$ as the average of 13 consecutive beats without a premature beat. Fourth, the longer R-R interval might affect $T_{1/2}$ values, however, Gilbert L et al. reported that isovolumic relaxation rate was independent of preload and afterload, and this was independent of HR, except at very HR. [9] Actually, there was no strong relationship between HR at baseline and $T_{1/2}$ in these subgroups (supplemental figure).

In conclusion, LV isovolumic relaxation function estimated by $T_{1/2}$ is a predictor of the occurrence of cardiac events in patients with cardiomyopathy, both IDC and HC.

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CONFLICT OF INTEREST

None declared.

FIGURE LEGENDS

Figure 1. The diastolic phase can be divided into four phases: isovolumic relaxation, rapid filling, diastasis, and atrial systole. Between the time the aortic valve closes and the time the mitral valve opens, the left ventricle is a closed chamber with little change of volume.

Figure 2. A total of 475 consecutive patients with cardiomyopathy were enrolled from April 2001 to March 2017. Ischemic cardiomyopathy, valvular heart disease, and secondary cardiomyopathy were excluded. Idiopathic dilated cardiomyopathy (IDC) was defined as left ventricular ejection fraction (LVEF) <50% and LV end-diastolic diameter ≥55 mm. Hypertrophic cardiomyopathy (HC) was defined as LVEF ≥50% and LV maximum wall thickness ≥15 mm. Finally, 145 patients with IDC and 116 with HC were enrolled.

Figure 3. Left ventricular relaxation half-time ($T_{1/2}$). $T_{1/2}$ is defined as the time required for the

cavity pressure at LV dP/dt_{min} to be reduced by half. A 6F pigtail catheter with a high-fidelity micromanometer was placed in the left ventricle to measure the left ventricular pressure, and $T_{1/2}$ was calculated directly.

Figure 4. Kaplan–Meier analysis of cumulative probability of events for the 145 patients with idiopathic dilated cardiomyopathy (IDC) and 116 patients with hypertrophic cardiomyopathy (HC). Each patient group was subdivided into High and Low subgroups according to the median left ventricular relaxation half-time. The D-H subgroup showed a significantly higher probability of a cardiac event than the D-L subgroup ($P = 0.001$; log-rank test). Similarly, the H-H subgroup showed a significantly higher probability of an event than the H-L subgroup ($P = 0.028$; log-rank test).

Figure 1.

