ORIGINAL PAPER

Association of heart failure duration with clinical prognosis in advanced heart failure

Atsushi Sugiura[1,2] · Hideki Kitahara[1] · Togo Iwahana[1] · Noriko Suzuki[1] · Sho Okada[1] · Hideyuki Miyauchi[1] · Yoshio Kobayashi[1] · Nikos Werner[2]

Abstract

Background Little is known about the prognostic impact of heart failure (HF) duration in patients with advanced HF.

Methods A total of 109 consecutive patients with advanced HF referred to the institutional heart transplant program between July 2014 and December 2017 were prospectively enrolled. The patients were divided into two groups according to the HF duration using a pre-specified cutoff (> 18 months, $n = 38$; ≤ 18 months, $n = 71$). The Cox proportional hazards model was generated to investigate the association between the HF duration and a 1-year composite endpoint (all-cause mortality, left ventricular assist device implantation, and hospitalization due to HF).

Results Patients with a longer HF duration were older and had significantly lower blood pressure, and greater left ventricular volume compared with those with a shorter HF duration. The 1-year event-free survival rate was significantly lower in patients with a longer HF duration (49.1% vs. 80.0%, log-rank $p < 0.001$). After adjustment, a longer HF duration was independently associated with an increased risk for the composite endpoint (hazard ratio, 2.44; 95% confidence interval, 1.03–5.76; $p = 0.04$). Additionally, longer HF duration was independently associated with an increased wall motion score index and a decreased heart-to-mediastinum ratio of ^{123}I-meta-iodobenzylguanidine (MIBG) myocardial scintigraphy (all associations, $p < 0.05$).

Conclusions A longer HF duration is associated with an increased risk of adverse outcomes as well as more severe myocardial damage among patients with advanced HF.

Graphic abstract
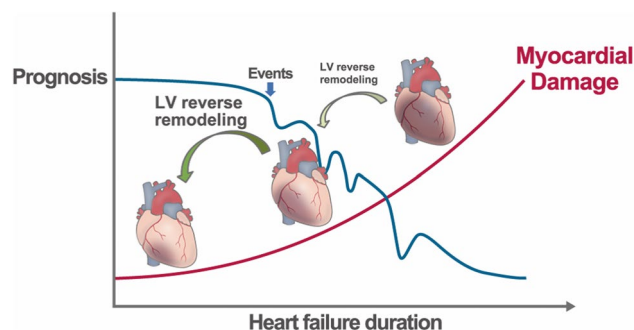
✉ Atsushi Sugiura
sssugi@me.com

Extended author information available on the last page of the article

Abbreviations

BMI	Body mass index
CI	Confidence interval
CRT	Cardiac resynchronization therapy
HF	Heart failure
H/M	Heart-to-mediastinum

HR	Hazard ratio
ICD	Implantable cardioverter defibrillation
^{123}I-MIBG	^{123}I-meta-iodobenzylguanidine
LVAD	Left ventricular assist device
LV	Left ventricular
NYHA	New York Heart Association
OR	Odds ratio

Introduction

Heart failure (HF) is a clinical syndrome with high mortality and affects 23 million people worldwide. Advanced HF is defined as a persistent or progressive severe symptomatic status with decreased cardiac function despite guideline-based optimized medical and device therapy. Recognizing the transition to this advanced stage is necessary to facilitate the triage of advanced surgical options, such as heart transplant or left ventricular assist device (LVAD) implantation, or allow physicians to initiate the management of end-of-life care.

