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AUTHOR(S):

Seko, Yuta; Kato, Takao; Morimoto, Takeshi; Yaku, Hidenori; Inuzuka, Yasutaka; Tamaki, Yodo; Ozasa, Neiko; ... Sato, Yukihito; Kuwahara, Koichiro; Kimura, Takeshi

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ORIGINAL RESEARCH ARTICLE

A decrease in tricuspid regurgitation pressure gradient associates with favorable outcome in patients with heart failure

Yuta Seko[1], Takao Kato[1]*, Takeshi Morimoto[2], Hidenori Yaku[1], Yasutaka Inuzuka[3], Yodo Tamaki[4], Neiko Ozasa[1], Masayuki Shiba[1], Erika Yamamoto[1], Yusuke Yoshikawa[1], Takeshi Kitai[5], Yugo Yamashita[1], Moritake Iguchi[6], Kazuya Nagao[7], Yuichi Kawase[8], Takashi Morinaga[9], Mamoru Toyofuku[10], Yutaka Furukawa[5], Kenji Ando[9], Kazushige Kadota[8], Yukihito Sato[11], Koichiro Kuwahara[12], Takeshi Kimura[1] and KCHF Study Investigators

[1]*Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto, 606-8507, Japan;* [2]*Clinical Epidemiology, Hyogo College of Medicine, Nishinomiya, Japan;* [3]*Cardiovascular Medicine, Shiga General Hospital, Moriyama, Japan;* [4]*Division of Cardiology, Tenri Hospital, Tenri, Japan;* [5]*Department of Cardiovascular Medicine, Kobe City Medical Center General Hospital, Kobe, Japan;* [6]*Department of Cardiology, National Hospital Organization Kyoto Medical Center, Kyoto, Japan;* [7]*Department of Cardiology, Osaka Red Cross Hospital, Osaka, Japan;* [8]*Department of Cardiology, Kurashiki Central Hospital, Kurashiki, Japan;* [9]*Department of Cardiology, Kokura Memorial Hospital, Kokura, Japan;* [10]*Department of Cardiology, Japanese Red Cross Wakayama Medical Center, Wakayama, Japan;* [11]*Department of Cardiology, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan; and* [12]*Department of Cardiovascular Medicine, Graduate School of Medicine, Shinshu University, Matsumoto, Japan*

Abstract

Aims Although the prognostic impact of the high tricuspid regurgitation pressure gradient (TRPG) has been investigated, the association of the decrease in TRPG during follow-up with clinical outcomes in heart failure (HF) has not been previously studied. The aim of this study was to investigate the association of a decrease in TRPG between hospitalization and 6 month visit with subsequent clinical outcomes in patients with acute decompensated HF (ADHF).

Methods and results Among 721 patients with available TRPG data both during hospitalization and a subsequent 6 month visit, the study population was divided into two groups: a decrease in TRPG group (>10 mmHg decrease at 6 month visit) (N = 179) and no decrease in TRPG group (N = 542). The primary outcome measure was a composite of all-cause death or HF hospitalization. The cumulative 6 month incidence of primary outcome measure was significantly lower in the decrease in TRPG group than in the no decrease in TRPG group (12.2% vs. 18.7%, P = 0.02). After adjusting for confounders, there was a significantly lower risk in decrease in TRPG group than in the no decrease in TRPG group for the measured primary outcome (hazard ratio: 0.56, 95% confidence interval 0.32–0.93, P = 0.02). The lower risk in decrease in TRPG group was not different among the basal TRPG values.

Conclusions Heart failure patients with a decrease in TRPG at 6 months after discharge from ADHF hospitalization had lower subsequent risk of all-cause death and HF hospitalization than those without a decrease in TRPG, regardless of TRPG values.

Keywords Tricuspid regurgitation pressure gradient; Heart failure; Mortality; Hospitalization; Prospective

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**Correspondence to: Takao Kato, Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan. Tel: +81-75-751-4254; Fax: +81-75-751-3289. Email: tkato75@kuhp.kyoto-u.ac.jp*

Introduction

Tricuspid regurgitation (TR) is a common echocardiographic finding that is present in 65–85% of the population.[1] The prevalence of TR is influenced by age as well as by sex.[1] TR is associated with heart failure (HF) and reduced functional capacity.[2,3] Secondary TR often complicates the natural course of HF, due to annular dilatation and increased tricuspid leaflet tethering in relation to right ventricular pressure and/or volume overload. The management of HF that underlies TR needs to be optimized as TR may decrease after treatment of its cause.[4] The prognostic association of TR has been implicated as significant in patients with moderate or severe mitral regurgitation and post mitral valve replacement, possibly independent of pulmonary pressure and right ventricular dysfunction.[2,5–7]

Tricuspid regurgitation pressure gradient (TRPG) is a representative noninvasive echocardiographic parameter for evaluation of pulmonary artery systolic pressure (PASP)[8] and pulmonary vascular resistance.[9] Previous reports have shown that elevated TRPG is associated with poor long-term outcome in patients with HF.[10–12] We routinely perform a follow-up echocardiography to check cardiac conditions and to assess the effect of therapy. However, no study has investigated the association of the difference in TRGP between hospitalization and 6 month follow-up with subsequent clinical outcomes. The aim of our study was to investigate the association of a decrease in TRPG between hospitalization and 6 month visit with subsequent clinical outcomes, using data from a large, contemporary, all-comer Japanese registry of patients with acute decompensated HF (ADHF).