Diagram of intracardiac pressure according to the cardiac cycle

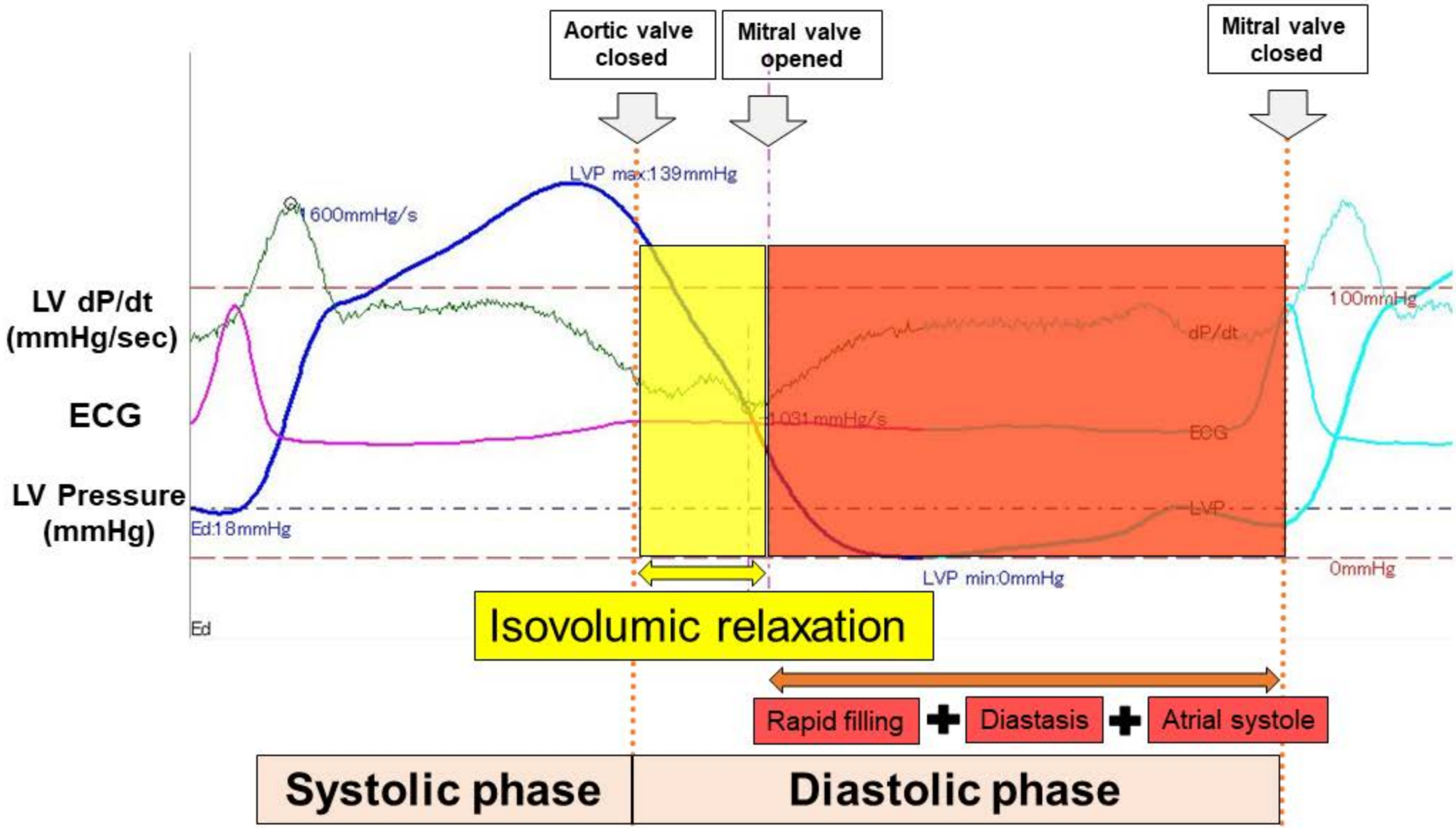


Figure 2.