Emerging evidence indicates that a longer duration from the initial HF diagnosis is linked to adverse outcomes [1–3]. A meta-analysis of 39,372 patients with HF generated a prognostic risk score, including HF duration, with the cutoff by 18 months. A post hoc study of the ASCEND-HF trial of 7141 chronic HF patients reported that a longer HF duration (i.e., > 1, > 12, or > 60 months) was associated with poor prognosis [4]. However, little is known about the prognostic impact of HF duration in patients with advanced HF considering the advanced surgical options. Additionally, a cohort study of 373 patients with LVAD support reported that a shorter HF duration prior to LVAD implantation was associated with cardiac recovery [5], suggesting an association between the HF duration and myocardial recovery capacity. To provide optimized treatment strategy for patients with advanced HF, further evidence regarding the association between HF duration and myocardial recovery capacity in this population should be accumulated.

In this study, we investigated the association between HF duration and adverse outcomes including all-cause mortality, LVAD implantation, and hospitalization due to HF and assessed the association between HF duration and myocardial recovery capacity in patients with advanced HF.

Methods

Study population

In this observational study, 109 consecutive patients with advanced HF referred to our institutional heart transplant program between July 2014 and December 2017 were prospectively enrolled. Advanced HF was defined as the advanced symptomatic status with a New York Heart Association (NYHA) functional scale ≥ 3 despite the guideline-based HF therapy or depending on the intravenous infusion of catecholamine [6, 7]. The date of the first HF admission was collected by reviewing the clinical data record. The HF duration was calculated in reference to the first HF admission. For analyses, the patients were divided into 2 groups according to the HF duration (> 18 or ≤ 18 months). The cutoff of the HF duration was chosen based on the literature [4, 8]. This study was approved by the ethics committee of Chiba University Hospital and performed in concordance with the Declaration of Helsinki. All patients provided written informed consent.

Outcome measures

The pre-specified primary outcome measure was the composite endpoint of all-cause mortality, LVAD implantation, and hospitalization due to HF. A multidisciplinary heart team including physicians and cardiac surgeons made the decision of whether or not to proceed with LVAD implantation. Echocardiography was performed after admission. In addition to the traditional measurement, we assessed the segmental myocardial contractility (grade 1 indicating normal; 2, hypokinesis; 3, akinesis; 4, dyskinesis) and calculated the wall motion score index [9, 10]. Two cardiologists blinded to the study design conducted each analysis.

Meta-iodobenzylguanidine myocardial scintigraphy

The myocardial sympathetic nerve activity was assessed in patients who underwent cardiac scintigraphy. Early and delayed anterior planar images were acquired at 15 and 210 min, respectively, after intravenously administering 111 MBq of ^{123}I-meta-iodobenzylguanidine (MIBG) (MyoMIBG; FUJIFILM Toyama Chemical Co., Ltd., Tokyo, Japan). The heart-to-mediastinum (H/M) ratio was calculated as the ratio of the average counts per pixel in the heart to those in the mediastinum using a semiautomatic software (Smart MIBG v3.0.0.0; FUJIFILM Toyama Chemical Co., Ltd., Tokyo, Japan) [11, 12].

Statistical analysis

Baseline characteristics were compared between groups. Continuous variables were reported as the mean $\pm$ standard deviation and were analyzed using the unpaired t test, while non-normally distributed variables were analyzed using the Mann–Whitney U test. Furthermore, categorical variables were reported as frequencies and percentages and were compared using the Chi-square test or the Fisher exact test as appropriate.

To compare the 1-year event-free survival between groups, we performed the survival analysis using the Kaplan–Meier method to estimate the event probabilities at 365 days and compare the distributions of event-free survival times among the groups using the log-rank test. Then, we estimated the hazard ratio (HR) and 95% confidence interval (CI) of a HF duration > 18 months for each outcome using the Cox proportional hazards analysis. The following were used in the final multivariate model: age, male sex, body mass index (BMI), hypertension, diabetes, atrial fibrillation (AF), coronary artery disease, NYHA functional scale, systolic blood pressure, left ventricular (LV) ejection fraction, and a HF duration > 18 months [1, 8].

We also performed sensitivity analyses to examine the consistency of inference. First, we repeated the Cox hazard multivariate analysis with another cutoff of HF duration (i.e., 12 months). Second, the propensity score (PS) was calculated using a logistic regression model. After PS matching, we estimated the HR and 95% CI of a HF duration > 18 months for the adverse outcomes using the Cox proportional hazards analysis.