Methods

Study design, setting, and population

The KCHF (Kyoto Congestive Heart Failure) registry is a physician-initiated, prospective, observational, multicentre cohort study enrolling consecutive patients who were admitted to the hospital due to ADHF for the first time between October 2014 and March 2016.[13,14] In parallel with the main KCHF study, we designed a prospective longitudinal follow-up study enrolling patients who were to have a visit and echocardiography at 6 ± 1 month. Among 4056 patients, we excluded 271 patients who died during index hospitalization and 2539 patients who did not meet the pre-specified criteria of follow-up such as no written informed consent (N = 238), patient age $<$20 years (N = 1), fever or infectious diseases at admission (N = 297), acute coronary syndrome at admission (N = 157), end-stage renal failure (N = 218), severe comorbidity (N = 112), ineligible for follow-up (unable to visit each participating hospital) (N = 1516). Consequently, 1246 patients were enrolled in the prospective longitudinal study. There were 23 patients who died within 6 months after the initial hospitalization, and 14 patients were lost to follow-up. Among 1209 patients, 748 patients completed the study criteria with a second echocardiography during the 6 month visit after enrolment. In this study, we analysed 721 patients who underwent echocardiography whose TRPG data were available, both during hospitalization and at the 6 month visit (*Figure 1A*). Clinical follow-up was performed 1 year after enrolment (6 months after the 6 month visit) (*Figure 1B*), and data were censored at 210 days after the 6 month visit and we performed a time-to-event analysis. The detailed definition of the baseline patient characteristics has been previously described (Supporting information).[14]

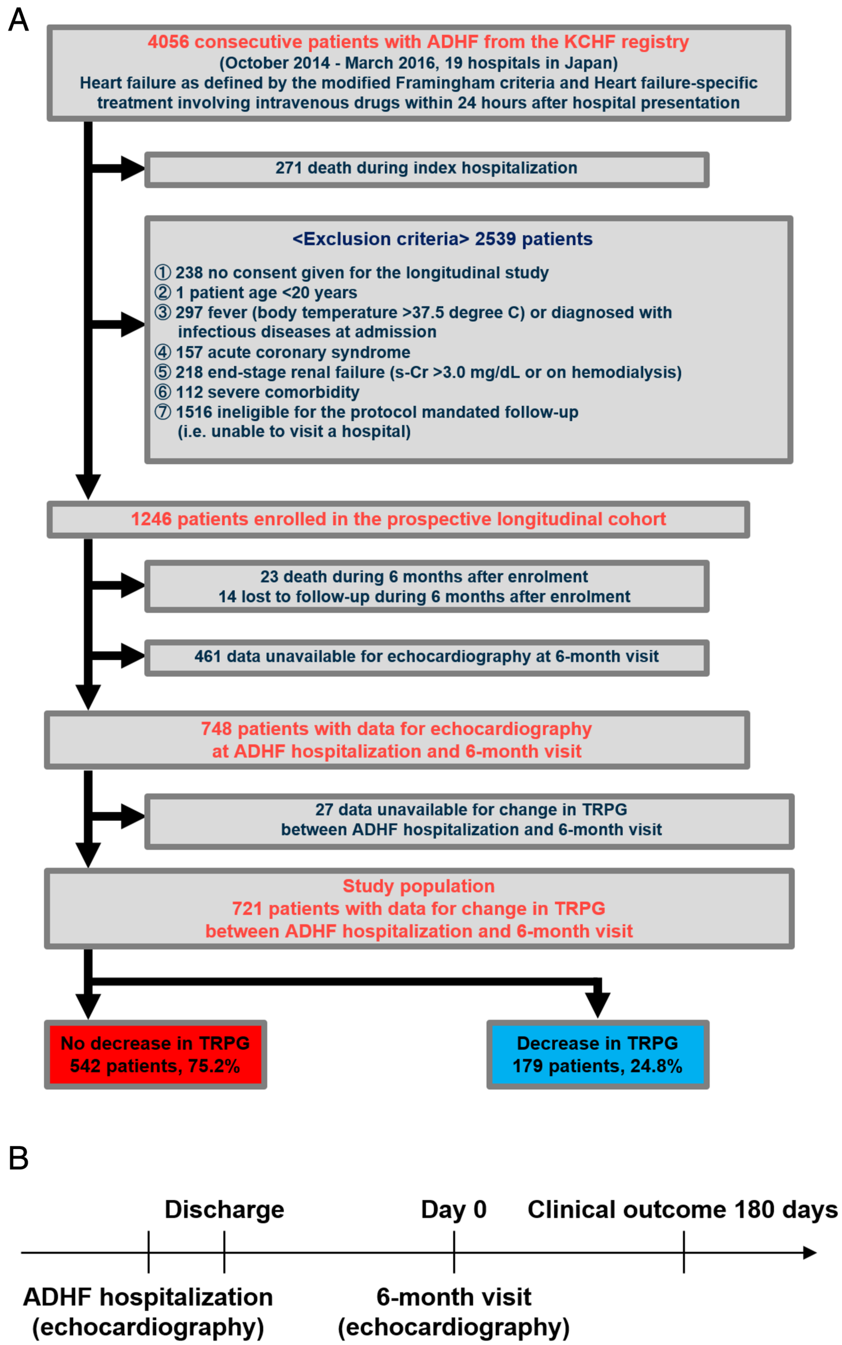
Ethics

The present investigation conforms to the principles outlined in the Declaration of Helsinki. The study protocol was approved by the ethical committee at the Kyoto University Hospital (local identifier: E2311), as well as each participating hospital. Written informed consent was obtained from the patients enrolled in the longitudinal, prospective cohort study.