Measurement of Relaxation half-time ($T_{1/2}$) from intracardiac pressure

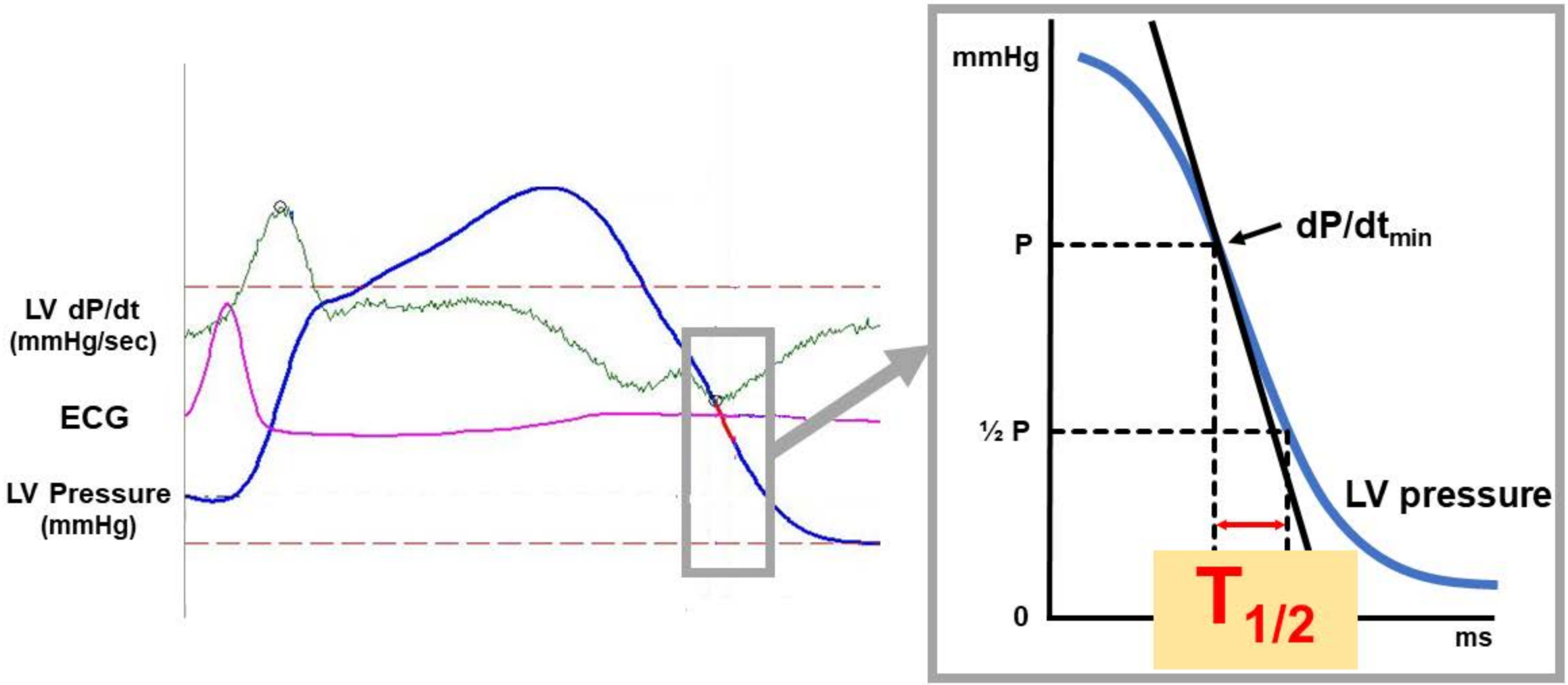


Figure 3.