The associations between the HF duration and wall motion score index and H/M ratio of I^{123}-MIBG were estimated from the logistic regression models adjusted for baseline characteristics (age, male sex, hypertension, diabetes, AF, coronary artery disease, NYHA functional scale, LV end-diastolic volume, and medication of β-blocker) [4, 10, 13].

All statistical analyses were performed using EZR version 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Two-tailed p values < 0.05 were considered statistically significant [14].

Results

Study population and baseline characteristics

A total of 109 consecutive patients with advanced HF were analyzed. Patients with a longer HF duration were older and more likely to show lower BMI, systolic blood pressure, and heart rate. In addition, these patients had a higher prevalence of anemia, renal dysfunction, and a greater LV volume compared with the patients with a shorter HF duration (Table 1).

Outcomes

The Kaplan–Meier analysis for the composite endpoint at 1 year is shown in Fig. 1. The event-free survival rate was significantly lower in patients with a longer HF duration (49.1% vs. 80.0%, p < 0.001) compared with those with a HF

duration ≤ 18 months. The difference in the composite endpoint was mainly impacted by two factors, LVAD implantation (66.1% vs. 89.0%, p = 0.005) and hospitalization due to HF (73.0% vs. 89.8%, p = 0.06). No significant difference in all-cause mortality between groups (90.5% vs. 96.6%, p = 0.20) was noted. In the Cox proportional hazards regression analysis, a HF duration > 18 months was significantly associated with the increased risk of composite events (HR, 2.44; 95% CI 1.03–5.76; p = 0.04; Table 2). Likewise, in the sensitivity analyses using other cutoff values (HF duration > 12 months: HR, 2.55; 95% CI 1.08–6.03; p = 0.03; Supplemental Table 1) and in the PS-matched cohort (Supplemental Table 2) (HR, 2.33; 95% CI 1.05–5.15; p = 0.04), a longer HF duration was associated with an increased risk of composite events.

Assessment of the echocardiographic wall motion score index

Figure 2 represents the wall motion score index in each segment according to the HF duration. The mean wall motion score index was significantly larger in patients with a HF duration > 18 months compared with those with a HF duration ≤ 18 months (2.5 ± 0.3 vs. 2.2 ± 0.3, p = 0.001). In the multivariate logistic regression analysis, a HF duration > 18 months was independently associated with an increased wall motion score index (OR, 9.10; 95% CI 1.40–59.4; p = 0.02; Supplemental Table 3).

Myocardial sympathetic nerve activity

Of the 109 patients, 64 underwent ^{123}I-MIBG myocardial scintigraphy. Patients with a HF duration > 18 months showed decreased ^{123}I-MIBG uptake with respect to the H/M ratio (early phase, 2.0 ± 0.5 vs. 2.3 ± 0.5, p = 0.03; delayed phase, 1.6 ± 0.4 vs. 2.0 ± 0.5, p = 0.005; Fig. 3) compared with those with a HF duration ≤ 18 months. After adjustment, a HF duration > 18 months was independently and negatively associated with a delayed H/M ratio (OR, 0.08; 95% CI 0.01–0.79; p = 0.03; Supplemental Table 4).

Discussion

In this prospective cohort-based study of patients with advanced HF in a single LVAD center, we found that a HF duration > 18 months was associated with a higher risk of the composite outcomes and this association remained significant after adjustment for potential confounders. The main finding was consistent across different statistical assumptions. Additionally, we found that a HF duration > 18 months was independently associated with an increased wall motion score index as well as a decreased H/M ratio.