Echocardiography

All patients underwent comprehensive two-dimensional and Doppler echocardiographic evaluation in each participating centre according to the guidelines.[15] All transthoracic echocardiography measurements were determined using an average of at least three cardiac cycles. The timing of echocardiography was variable among the patients, but we adopted the data in the earliest echocardiography as possible after admission. TR was evaluated in the apical four-chamber view, the parasternal short-axis view at the level of the aortic valve, and the right ventricular inflow view. TR grade was evaluated according to the previously defined guidelines.[16] TRPG was estimated using Doppler echocardiography by calculating the right ventricular to right atrial pressure gradient during systole; a modified Bernoulli equation ($\Delta P = 4\,v^2$) was used to calculate the gradients from the velocities.[8] We defined the decrease in TRPG as an absolute decrease of TRPG $>$10 mmHg from the first echocardiography during hospitalization to the second one at 6 month visit that was regarded as clinically significant. The changes (delta) in TRPG were calculated according to the following equation: (the value at 6 month visit) − (the value of the first echocardiography during hospitalization). For the sensitivity analysis, we categorized the patients into the following three groups according to the magnitude of decrease in TRPG: ΔTRPG < -10 mmHg, -10 mmHg $\leq \Delta$TRPG $\leq$ 10 mmHg, and ΔTRPG $>$10 mmHg. TR velocity $\geq$2.9 m/s that is equivalent to TRPG = 33.64 mmHg was defined as high TR velocity based on a previous report on pulmonary hypertension.[17] PASP were calculated according to the following equation: TRPG plus right atrial pressure (RAP). RAP was estimated by the diameter and respiratory variation in diameter of the inferior vena cava (IVC) from echocardiography: an IVC diameter $<$2.1 cm that collapses $<$50% with a sniff suggests a normal RAP of 3 mmHg, whereas an IVC diameter $>$2.1 cm that collapses $<$50% with a sniff or $<$20% on quiet inspiration suggests a high RAP of 15 mmHg. In cases where the IVC diameter and collapse do not fit this paradigm, an intermediate value of 8 mmHg was used.[17]

Figure 1 (A) Patient study flow diagram decrease in TRPG was defined as >10 mmHg decrease from ADHF hospitalization to 6 month visit. Fever was defined as body temperature >37.5°C. End-stage renal failure was defined as serum creatinine >3.0 mg/dL or on haemodialysis. ADHF, acute decompensated heart failure; KCHF, Kyoto Congestive Heart Failure; TRPG, tricuspid regurgitation pressure gradient. (B) Time course of the study.



Outcomes

The primary outcome measure for the present analysis was a composite of all-cause death and HF hospitalization during 6 months,[13] after the second echocardiography at 6 month visit. Secondary outcome measures were the individual components of the primary outcome measure such as HF hospitalization and all-cause death. HF hospitalization was defined as hospitalization due to worsening of HF, requiring intravenous drug therapy.[13]

Statistical analysis

Categorical variables are presented as numbers with percentages and were compared using the χ^2 test. Continuous variables are expressed as mean with standard deviation or median with interquartile range and compared using the Student's *t* test or Wilcoxon rank sum test based on their distribution. When we compared the longitudinal echocardiographic data from ADHF hospitalization to the 6 month visit, we used paired Student's *t* test for the continuous variables and sign test for binary variables. We specified the date of the second echocardiography at 6 month visit as time zero for clinical follow-up.

The cumulative incidence of clinical events during 6 months after the 6 month visit were estimated using the Kaplan–Meier method with between-groups difference assessed by log-rank test. To estimate the risk of decrease in TRPG group relative to no decrease in TRPG group, a multivariable Cox proportional hazards model was developed for the primary and secondary outcome measures after adjusting for the confounders. We included the following 11 clinically relevant covariates into the model: age ≥80 years; sex; atrial fibrillation or flutter; anaemia; estimated glomerular filtration rate < 30 mL/min/1.73 m^2; left ventricular (LV) ejection fraction (LVEF) <40% by echocardiography at 6 month visit; moderate or severe mitral regurgitation at 6 month visit; and medication at 6 month visit (angiotensin converting enzyme inhibitors [ACEIs] or angiotensin II receptor blockers [ARBs], β-blockers, mineralocorticoid receptor antagonists and diuretics). The results are expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). In the subgroup analysis, we evaluated the interaction between eight subgroup factors at 6 month visit and the effect of decrease, relative to no decrease in TRPG for the primary outcome measure. All statistical analyses were conducted by two physicians (Y. S. and T. K.) and a statistician (T. M.) using JMP 14. All the reported

