TABLE 3] Logistic Regression Analysis for Determinants of Positive LGE

Variable	Univariate			Multivariate		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
IVS thinning	14.3	1.81-112.3	.01	11.7	1.49-92.0	.019
Multiorgan involvement	4.2	0.77-23.0	.09	2.7	0.45-16.4	.28
Female patients	1.7	0.30-9.06	.56	...	...	...
Age ≥62 y	2.1	0.46-10.0	.33	...	...	...
ECG abnormality	2.6	0.52-12.93	.24	...	...	...
Positive for Ga-scintigram	5.6	0.31-99.87	.24	...	...	...
Bilateral hilar lymphoadenopathy	1.1	0.19-5.97	.94	...	...	...
Time since diagnosis of extracardiac sarcoidosis ≥45 mo	0.5	0.12-2.57	.45	...	...	...
ACE ≤23.4 mg/dL	1.7	0.37-8.12	.48	...	...	...
Steroid use	3.7	0.55-24.5	.18	...	...	...

See Table 1 and 2 legends for expansion of abbreviations.

respect to disease duration, this study cohort had been diagnosed with sarcoidosis for a median of approximately 3 years as compared with 7 and 8 years in the previous studies, which may explain why cardiac involvement was more prevalent in the previous studies compared with the present study. Our LGE-positive group also had markedly lower use of steroids (11% vs 41% to 65%), and other immunosuppressants (0% vs 9% to 28%), indicating that they had a relatively stable disease condition. Further, the previous studies did not exclude patients with cardiac symptoms, severe ECG abnormalities, reduced left ventricular systolic function, or patients satisfying the JMHW criteria, which may also have led to the higher detection rates of cardiac involvement and poorer long-term outcomes.

We also found that IVS thinning detected by echocardiography was an independent determinant of positive LGE findings. Although thinning of the IVS was reported to be a characteristic manifestation of cardiac involvement,[20] IVS thinning was only observed in 38% of patients who were LGE positive. However, this rate of detection was considerably higher than that of 20% reported in a study of Japanese patients with cardiac sarcoidosis.[21] Although our present findings suggest that IVS thinning may be a predictor of myocardial damage detected by LGE, future prospective studies with larger cohorts are needed to confirm this possibility.

The treatment of patients with LGE-positive, extracardiac sarcoidosis without cardiac manifestations and preserved systolic function presents a challenge in the clinical setting with respect to steroid treatment. In the present study, five patients in the LGE-positive group were recommended for immunosuppressant therapy to treat the myocardial damage detected by CMR; however, four of these patients declined immunosuppressant therapy because of concerns related to adverse effects. Similar to the patients treated with steroid medications, however, none of the patients who declined steroid therapy had detectable progression or improvement of cardiac damage by LGE-CMR after 6 months. Notably, in one patient who agreed to steroid induction after the initial CMR, the small amount of myocardial damage had disappeared after 6 months. Patel et al[8] reported that the dense fibrosis or granulomatous inflammation within patchy fibrotic lesions observed in autopsy heart specimens matched the LGE-CMR imaging findings. In addition, our present findings are consistent with a report showing that steroid treatment reduced the size of enhanced areas in LGE-CMR.[22] However, close, long-term observation of the clinical course and outcome of patients with extracardiac sarcoidosis with cardiac involvement detected by LGE and who are not treated with steroid therapy after initial CMR should also provide critical information regarding the effectiveness of steroid therapy. Therefore, the detection of minor myocardial damage by LGE-CMR in patients with extracardiac sarcoidosis might provide a basis for discussion about steroid treatment in patients who would not otherwise meet indications for immunosuppressant therapy for extracardiac organs.

Further studies are needed to determine how LGE-CMR could contribute to the selection of therapeutic strategies for improving the long-term prognosis of extracardiac sarcoidosis with cardiac involvement, as has

TABLE 4] Characteristics of Patients Positive for LGE

Case	1	2	3	4	5	6	7	8
Age, y	54	73	60	74	66	73	76	56
Sex	Female	Male	Male	Female	Female	Female	Female	Female
Time since diagnosis of extracardiac sarcoidosis, mo	7	8	12	162	49	5	38	91
Organ involvement	Lung, eye	Lung, skin	Lung, skin	Lung	Lung, skin	Eye	Lung	Lung, eye
ECG abnormality	Wenckebach AVB Right BBB	Nonspecific ST change	Right BBB	None	None	None	None	None
Thinning of IVS	No	Yes	No	No	Yes	Yes	No	No
Wall-motion abnormality	Yes	No	No	No	No	Yes	No	No
Ga-scintigram	Positive	Negative	Negative	Negative	Negative	Negative	Negative	Negative
ACE, mg/dL	15.2	18.0	29.1	16.9	23.4	12.3	24.1	25.4
LGE pattern	Transmyocardial	Perimyocardial	Intramyocardial	Intramyocardial	Perimyocardial	Transmyocardial	Intramyocardial	Intramyocardial
LGE location	IVS	IVS posterior	Anterior	Posterior	IVS	Posterior	IVS posterior	Anterior
Cardiac events	Advanced AVB (day 22); pacemaker implantation	None	None	None	None	None	None	None

See Table 1 and 2 legends for expansion of abbreviations.