Table 1 Baseline characteristics in patients with longer and shorter heart failure duration

	HF duration > 18 months (n = 38)	HF duration ≤ 18 months (n = 71)	p value
Age (years), mean ± SD	57 ± 11	47 ± 14	< 0.001
Sex male, n (%)	29 (76.3)	55 (77.5)	0.33
Body mass index (kg/m^2), mean ± SD	22.9 ± 4.5	25.3 ± 6.6	0.049
Comorbidities, n (%)			
Hypertension	11 (28.9)	16 (22.5)	0.49
Dyslipidemia	13 (34.2)	14 (19.7)	0.11
Diabetes	8 (21.1)	12 (16.9)	0.78
Atrial fibrillation	7 (18.4)	11 (15.5)	0.90
Coronary artery disease	4 (10.5)	6 (8.5)	0.77
Chronic obstructive pulmonary disease	0 (0)	3 (4.2)	0.55
Prior ICD/CRT, n (%)	14 (36.8)	4 (5.6)	< 0.001
New York Heart Association functional scale, mean ± SD	3.4 ± 0.6	3.4 ± 0.7	0.71
Systolic blood pressure (mmHg), mean ± SD	101.2 ± 24.8	114.0 ± 22.9	0.008
Heart rate (bpm), mean ± SD	83.8 ± 20.4	98.9 ± 20.5	< 0.001
Laboratory findings, mean ± SD			
Hemoglobin (g/dl)	13.0 ± 2.2	13.8 ± 2.1	0.04
Brain natriuretic peptide (pg/ml)	889.5 [398–1744]	757 [478–1495]	0.50
Estimated glomerular filtration rate (ml/min/1.73 m^2)	45.8 ± 18.7	65.4 ± 27.7	< 0.001
Transthoracic echocardiography at enrollment, mean ± SD			
Left ventricular end-diastole volume (ml)	282.3 ± 122.1	228.3 ± 92.7	0.01
Left ventricular end-systole volume (ml)	220.5 ± 101.5	176.1 ± 78.9	0.01
Left ventricular ejection fraction (%)	23.1 ± 7.7	24.4 ± 10.2	0.47
Mitral regurgitation ≥ 3, n (%)	17 (44.7)	22 (31.0)	0.22
Tricuspid regurgitation pressure gradient (mmHg)	35.4 ± 17.0	32.5 ± 12.3	0.36
Number of prior admission due to HF, mean ± SD	4.6 ± 4.1	1.5 ± 1.1	< 0.001
Medications, n (%)			
β-blocker	35 (92.1)	60 (84.5)	0.41
ARB/ACE-I	28 (73.7)	61 (73.7)	0.13
Mineralocorticoid receptor antagonist	31 (81.6)	51 (71.8)	0.37
Diuretics	31 (81.6)	39 (54.9)	0.006

Patients with a longer HF duration were older, had a higher prevalence of anemia, renal dysfunction, a greater LV volume, lower systolic blood pressure, and lower heart rate compared with the patients with a shorter HF duration

ACE-I angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *CRT* cardiac resynchronization therapy, *ICD* implantable cardioverter defibrillator, *SD* standard deviation

Importance of HF duration

The relation of HF duration with adverse outcomes is novel but consistent with earlier studies showing that patients with a shorter HF duration have favorable survival outcomes compared with those with a longer HF duration [1, 4, 15]. For example, a post hoc analysis of a randomized controlled study of 7141 hospitalized patients with acute HF reported that a HF duration < 1 month was independently associated with better survival [1]. More recently, a post hoc analysis of the SHIFT trial of 6505 patients with stable HF and reduced LV ejection fraction (< 35%) reported the parallel association between HF duration and adverse outcomes

[4]. However, the prediction of adverse outcomes is more critical in patients with advanced HF and still desirable to make a strategical approach (i.e., LVAD implantation, heart transplant, end-of-life care). Our main observation is consistent with these earlier findings, and we extend them by demonstrating the association between a longer HF duration and increased risk of adverse outcomes in patients with advanced HF.

Myocardial capacity to recover

The reasons for the association between a longer HF duration and worse clinical prognosis remain to be elucidated.