Table 1 Characteristics, laboratory data and medication at 6 month visit

	Total (*N* = 721)	Decrease in TRPG (*N* = 179)	No decrease in TRPG (*N* = 542)	*P* value	Total data
Clinical characteristic					
Age, years	77 (69–83)	77 (65–84)	77 (70–83)	0.37	721
Age ≥ 80 years	302 (41.9)	74 (41.3)	228 (42.1)	0.86	721
Women	314 (43.6)	68 (38.0)	246 (45.4)	0.08	721
BMI	22.7 ± 4.7	22.2 ± 4.6	22.9 ± 4.7	0.052	541
BMI < 22	267 (49.4)	71 (53.8)	196 (47.9)	0.24	541
Medical history					
Atrial fibrillation or flutter	403 (55.9)	82 (45.8)	321 (59.2)	0.002	721
Hypertension	534 (74.1)	119 (66.5)	415 (76.6)	0.008	721
Diabetes	279 (38.7)	60 (33.5)	219 (40.4)	0.10	721
Dyslipidaemia	288 (39.9)	60 (33.5)	228 (42.1)	0.043	721
Previous myocardial infarction	167 (23.2)	35 (19.6)	132 (24.4)	0.19	721
Chronic kidney disease	319 (44.2)	69 (38.6)	250 (46.1)	0.08	721
Chronic lung disease	92 (12.8)	20 (11.2)	72 (13.3)	0.46	721
Laboratory test results at 6 month visit					
BNP, pg/mL	172.4 (78.9–376.1)	152.1 (57.5–377.4)	185.6 (84.5–376.1)	0.11	527
ΔBNP, pg/mL	−588 ± 723	−821 ± 921	−504 ± 618	<0.001	501
Serum creatinine, mg/dL	1.32 ± 0.66	1.30 ± 0.70	1.33 ± 0.65	0.33	684
eGFR, mL/min/1.73 m^2	45.3 ± 20.4	47.8 ± 21.9	44.4 ± 19.8	0.10	684
<30 mL/min/1.73 m^2	169 (24.7)	36 (21.3)	133 (25.8)	0.24	684
Blood urea nitrogen, mg/dL	27.3 ± 14.9	26.1 ± 15.0	27.7 ± 14.8	0.14	680
Albumin, g/dL	3.9 ± 0.5	4.00 ± 0.46	3.86 ± 0.55	0.009	637
<3.0 g/dL	24 (3.8)	3 (2.0)	21 (4.3)	0.19	637
Sodium, mEq/L	139.9 ± 3.1	139.6 ± 3.7	139.9 ± 2.9	0.69	680
<135 mEq/L	34 (5.0)	14 (8.3)	20 (3.9)	0.02	680
Haemoglobin, g/dL	12.0 ± 2.2	12.2 ± 2.4	11.9 ± 2.2	0.22	679
Anaemia	402 (59.2)	96 (56.8)	306 (60.0)	0.46	679
Medications at 6 month visit					
ACEI or ARB	351 (60.9)	98 (69.5)	253 (58.2)	0.02	576
β blockers	449 (77.7)	113 (80.1)	336 (76.9)	0.42	578
MRA	263 (45.7)	73 (51.8)	190 (43.7)	0.09	576
Diuretics	482 (83.2)	114 (81.4)	368 (83.8)	0.51	579

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BMI, body mass index; BNP, brain-type natriuretic peptide; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; TRPG, tricuspid regurgitation pressure gradient.
Values are number (%), mean ± SD, or median (interquartile range). *P* values were calculated using the χ^2 test for categorical variables and the Student's *t* test or Wilcoxon rank sum test for continuous variables.
Renal dysfunction was defined as estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 at admission. Anaemia was defined using the World Health Organization criteria (haemoglobin <12.0 g/dL in women and <13.0 g/dL in men). The change (delta, Δ) in brain natriuretic peptide (BNP) was calculated according to the following equation: (the value at 6 month visit) − (the value at admission).

P values are two tailed, and the level of statistical significance was set at $P < 0.05$.

Results

Comparison of patient characteristics and laboratory data during discharge and 6 month visit

There were 179 patients (24.8%) with a decrease in TRPG and 542 patients (75.2%) without a decrease in TRPG at 6 month visit (*Figure 1A*). Regarding the patient characteristics, patients with a decrease in TRPG less often had hypertension (P = 0.008), dyslipidaemia (P = 0.0043), and atrial fibrillation or flutter (P = 0.002) (*Table 1*). With respect to the medical treatment at discharge, ACE-I or ARB were more frequently prescribed in patients with a decrease in TRPG (P = 0.03) (Supporting information, *Table S1*). Furthermore, in the laboratory test at 6 month visit (*Table 1*), patients with a decrease in TRPG more often had higher levels of serum albumin (P = 0.009) and lower Δbrain-type natriuretic peptide ($P < 0.001$) than those with no decrease in TRPG. With reference to medical treatment at the 6 month visit, ACE-I or ARB were more likely to be prescribed in patients with a decrease in TRPG (P = 0.02) (*Table 1*).

Echocardiographic parameters

In the initial echocardiography during hospitalization, LV diastolic ($P < 0.001$) and systolic dimension ($P < 0.001$), TRPG ($P < 0.001$), and PASP ($P < 0.001$) were significantly greater in the decrease in TRPG group than in the no decrease in TRPG group. LVEF was significantly lower in the decrease in TRPG group than in the no decrease in TRPG group ($P < 0.001$). The prevalence of moderate or severe MR ($P < 0.001$) and TR ($P < 0.001$) were higher in the decrease in TRPG group than in the no decrease in TRPG group (*Table 2*). During the second echocardiography at the 6 month visit, left atrial dimension (P = 0.007), TRPG ($P < 0.001$), and PASP ($P < 0.001$) were significantly lower in the decrease in TRPG group than in the no decrease in TRPG group. The prevalence of moderate or severe TR (P = 0.005) were lower in the decrease in TRPG group than in the no decrease in TRPG group (*Table 2*). Compared with the first echocardiography during hospitalization to the one during the 6 month visit, LV diastolic, systolic dimensions, and left atrial dimension significantly decreased; whereas, LVEF significantly increased in both groups (all $P < 0.001$). Patients in the decrease in TRPG group showed a greater increase in LVEF during 6 months than in the no decrease in TRPG group (P = 0.003). Patients in the decrease in TRPG group showed a greater decrease in

Table 2 Echocardiographic parameters during hospitalization and at 6 month visit in the decrease and no decrease in TRPG groups