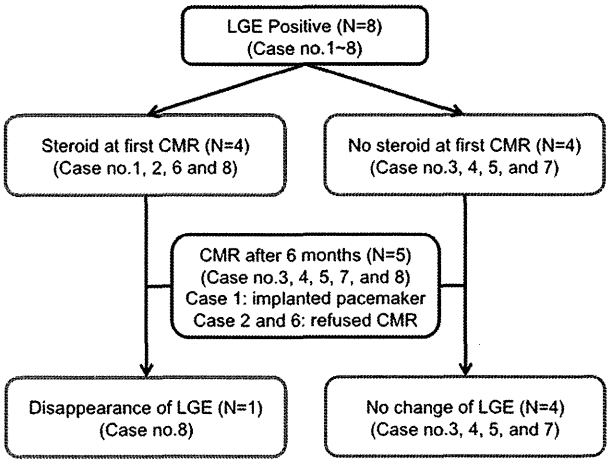

Figure 2 – *Steroid therapy at first CMR and change in LGE after 6 mo. LGE = late gadolinium enhancement; CMR = cardiovascular MRI.*

been suggested for various types of nonischemic cardiomyopathy.[23] Mehta et al[24] reported that positive programmed electric stimulation (PES) of the ventricle might help to identify patients with asymptomatic cardiac sarcoidosis at risk for ventricular arrhythmia; patients with negative PES also appeared to have a benign clinical course for the first several years following diagnosis. Therefore, this type of risk stratification together with LGE-CMR might be useful in further prospective studies of asymptomatic cardiac sarcoidosis. However, PES would be an invasive strategy, and difficult to use routinely for asymptomatic patients in clinical practice.

Several limitations of this study warrant mention. First, the number of patients positive for LGE was relatively small. However, we believe that the sample is representative of patients with extracardiac sarcoidosis. Second, the estimation of IVS thinning was based on qualitative assessment performed by two technicians and, as such, may have suffered from inaccuracy. Therefore, the use of

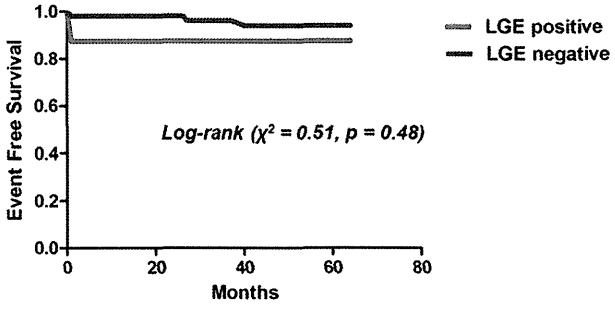

Figure 3 – *Kaplan-Meier curves for long-term adverse events (all-cause death, symptomatic arrhythmias, and heart failure necessitating admission). See Figure 2 legend for expansion of abbreviation.*

standard assessment methods will be necessary in future studies investigating IVS thinning. Third, because patients were not monitored by 24-h ECG, it is possible that several tachyarrythmias and bradyarrhythmias were missed. For this reason, one of the study end points regarding arrhythmic events was defined as symptomatic arrhythmia including ventricular tachyarrhythmia necessitating admission and bradycardia leading to pacemaker implantation. Fourth, ^{18}F-fluorodeoxyglucose PET, in addition to LGE-CMR, for detecting inflammatory activity was not performed, and there may be several uncertainties on the precise pathophysiologic interpretation of myocardial hyperenhancement. Fifth, we did not completely exclude CAD as a cause of LGE by coronary angiography, because the American Heart Association guidelines state that neither CT angiography nor magnetic resonance angiography should be used to screen for CAD in patients who have no signs or symptoms suggestive of CAD,[25] and no patients in the current cohort had such signs or symptoms. In addition, no patient in the LGE-positive group had typical subendomyocardial damage (CAD pattern), as reported in the Results section. Sixth, cardiac involvement may be present in the absence of any abnormality on standard cardiac testing, may manifest as an abnormal ECG alone, or may be recognized as an asymptomatic abnormality on echocardiogram, or even on LGE-CMR. Considering these facts and the findings of our study, it would be difficult to distinguish between an earlier and clinically silent phase of cardiac sarcoidosis with detection of myocardial damage by multimodalities including LGE-CMR. Finally, the sample size was small, thereby limiting the ability to generalize the findings and the statistical power for detecting differences in negative data. Regarding the follow-up period, although it was longer than that of previous studies, it might be still inadequate to conclude that asysmptomatic patients in the LGE-positive and LGE-negative groups had similar outcomes; namely, the chance of a type 2 error is a possibility. Therefore, further prospective studies with a larger asymptomatic population and longer follow-up are warranted.