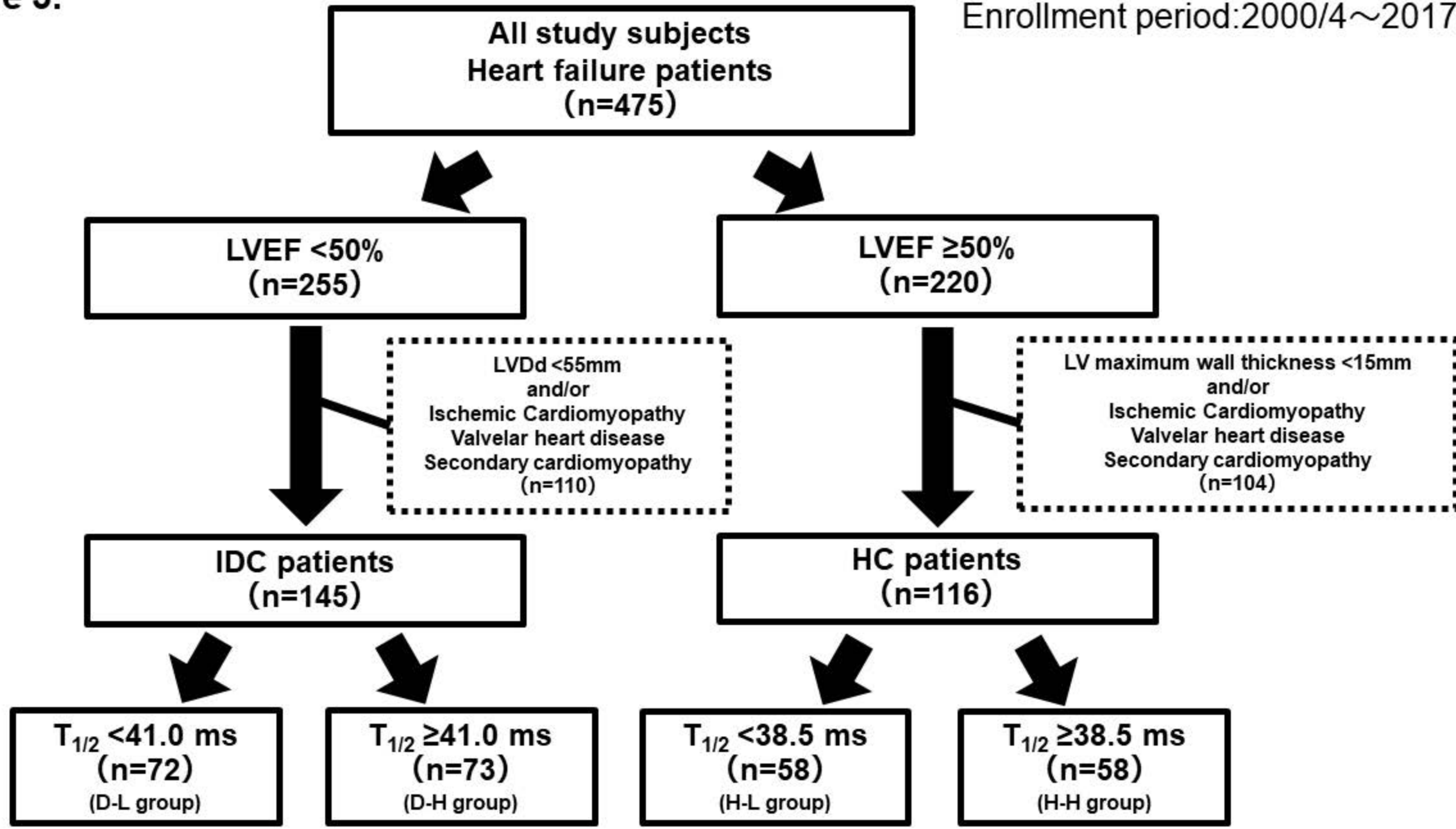
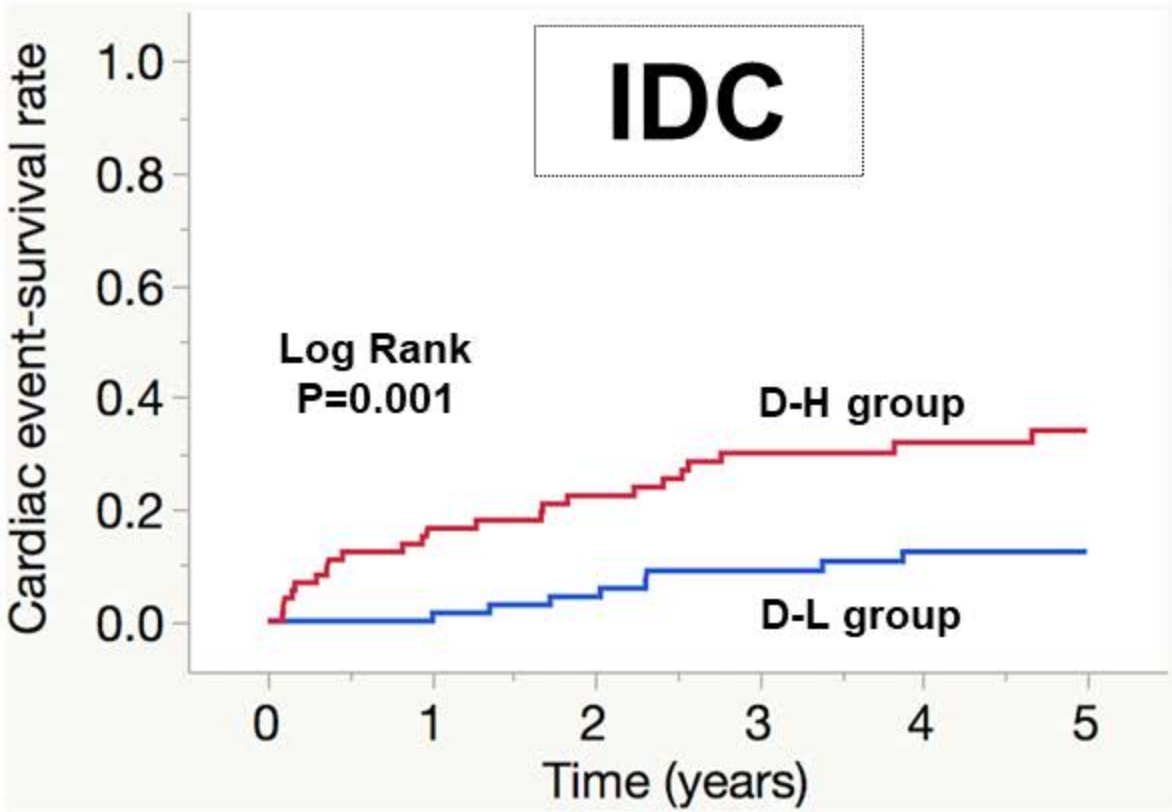