Fig. 1 Event-free survival in patients with longer and shorter heart failure duration. At 1-year follow-up, patients with a heart failure duration > 18 months showed significantly lower overall event-free survival rates (49.1% vs. 80.0%, log-rank $p < 0.001$) compared with those with a heart failure duration ≤ 18 months
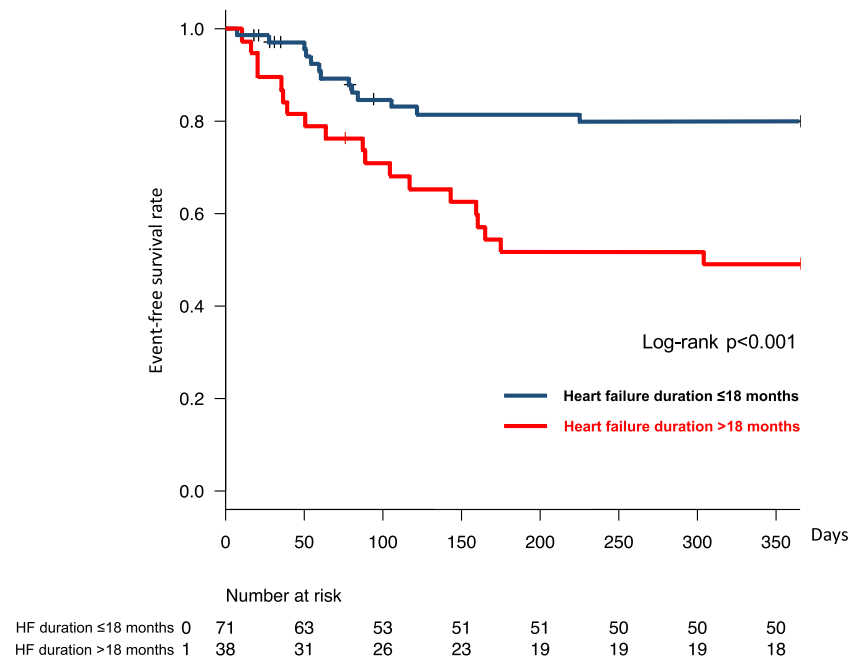

	Number at risk							
HF duration ≤18 months	0 71	63	53	51	51	50	50	50
HF duration >18 months	1 38	31	26	23	19	19	19	18

Table 2 Cox proportional hazard analysis for composite outcomes

	Univariate			Multivariate		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Heart failure duration > 18 months	3.03	1.50–6.14	0.002	2.53	1.04–6.15	0.04
Age (years)	1.01	0.99–1.04	0.40	0.99	0.95–1.02	0.38
Sex male	1.35	0.63–2.92	0.44	0.57	0.24–1.37	0.21
Body mass index (kg/cm^2)	0.90	0.83–0.98	0.02	0.97	0.88–1.07	0.55
Hypertension	0.61	0.25–1.47	0.27	0.74	0.23–2.34	0.60
Diabetes	0.84	0.32–2.19	0.73	1.07	0.33–3.49	0.90
Coronary artery disease	2.05	0.79–5.33	0.14	2.16	0.63–7.40	0.22
Atrial fibrillation	0.72	0.25–2.05	0.54	0.53	0.14–1.92	0.33
New York Heart Association functional scale	3.07	1.47–6.39	0.003	2.26	1.02–4.99	0.04
Systolic blood pressure (mmHg)	0.96	0.94–0.98	< 0.001	0.97	0.94–0.99	0.01
Left ventricular ejection fraction (%)	0.98	0.94–1.02	0.35	1.00	0.96–1.04	0.95

After adjustment for baseline characteristics, a heart failure duration > 18 months was significantly associated with the increased risk of composite events

CI confidence interval, *HR* hazard ratio

Several plausible underlying mechanisms linking HF duration to adverse outcomes are noted. Patients with a longer HF duration were older and more likely to have multiple comorbidities (e.g., AF, renal dysfunction) [1, 8] or HF-related physiological changes (e.g., higher age, sarcopenia) [16–18], which may contribute to the worsened clinical prognosis. Although these comorbidities play a role, the association between HF duration and adverse outcomes persisted significantly after adjusting these comorbidities in the earlier studies [1, 4] and in the present report.