In conclusion, the present findings suggest that LGE-CMR is useful for the detection of cardiac involvement in patients with extracardiac sarcoidosis and no cardiac symptoms, preserved LVEF, and not satisfying JMHW criteria. Even in patients without cardiac manifestation, cardiac damage was detected in approximately 15% of patients, although those with and without LGE had similar clinical outcomes.

Acknowledgments

Author contributions: T. N. and S. K. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. T. N. served as principal author. T. N., S. K., S. O., T. A., K. A., and K. F. contributed to the study design and data analysis; T. N., S. K., S. O., T. A., and K. A. contributed to data interpretation; T. N. and S. K. drafted the original manuscript and revised it critically with respect to intellectual content; and T. N., S. K., S. O., T. A., K. A., and K. F. approved the final version of the submitted manuscript.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Other contributions: We thank Mizue Sato, AS; Ikuko Ueda, PhD; Jun Makino, BS; Mariko Kondo, BS; and Yukiho Hirota, BS (Keio University) for contributions to data collection and monitoring.

References

1. Longcope WT, Freiman DG. A study of sarcoidosis; based on a combined investigation of 160 cases including 30 autopsies from The Johns Hopkins Hospital and Massachusetts General Hospital. *Medicine (Baltimore)*. 1952;31(1):1-132.
2. Yager JE, Hernandez AF, Steenbergen C, et al. Recurrence of cardiac sarcoidosis in a heart transplant recipient. *J Heart Lung Transplant*. 2005;24(11):1988-1990.
3. Zipes DP, Camm AJ, Borggrefe M, et al; European Heart Rhythm Association; Heart Rhythm Society; American College of Cardiology; American Heart Association Task Force; European Society of Cardiology Committee for Practice Guidelines. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). *J Am Coll Cardiol*. 2006;48(5):e247-e346.
4. Silverman KJ, Hutchins GM, Bulkley BH. Cardiac sarcoid: a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. *Circulation*. 1978;58(6):1204-1211.
5. Yazaki Y, Isobe M, Hiroe M, et al; Central Japan Heart Study Group. Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. *Am J Cardiol*. 2001;88(9):1006-1010.
6. Sharma OP. Cardiac and neurologic dysfunction in sarcoidosis. *Clin Chest Med*. 1997;18(4):813-825.
7. Perry A, Vuitch F. Causes of death in patients with sarcoidosis. A morphologic study of 38 autopsies with clinicopathologic correlations. *Arch Pathol Lab Med*. 1995;119(2):167-172.
8. Patel MR, Cawley PJ, Heitner JF, et al. Detection of myocardial damage in patients with sarcoidosis. *Circulation*. 2009;120(20):1969-1977.
9. Patel AR, Klein MR, Chandra S, et al. Myocardial damage in patients with sarcoidosis and preserved left ventricular systolic function: an observational study. *Eur J Heart Fail*. 2011;13(11):1231-1237.
10. Krittayaphong R, Boonyasirinant T, Saiviroonporn P, Udompunturak S. Late gadolinium enhancement from cardiac magnetic resonance in ischemic and nonischemic cardiomyopathy. *J Med Assoc Thai*. 2011;94(suppl 1):S33-S38.
11. Watanabe E, Kimura F, Nakajima T, et al. Late gadolinium enhancement in cardiac sarcoidosis: characteristic magnetic resonance findings and relationship with left ventricular function. *J Thorac Imaging*. 2013;28(1):60-66.
12. Doughan AR, Williams BR. Cardiac sarcoidosis. *Heart*. 2006;92(2):282-288.
13. Serra JJ, Monte GU, Mello ES, et al. Images in cardiovascular medicine. Cardiac sarcoidosis evaluated by delayed-enhanced magnetic resonance imaging. *Circulation*. 2003;107(20):e188-e189.
14. Smedema JP, Snoep G, van Kroonenburgh MP, et al. The additional value of gadolinium-enhanced MRI to standard assessment for cardiac involvement in patients with pulmonary sarcoidosis. *Chest*. 2005;128(3):1629-1637.
15. Smedema JP, Snoep G, van Kroonenburgh MP, et al. Evaluation of the accuracy of gadolinium-enhanced cardiovascular magnetic resonance in the diagnosis of cardiac sarcoidosis. *J Am Coll Cardiol*. 2005;45(10):1683-1690.
16. Hiraga H, Yuwa K, Hiroe M. *Guideline for the Diagnosis of Cardiac Sarcoidosis: Study Report on Diffuse Pulmonary Disease* [in Japanese]. Tokyo, Japan: Japanese Ministry of Health and Welfare; 1993:23-24.
17. Tsuda T, Ishihara M, Okamoto H. Diagnostic standard and guideline for sarcoidosis-2006. *Jpn J Sarcoidosis and Other Granulomatous Disorders*. 2006;27:89-102.
18. Kasahara Y, Ashihara Y. Colorimetry of angiotensin-I converting enzyme activity in serum. *Clin Chem*. 1981;27(11):1922-1925.
19. Uemura A, Morimoto S, Hiramitsu S, Kato Y, Ito T, Hishida H. Histologic diagnostic rate of cardiac sarcoidosis: evaluation of endomyocardial biopsies. *Am Heart J*. 1999;138(2 pt 1):299-302.
20. Valantine HA, Tazelaar HD, Macoviak J, et al. Cardiac sarcoidosis: response to steroids and transplantation. *J Heart Transplant*. 1987;6(4):244-250.
21. Uemura A, Morimoto S, Kato Y, et al. Relationship between basal thinning of the interventricular septum and atrioventricular block in patients with cardiac sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2005;22(1):63-65.
22. Schulz-Menger J, Wassmuth R, Abdel-Aty H, et al. Patterns of myocardial inflammation and scarring in sarcoidosis as assessed by cardiovascular magnetic resonance. *Heart*. 2006;92(3):399-400.
23. Karamitsos TD, Neubauer S. The prognostic value of late gadolinium enhancement CMR in nonischemic cardiomyopathies. *Curr Cardiol Rep*. 2013;15(1):326.
24. Mehta D, Mori N, Goldbarg SH, Lubitz S, Wisnivesky JP, Teirstein A. Primary prevention of sudden cardiac death in silent cardiac sarcoidosis: role of programmed ventricular stimulation. *Circ Arrhythm Electrophysiol*. 2011;4(1):43-48.
25. Bluemke DA, Achenbach S, Budoff M, et al. Noninvasive coronary artery imaging: magnetic resonance angiography and multidetector computed tomography angiography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention, and the councils on Clinical Cardiology and Cardiovascular Disease in the Young. *Circulation*. 2008;118(5):586-606.