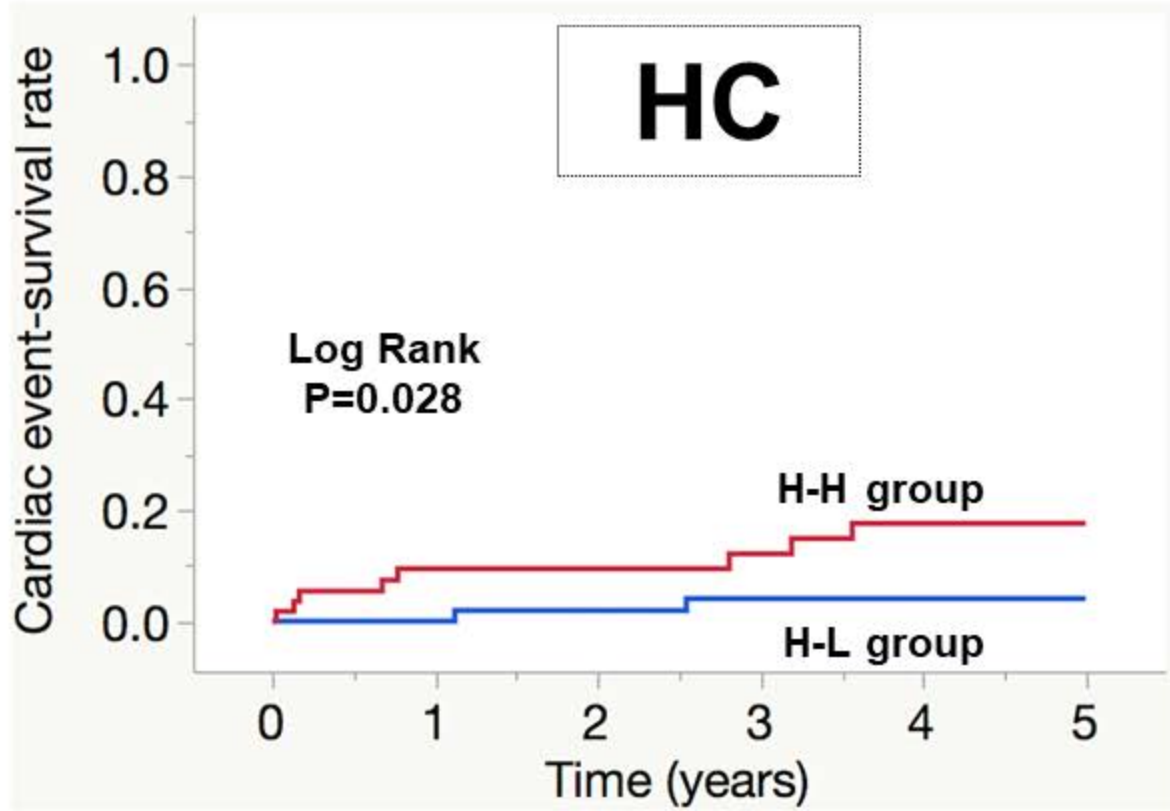