	Decrease in TRPG (N = 179)				No decrease in TRPG (N = 542)				Comparison between the 2 groups		
	During hospitalization	At 6 month visit	Delta[a]	P value (paired)	During hospitalization	At 6 month visit	Delta[a]	P value (paired)	P value (during hospitalization)	P value (6 month visit)	P value (delta)
LV diastolic dimension, mm	55.5 ± 9.9	51.6 ± 10.0	−3.9 ± 6.4	<0.001	52.1 ± 9.0	50.2 ± 9.2	−2.0 ± 5.5	<0.001	<0.001	0.13	<0.001
LV systolic dimension, mm	43.9 ± 12.7	39.0 ± 12.5	−4.9 ± 9.1	<0.001	39.5 ± 11.4	36.5 ± 11.0	−3.1 ± 7.0	<0.001	<0.001	0.02	0.02
IVSTd, mm	9.7 ± 2.2	9.5 ± 2.1	−0.2 ± 1.7	0.12	9.9 ± 2.0	9.9 ± 2.0	−0.07 ± 1.5	0.31	0.049	0.045	0.63
LVPWd, cm	9.8 ± 1.8	9.5 ± 1.8	−0.4 ± 1.9	0.01	9.9 ± 1.9	9.6 ± 1.9	−0.3 ± 1.5	<0.001	0.56	0.44	0.31
LAD, cm	45.0 ± 8.1	41.8 ± 9.1	−3.5 ± 7.5	<0.001	44.9 ± 8.9	43.9 ± 9.0	−1.2 ± 6.3	<0.001	0.44	0.007	<0.001
LVEF, %	40.5 ± 17.5	48.2 ± 16.3	7.7 ± 13.9	<0.001	46.5 ± 16.3	51.2 ± 15.6	4.7 ± 12.4	<0.001	<0.001	0.03	0.003
HFrEF (LVEF < 40%)	94/178 (52.8)	58/178 (32.6)	−36 (−20.2)	<0.001	199/542 (36.7)	142/542 (26.2)	−52 (−10.5)	<0.001	<0.001	0.10	0.36
TRPG, mmHg	41.3 ± 14.6	18.3 ± 13.3	−23.0 ± 11.8	<0.001	20.8 ± 15.8	27.9 ± 15.4	7.1 ± 13.8	<0.001	<0.001	<0.001	<0.001
TR velocity ≥2.9 m/s	125/179 (69.8)	22/179 (12.3)	−103 (−57.5)	<0.001	107/542 (19.7)	164/542 (30.3)	57 (10.6)	<0.001	<0.001	<0.001	<0.001
PASP, mmHg	47.6 ± 15.6	21.9 ± 13.6	−25.7 ± 12.4	<0.001	26.2 ± 16.6	31.7 ± 16.0	5.5 ± 13.5	<0.001	<0.001	<0.001	<0.001
Moderate or severe TR	82/179 (45.8)	34/179 (19.0)	−48 (−26.8)	<0.001	116/542 (21.4)	162/542 (29.9)	46 (8.5)	<0.001	<0.001	0.005	<0.001
Moderate or severe MR	83/178 (46.6)	47/178 (26.4)	−36 (−20.2)	<0.001	170/517 (32.9)	174/517 (33.7)	4 (0.8)	0.69	0.001	0.07	<0.001

IVSTd, diastolic interventricular septal wall thickness; LAD, left atrial dimension; LV, left ventricular; LVEF, left ventricular ejection fraction; LVPWd, diastolic left ventricular posterior wall thickness; MR, mitral regurgitation; PASP, pulmonary artery systolic pressure; TR, tricuspid regurgitation; TRPG, tricuspid regurgitation pressure gradient.

[a]Delta was calculated according to the following equation: Continuous variables = (the value at 6 month visit) − (the value during hospitalization). Binary variables, we calculated delta according to the following equation: (the numbers at 6 month visit) − (the numbers during hospitalization).

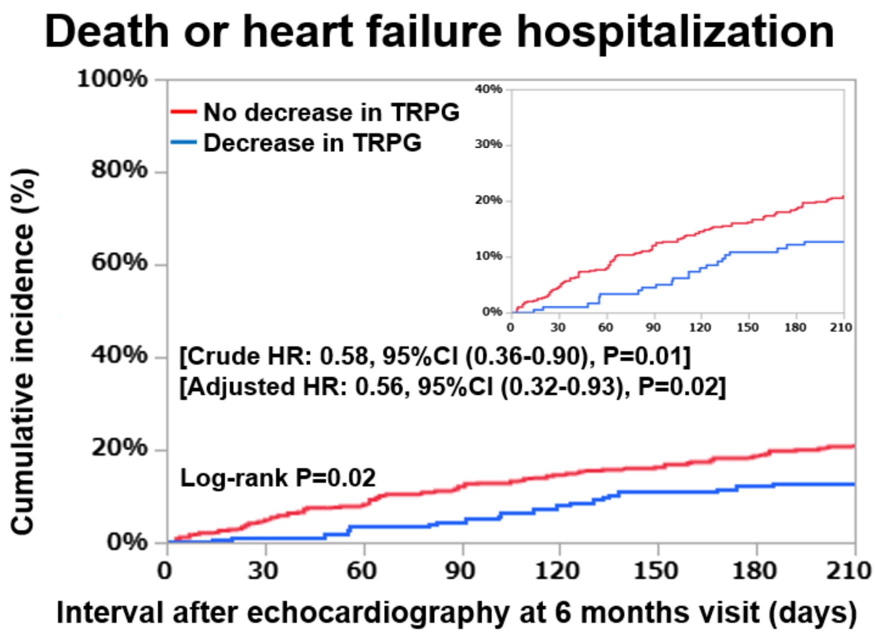
PASP ($P < 0.001$) during 6 months than in the no decrease in TRPG group. The prevalence of moderate or severe MR ($P < 0.001$) and TR ($P < 0.001$) significantly decreased in the decrease in TRPG group (*Table 2*).