Another possible explanation for the association may be linked to myocardial remodeling. Since HF is accompanied by myocardial remodeling as well as comorbidities, it is likely that patients with a longer HF duration have a progressive cardiac remodeling through long-standing neuroendocrine activation followed by calcium handling defects or beta-adrenergic signal transduction [19, 20]. In the present study, we found that a longer HF duration was independently associated with an increased wall motion score index, suggesting more advanced myocardial damage. These findings are in line with previous studies investigating patients with advanced HF [3, 21, 22]. For example, a cohort study of 373 patients treated with LVAD reported that a longer HF duration was associated with the smaller improvement of
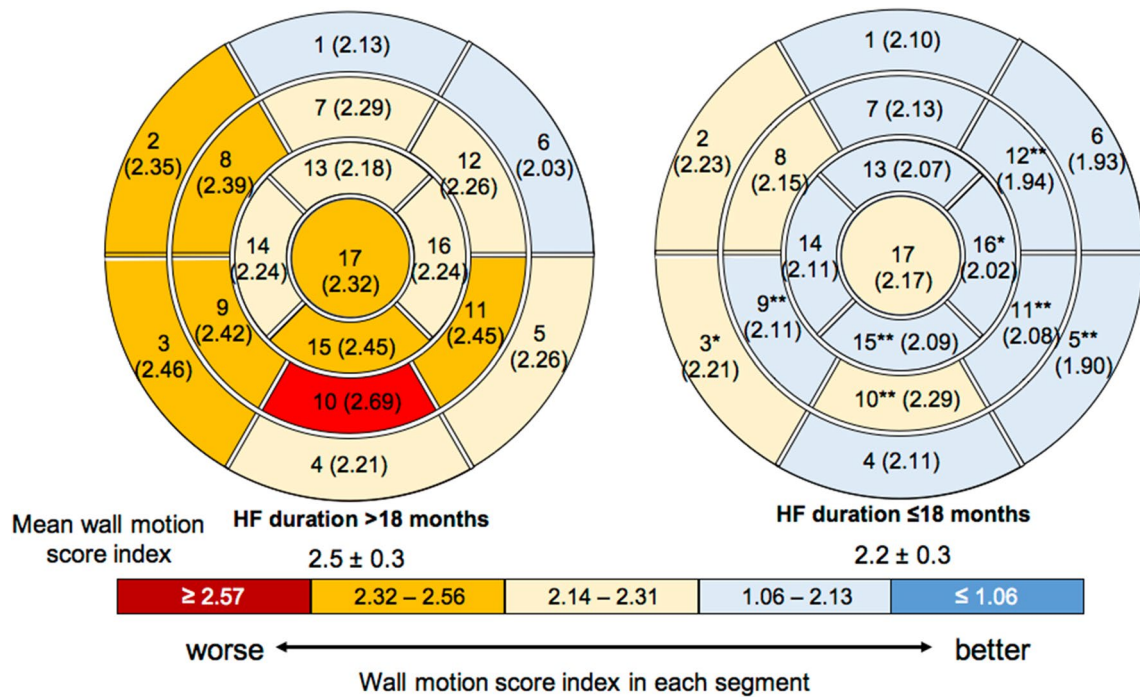
Fig. 2 Wall motion score index in patients with longer and shorter heart failure duration. The wall motion score index was analyzed in each of the 17 wall segments in patients with longer and shorter duration of heart failure. Scores on the wall motion index are as follows: 1—normal; 2—hypokinetic; 3—akinetic; and 4—dyskinetic. Patients with a heart failure duration > 18 months showed significantly higher wall motion score index (2.5 ± 0.3 vs. 2.2 ± 0.3, $p = 0.001$) compared with those with a heart failure duration ≤ 18 months. $*p < 0.05$; $**p < 0.01$
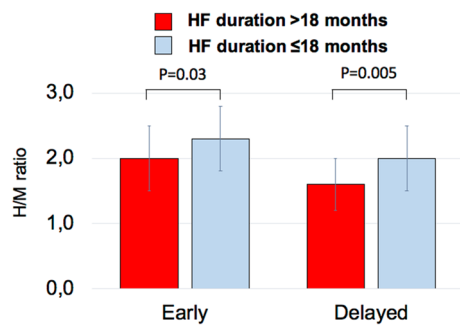