Enrollment period:2000/4～2017/3
All study subjects
Heart failure patients
(n=475)
LVEF <50%
(n=255)
LVEF ≥50%
(n=220)
LVDd <55mm
and/or
Ischemic Cardiomyopathy
Valvelar heart disease
Secondary cardiomyopathy
(n=110)
LV maximum wall thickness <15mm
and/or
Ischemic Cardiomyopathy
Valvelar heart disease
Secondary cardiomyopathy
(n=104)
IDC patients
(n=145)
HC patients
(n=116)
T1/2 <41.0 ms
(n=72)
(D-L group)
T1/2 ≥41.0 ms
(n=73)
(D-H group)
T1/2 <38.5 ms
(n=58)
(H-L group)
T1/2 ≥38.5 ms
(n=58)
(H-H group)
Follow up period: 4.7 (2.3 - 5.0) years
Follow up period: 4.7 (2.0 - 5.0) years

Figure 4.





D-H group	73	58	51	42	35	25
D-L group	72	70	64	54	48	41

H-H group	58	44	41	33	29	24
H-L group	58	53	47	44	37	31

Table 1. Baseline Characteristics of the study Patients

Variable	IDC				HC			
	Total (n=145)	D-L group	D-H group	P value	Total (n=116)	H-L group	H-H group	P value
Age (years)	52.0 ± 12.0	50.7 ± 11.5	53.3 ± 12.4	0.203	57.1 ± 12.4	57.6 ± 11.3	56.6 ± 13.4	0.666
Female	35 (24.1%)	16 (22.2%)	19 (26.0%)	0.592	33 (28.4%)	14 (24.1%)	19 (32.7%)	0.302
Body mass index (kg/m^2)	24.0 ± 4.6	24.9 ± 5.4	23.2 ± 3.3	0.022	24.1 ± 3.5	23.7 ± 2.8	24.6 ± 4.1	0.193
New York Heart Association functional class I, II/ III	134 / 11	70 / 2	64 / 9	0.024	116 / 0	58 / 0	58 / 0	1.000
Serum creatinine (mg/dL)	0.86 ± 0.23	0.83 ± 0.20	0.88 ± 0.25	0.214	0.80 ± 0.22	0.80 ± 0.21	0.79 ± 0.23	0.798
Estimated glomerular filtration rate (mL/min/1.73m^2)	72.2 ± 19.5	75.1 ± 21.3	69.3 ± 17.2	0.075	89.3 ± 74.3	82.4 ± 21.3	96.3 ± 102.9	0.317
Serum hemoglobin (g/dL)	14.1 ± 1.7	14.3 ± 1.7	13.9 ± 1.7	0.186	14.0 ± 1.5	13.9 ± 1.6	14.2 ± 1.5	0.492
Plasma brain natriuretic peptide (pg/mL)	90.0 (55.5 - 284.1)	75.0 (32.9 - 167.5)	150.3 (67.9 - 363.2)	0.001	82.6 (35.5 – 242.0)	59.7 (15.3 - 127.3)	148.1 (51.3 - 341.6)	0.016
Echocardiography								
Left ventricular diastolic dimension (mm)	65.9 ± 8.3	64.0 ± 6.8	67.8 ± 9.2	0.005	45.4 ± 5.4	45.4 ± 4.5	45.4 ± 6.1	0.981
Left ventricular ejection fraction (%)	31.8 ± 9.1	32.8 ± 9.3	30.9 ± 8.9	0.222	70.9 ± 7.3	70.4 ± 5.7	71.4 ± 8.6	0.471
E/A ratio	1.1 ± 0.7	1.0 ± 0.7	1.1 ± 0.8	0.603	0.9 ± 0.4	0.8 ± 0.3	1.0 ± 0.5	0.022
E/e' ratio	15.9 ± 8.4	14.5 ± 7.3	17.3 ± 9.2	0.112	15.6 ± 8.2	14.3 ± 6.7	16.9 ± 9.4	0.172
Deceleration time (ms)	182.4 ± 65.5	189.0 ± 58.0	176.3 ± 71.6	0.321	241.6 ± 75.2	237.4 ± 70.4	245.9 ± 80.1	0.588
Cardiac catheterization								