Clinical outcomes in the decrease in TRPG group vs. no decrease in TRPG group

The follow-up rate after the 6 month visit was 96.0%. The cumulative 6 month incidence of the primary outcome measure was significantly lower in the decrease in TRPG group than in the no decrease in TRPG group (12.2% vs. 18.7%, P = 0.02) (*Figure 2A*). After adjusting for the confounders, the lower risk of decrease in TRPG relative to no decrease in TRPG for the primary outcome measure remained significant (HR: 0.56. 95% CI 0.32–0.93, P = 0.02). The cumulative 6 month incidence of all-cause death was significantly lower in the decrease in TRPG group than in the no decrease in TRPG group (3.5% vs. 7.9%, P = 0.03) (*Figure 2B*). After adjusting for the confounders, lower risk of decrease in TRPG relative to no decrease in TRPG for all-cause death was no longer significant (HR: 0.50. 95% CI 0.19–1.13, P = 0.10). The cumulative 6 month incidence of HF hospitalization was not

Figure 2 Kaplan–Meier curves for the primary outcome measure and its individual components. (A) The primary outcome measure: a composite of all-cause death and heart failure hospitalization, (B) all-cause death, and (C) heart failure hospitalization. CI, confidence interval; HR, hazard ratio; TRPG, tricuspid regurgitation pressure gradient.

A



Interval (days)	0	60	120	180
No decrease in TRPG				
N of patients with at least 1 event		44	78	100
N of patients at risk	542	494	453	405
Cumulative incidence		8.1%	14.5%	18.7%
Decrease in TRPG				
N of patients with at least 1 event		6	14	21
N of patients at risk	179	169	160	141
Cumulative incidence		3.4%	8.0%	12.2%

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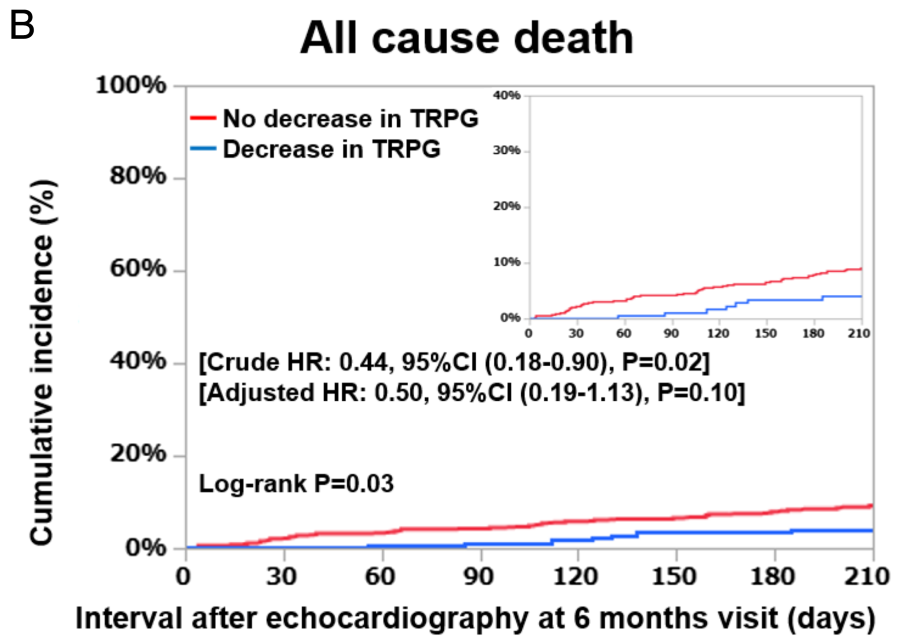
Figure 2 Continued



Interval (days)	0	60	120	180
No decrease in TRPG				
N of patients with event		18	31	42
N of patients at risk	542	520	500	460
Cumulative incidence		3.3%	5.8%	7.9%
Decrease in TRPG				
N of patients with event		1	3	6
N of patients at risk	179	174	171	153
Cumulative incidence		0.6%	1.7%	3.5%

significantly different between the decrease in TRPG group and in the no decrease in TRPG group (9.9% vs. 12.4%, P = 0.21) (*Figure 2C*). After adjusting for the confounders, lower risk of decrease in TRPG relative to no decrease in TRPG for HF hospitalization was not significant (HR: 0.65. 95% CI 0.34–1.17, P = 0.16).

Subgroup analysis

There were no significant interactions between the subgroup factors and the effect of decrease in TRPG relative to no decrease in TRPG for the primary outcome measure (*Figure 3*).