Fig. 3 Heart to mediastinum ratio of ^{123}I-MIBG uptake in patients with longer and shorter heart failure duration. Sixty-nine patients underwent ^{123}I-MIBG myocardial scintigraphy during a hospital stay. Patients with longer heart failure duration showed significantly lower H/M ratio both in the early and delayed phase compared to those with shorter heart failure duration. *H/M* heart-to-mediastinum, ^{123}I-MIBG ^{123}I-meta-iodobenzylguanidine

LV function during LVAD treatment [5]. Additionally, in the sub-cohort of ^{123}I-MIBG myocardial scintigraphy in the present study, we found that patients with a longer HF duration were independently associated with a decreased delay H/M ratio, suggesting the poor myocardial capacity to recover in response to medical or advanced device therapy [13, 23]. In conclusion, consistent with earlier studies, our findings

(a longer HF duration is associated with an increased wall motion score index and decreased H/M ratio) suggest that a longer HF duration is linked to irreversible myocardial damage, resulting in poor prognosis.

Limitations

The present study has several limitations. First, the present study was based on a prospective cohort study in a single LVAD center with a relatively small number of patients. Therefore, the number of covariates in the multivariate models is limited. However, our main findings are consistent across different statistical assumptions, including PS matching, adjusting for baseline characteristics and echocardiography findings. Second, while our finding (the association between longer HF duration and increased wall motion score index) suggests more advanced myocardial damage in patients with a longer HF duration, we did not assess follow-up echocardiography findings. Nevertheless, the adjunctive findings of ^{123}I-MIBG suggest the poor myocardial capacity to recover by demonstrating the association between a longer HF duration and H/M ratio. Third, since our data was based on patients with advanced HF referred to institutional heart transplant program, caution should be used in generalizing the current results. Nevertheless, our findings will serve as

an important foundation for further investigation to establish strategic approaches in patients with HF and determine the mechanisms of association between HF duration and clinical prognosis.

Conclusions

In patients with advanced HF, a longer HF duration is associated with an increased risk of adverse events compared with a shorter HF duration. Additionally, a longer HF duration is independently associated with impaired myocardial motion and decreased sympathetic nerve activity, suggesting lower myocardial recovery capacity.

Compliance with ethical standards

Conflict of interest Sugiura A, Kitahara H, Iwahana T, Eguchi N, Okada S, Miyauchi H and Kobayashi Y report no relationships that could be construed as a conflict of interest. Werner N reports having received speaker honoraria and research grants from Medtronic, Boston scientific, Abbott, and Edwards Lifesciences.

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Affiliations

Atsushi Sugiura[1,2] · **Hideki Kitahara**[1] · **Togo Iwahana**[1] · **Noriko Suzuki**[1] · **Sho Okada**[1] · **Hideyuki Miyauchi**[1] · **Yoshio Kobayashi**[1] · **Nikos Werner**[2]

[1] Department of Cardiovascular Medicine, Chiba University Graduate School of Medicine, Chiba, Japan

[2] Medizinische Klinik und Poliklinik II, Universitätsklinikum Bonn, 53105 Bonn, Germany