Heart rate (beats/min)	77.3 ± 14.2	79.5 ± 13.6	75.2 ± 14.6	0.075	64.4 ± 11.4	67.2 ± 11.5	61.8 ± 10.9	0.015
Cardiac index (L/min/m^2)	2.3 ± 0.3	2.3 ± 0.3	2.2 ± 0.2	0.701	2.9 ± 0.6	3.1 ± 0.5	2.7 ± 0.5	<0.001
Pulmonary capillary wedge pressure (mmHg)	12.6 ± 6.4	11.1 ± 5.5	14.2 ± 6.9	0.003	11.8 ± 5.4	9.9 ± 4.6	13.7 ± 5.6	<0.001
Mean pulmonary artery pressure (mmHg)	18.9 ± 7.4	18.0 ± 7.0	19.8 ± 7.6	0.256	17.8 ± 6.2	15.9 ± 5.6	19.6 ± 6.4	0.011
LV dP/dt $_{max}$ (mmHg/s)	1019.7 ± 243.4	1085.2 ± 261.2	954.3 ± 205.9	0.001	1669.5 ± 368.2	1809.7 ± 357.9	1525.9 ± 323.2	<0.001
Heart rate (beats/min) at follow-up period	73.7 ± 12.2	75.1 ± 11.3	72.4 ± 13.0	0.231	64.2 ± 11.5	68.2 ± 12.2	59.7 ± 8.9	<0.001
Medication before examination								
Renin-angiotensin system - inhibitor	88 (60.6%)	42 (58.3%)	46 (63.0%)	0.711	41 (35.3%)	20 (34.4%)	21 (36.2%)	0.629
Beta-blockers	68 (46.8%)	26 (36.1%)	42 (57.5%)	0.012	43 (37.0%)	17 (29.3%)	26 (44.8%)	0.082
Carvedilol equivalents (mg/day)	5.0 (2.5 - 9.3)	4.0 (2.5 - 5.0)	5.0 (2.5 - 10.0)	0.169	12.5 (5.0 - 23.7)	10.0 (5.0 - 23.7)	12.5 (6.25 - 23.7)	0.765
Aldosterone antagonists	60 (41.3%)	25 (34.7%)	35 (47.9%)	0.126	4 (3.4%)	0	4 (6.8%)	0.017
Diuretics	84 (57.9%)	38 (52.7%)	46 (63.0%)	0.258	11 (9.4%)	3 (5.1%)	8 (13.7%)	0.097
Amiodarone	10 (6.8%)	3 (4.1%)	7 (9.5%)	0.208	2 (1.7%)	0	2 (3.4%)	0.091
Medication at follow-up period								
Renin-angiotensin system - inhibitor	124 (85.5%)	58 (80.5%)	66 (90.4%)	0.254	59 (50.8%)	30 (51.7%)	29 (50.0%)	0.777
Beta-blockers	123 (91.9%)	58 (80.5%)	65 (89.0%)	0.382	72 (62.0%)	36 (62.0%)	36 (62.0%)	1.000
Carvedilol equivalents (mg/day)	10.0 (5.0 - 12.5)	10.0 (5.0 - 15.0)	10.0 (5.0 - 12.5)	0.515	12.5 (6.25 - 25.0)	10.0 (5.3 - 12.5)	12.5 (10.0 - 25.0)	0.116
Aldosterone antagonists	71 (48.9%)	33 (45.8%)	38 (52.0%)	0.614	7 (6.0%)	0	7 (12.0%)	0.001
Diuretics	78 (53.7%)	34 (47.2%)	44 (60.2%)	0.187	11 (9.4%)	1 (1.7%)	10 (17.2%)	0.002
Amiodarone	15 (10.3%)	4 (5.5%)	11 (15.0%)	0.067	6 (5.1%)	3 (5.1%)	3 (5.1%)	1.000

Data are means ± SD or median (interquartile range)

IDC = idiopathic dilated cardiomyopathy; HC = hypertrophic cardiomyopathy; E/A ratio = ratio of early transmitral flow velocity to atrial flow velocity; E/e' ratio = ratio of early transmitral flow velocity to early diastolic mitral annular velocity; LV dP/dt max = Maximal first derivative of left ventricular pressure