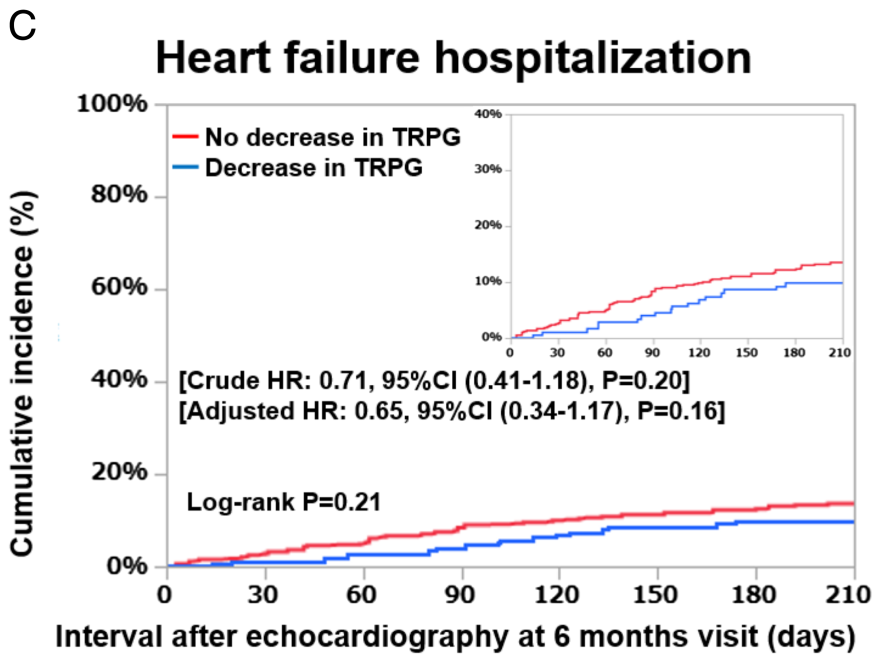
Sensitivity analysis

When we divided patients into the three groups according to the magnitude of decrease in TRPG (ΔTRPG < -10 mmHg, -10 mmHg $\leq \Delta$TRPG ≤ 10 mmHg, and ΔTRPG > 10 mmHg), the cumulative 6 month incidence of primary outcome measure decreased with larger decrease in TRPG (12.2%, 16.3%, and 24.3%, respectively, P = 0.002) (*Figure S1*).

Discussion

The main findings of this study are as follows: (i) the decrease in TRPG group less often had atrial fibrillation or flutter, and

Figure 2 Continued



Interval (days)	0	60	120	180
No decrease in TRPG				
N of patients with at least 1 event		27	52	64
N of patients at risk	542	494	453	405
Cumulative incidence		5.1%	9.9%	12.4%
Decrease in TRPG				
N of patients with at least 1 event		5	12	17
N of patients at risk	179	169	160	141
Cumulative incidence		2.9%	6.9%	9.9%

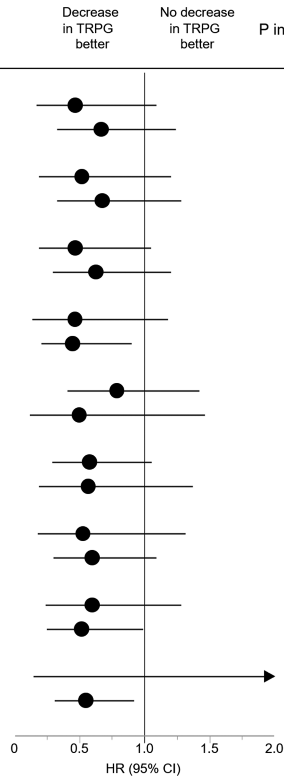
more often had moderate to severe mitral regurgitation; and had a higher TRPG at hospitalization and a greater increase in LVEF at 6 month visit than the no decrease in TRPG group. (ii) The decrease in TRPG during the 6 month visit was associated with better subsequent outcome in terms of composite all-cause death and HF hospitalization in patients after discharge with ADHF, regardless of the TRPG values.

A novel finding of the present study is that decrease in TRPG during follow-up was associated with better outcomes, despite higher TRPG values during hospitalization. Previous reports have shown worsening effect of high TRPG on the prognosis of patients with HF.[10–12] However, in the present study, the decrease in TRPG group had a significantly higher TRPG value and a lower LVEF at ADHF hospitalization, but nevertheless showed favourable outcomes. This implies that decrease in TRPG during 6 months reflects successful treatment of HF during the 6 months regardless of TRPG basal values in conjunction with the results of subgroup analyses.

Tricuspid regurgitation pressure gradient is closely related to TR and could be a representative echocardiographic parameter for the estimation of PASP and pulmonary vascular resistance.[8,9] The comprehensive evaluation of TR should involve the assessment of the severity of TR, the tricuspid valve morphology, right ventricular size and function, left heart chamber size and function, and concomitant valvular function, as well as pre-capillary and post-capillary pulmonary

Figure 3 Subgroup analysis for the effect of decrease in TRPG relative to no decrease in TRPG for the primary outcome measure. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; TR, tricuspid regurgitation; TRPG, tricuspid regurgitation pressure gradient. CI, confidence interval; HR, hazard ratio.