Table 2. Cardiac events

	IDC		HC	
Variable	**D-L group**	**D-H group**	**H-L group**	**H-H group**
Sudden cardiac death	**0**	**3 (4.0%)**	**1 (1.7%)**	**2 (3.4%)**
Ventricular tachycardia	**1 (1.3%)**	**3 (4.0%)**	**1 (1.7%)**	**4 (6.8%)**
Admission due to worsening heart failure	**8 (11.1%)**	**17 (22.9%)**	**0**	**2 (3.4%)**

Table 3. Cox proportional hazard regression analysis for cardiac events.

Variable	IDC				HC			
	HR (95%CI)	χ^2 value	P value	Joint χ^2	HR (95%CI)	χ^2 value	P value	Joint χ^2
Univariate analysis								
Age (years)	0.968 (0.939 - 0.997)	4.4	0.034		1.038 (0.983 - 1.105)	1.7	0.181	
Serum creatinine (mg/dL)	5.334 (1.107 - 22.975)	4.3	0.037		2.186 (0.157 - 17.551)	0.3	0.530	
Serum hemoglobin (g/dl)	0.709 (0.591 - 0.860)	11.6	<0.001		1.022 (0.708 - 1.513)	<0.1	0.907	
Log plasma brain natriuretic peptide	4.220 (1.963 - 9.338)	14.0	<0.001		1.470 (0.494 - 4.552)	0.4	0.491	
Left ventricular ejection fraction (%)	0.951 (0.911 - 0.990)	5.8	0.015		0.929 (0.854 - 1.015)	2.6	0.103	
E/A ratio	1.958 (1.201 - 2.990)	6.8	0.009		6.129 (1.496 - 23.184)	6.0	0.013	
E/e' ratio	1.038 (0.987 - 1.082)	2.2	0.135		1.052 (0.980 - 1.114)	2.1	0.143	
Heart rate (beats/min)	1.006 (0.980 - 1.032)	0.2	0.613		0.976 (0.917 - 1.030)	0.7	0.396	
Pulmonary capillary wedge pressure (mmHg)	1.085 (1.031 - 1.138)	9.4	0.002		1.109 (1.012 - 1.206)	4.8	0.027	
Mean pulmonary artery pressure (mmHg)	1.013 (0.983 - 1.043)	0.7	0.374		1.105 (1.009 - 1.210)	4.5	0.032	
$T_{1/2}$ (msec)	1.082 (1.039 - 1.122)	13.4	<0.001		1.060 (1.011 - 1.100)	5.6	0.017	
Multivariate analysis *								
Age (years)	0.929 (0.877 - 0.984)	7.3	0.006	31.3	-	-	-	
Serum creatinine (mg/dL)	116.3 (4.021 - 3366.8)	9.9	0.016		-	-	-	
Serum hemoglobin (g/dl)	0.616 (0.402 - 0.944)	5.2	0.022		-	-	-	
Log plasma brain natriuretic peptide	0.914 (0.175 - 5.099)	<0.1	0.947		-	-	-	
Left ventricular ejection fraction (%)	0.988 (0.899 - 1.101)	<0.1	0.930		-	-	-	
E/A ratio	1.247 (0.368 - 3.544)	<0.1	0.818		4.360 (0.559 - 25.705)	2.2	0.135	8.3
Pulmonary capillary wedge pressure (mmHg)	1.033 (0.911 - 1.146)	0.1	0.708		1.052 (0.773 - 1.359)	0.1	0.723	
Mean pulmonary artery pressure (mmHg)	-	-	-		0.986 (0.767 - 1.313)	<0.1	0.921	
$T_{1/2}$ (msec)	1.109 (1.032 - 1.232)	7.0	0.007		1.062 (1.002 - 1.122)	4.1	0.041	

* The final model included all univariate predictors. HR, hazard ratio; CI, confidence interval

Other abbreviations as in Table 1

Supplemental Figure