	N of patients with at least 1 event / N of patients at risk (Cumulative 180 days incidence after 6-month visit)				
Subgroups	Decrease in TRPG	No decrease in TRPG	Crude HR (95% CI)	Adjusted HR (95% CI)	P interaction
Atrial fibrillation/flutter					
No	8/97 (8.6)	39/221 (18.0)	0.40 (0.17-0.81)	0.47 (0.17-1.09)	0.39
Yes	13/82 (16.3)	61/321 (19.3)	0.79 (0.43-1.36)	0.67 (0.33-1.24)	
eGFR					
<30ml/min/1.73m^2	8/36 (22.3)	37/133 (28.4)	0.71 (0.31-1.45)	0.52 (0.19-1.20)	0.47
≥30ml/min/1.73m^2	13/133 (10.3)	57/382 (15.1)	0.62 (0.33-1.06)	0.68 (0.33-1.28)	
LVEF					
<40%	9/58 (16.2)	41/142 (29.7)	0.47 (0.22-0.93)	0.47 (0.19-1.05)	0.43
≥40%	12/120 (10.3)	59/400 (14.9)	0.62 (0.33-1.09)	0.63 (0.30-1.20)	
TRPG at hospitalization					
<33.64mmHg (TR velocity 2.9m/s)	5/42 (10.1)	68/335 (15.9)	0.54 (0.19-1.21)	0.47 (0.14-1.18)	0.79
≥33.64 mmHg	16/100 (13.0)	32/70 (30.2)	0.35 (0.19-0.61)	0.45 (0.21-0.90)	
TRPG at 6-month visit					
<33.64mmHg (TR velocity 2.9m/s)	16/157 (10.6)	46/378 (12.4)	0.80 (0.45-1.35)	0.79 (0.41-1.42)	0.42
≥33.64mmHg	5/22 (23.3)	54/164 (33.4)	0.57 (0.20-1.28)	0.50 (0.12-1.46)	
Mitral regurgitation					
None or mild	12/131 (9.5)	53/354 (15.3)	0.59 (0.31-1.04)	0.58 (0.29-1.05)	0.97
Moderate or severe	9/47 (19.7)	47/180 (26.4)	0.61 (0.28-1.18)	0.57 (0.19-1.37)	
β blocker					
No	5/28 (18.5)	32/101 (32.1)	0.44 (0.15-1.02)	0.53 (0.18-1.31)	0.59
Yes	11/113 (10.2)	56/336 (17.0)	0.58 (0.30-1.04)	0.60 (0.30-1.09)	
ACEI/ARB					
No	6/43 (15.1)	43/182 (24.1)	0.64 (0.26-1.32)	0.60 (0.24-1.28)	0.75
Yes	11/98 (11.6)	45/253 (18.1)	0.54 (0.27-0.99)	0.52 (0.25-0.99)	
Diuretics					
No	1/26 (4.0)	4/71 (5.7)	0.69 (0.04-4.68)	4.98 (0.15-235.4)	0.64
Yes	16/114 (14.7)	84/368 (23.2)	0.57 (0.33-0.92)	0.55 (0.31-0.92)	



hypertension.[18] This study shows indirectly the importance of the right ventricle, when evaluating patients with HF.

Understanding the differences in patient characteristics between those who present with a decrease in TRPG and those who do not, upon hospitalization, might be important to improve management of patients with HF. TRPG is defined by hemodynamic congestion and pulmonary vascular resistance due to primary or secondary causes.[9,19,20] In our study, a decrease in TRPG during 6 months is thought to be one of markers of successful treatment of HF. Our result is in line with evidence that better control of congestion reduced re-hospitalization with HF after discharge.[21] More severe TR was often associated with more advanced left-sided heart disease.[22] However, there were no significant interactions between the effect of the decrease in TRPG and important subgroup factors, such as LVEF, mitral regurgitation, TR velocity, and use of diuretics. Blockers of renin–angiotensin–aldosterone system, but not β-blockers or diuretics, were more often prescribed in patients with a decrease in TRPG at 6 month visit. Blockers of renin–angiotensin–aldosterone system can be related to the decrease in TRPG during follow-up through reverse remodelling of left HF with reduced mitral regurgitation. Atrial fibrillation is caused by atrial remodelling. Furthermore, atrial remodelling leads to annular dilatation of tricuspid valve and increases TR grade and vice versa.[22,23] In our study, patients in the no decrease in TRPG group had a higher prevalence of atrial fibrillation than those in the decrease in TRPG group. Although the cause–effect relationship could not be determined in the present study, management of atrial fibrillation might be a potential strategy to decrease the TRPG. It remains unclear if a decrease in TRPG can be a therapeutic target in the management of HF through the management of congestion and/or decreasing the LV end-diastolic pressure. Our study presents the importance of assessing the temporal change in TRPG in HF.

This study has several limitations. First, the patients in the prospective longitudinal cohort had clearly less size of sample than in the entire cohort and might influence the results. In addition, echocardiography during the 6 month visit was not available in a substantial proportion of patients. The advanced age of longitudinal study population might be one of the reasons for low rate of echocardiography at the

6 month visit. Second, an observational study design is subject to selection bias and residual confounding. Third, the timing of performing first echocardiography after admission was variable. We chose the earliest available echocardiography test after admission. However, there were patients who received diuretic therapy prior to echocardiography. Fourth, the second echocardiographic period in this study was set at 6 months after discharge, but our study does not provide data regarding the optimal time interval of follow-up. Fifth, although the echocardiographic parameters were usually obtained in the context of routine examination, measurement errors and variability might exist. Sixth, TR is not present in all patients with HF. TRPG is available in selected patients. Seventh, there were no data available on the right ventricular function, such as tricuspid annular plane systolic excursion or right ventricular ejection fraction. Eighth, the patients with no decrease in TRPG had lower prescription of ACEI/ARB than the patients with the decrease in TRPG because the patients with no decrease in TRPG had lower prevalence of LVEF <40% than the patients with the decrease in TRPG. The difference of prescription might influence the results even after adjusting in multivariable Cox proportional hazards model; however, there were no interactions between LVEF or the prescription of ACE-I/ARB and the effect of decrease in TRPG relative to no decrease in TRPG for the primary outcome measure.

Conclusion

Heart failure patients with decrease in TRPG at 6 months after discharge from ADHF hospitalization had a lower risk of all-cause death and HF hospitalization than those without a decrease in TRPG, suggesting the importance of assessing TRPG during the follow-up.

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Conflict of interest

None reported.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Medical history at discharge.
Figure S1. Kaplan–Meier curves in the Sensitivity analysis.
CI, Confidence interval; HR, Hazard ratio; TRPG, tricuspid regurgitation pressure gradient.

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