PLOS ONE

Prognostic Implication of Physical Signs of Congestion in Acute Heart Failure Patients and Its Association with Steady-State Biomarker Levels

Sayoko Negi[1], Mitsuaki Sawano[1], Shun Kohsaka[1]*, Taku Inohara[1], Yasuyuki Shiraishi[1], Takashi Kohno[1], Yuichiro Maekawa[1], Motoaki Sano[1], Tsutomu Yoshikawa[2], Keiichi Fukuda[1]

1 Department of Cardiology, Keio University School of Medicine, Tokyo, Japan, **2** Sakakibara Heart Institute, Tokyo, Japan

Abstract

Background: Congestive physical findings such as pulmonary rales and third heart sound (S3) are hallmarks of acute heart failure (AHF). However, their role in outcome prediction remains unclear. We sought to investigate the association between congestive physical findings upon admission, steady-state biomarkers at the time of discharge, and long-term outcomes in AHF patients.

Methods: We analyzed the data of 133 consecutive AHF patients with an established diagnosis of ischemic or non-ischemic (dilated or hypertrophic) cardiomyopathy, admitted to a single-center university hospital between 2006 and 2010. The treating physician prospectively recorded major symptoms and congestive physical findings of AHF: paroxysmal nocturnal dyspnea, orthopnea, pulmonary rales, jugular venous distension (JVD), S3, and edema. The primary endpoint was defined as rehospitalization for HF.

Results: Majority (63.9%) of the patients had non-ischemic etiology and, at the time of admission, S3 was seen in 69.9% of the patients, JVD in 54.1%, and pulmonary rales in 43.6%. The mean follow-up period was 726 ± 31days. Patients with pulmonary rales ($p < 0.001$) and S3 ($p = 0.011$) had worse readmission rates than those without these findings; the presence of these findings was also associated with elevated troponin T (TnT) levels at the time of discharge (odds ratio [OR] 2.8; $p = 0.02$ and OR 2.6; $p = 0.05$, respectively).

Conclusion: Pulmonary rales and S3 were associated with inferior readmission rates and elevated TnT levels on discharge. The worsening of the readmission rate owing to congestive physical findings may be a consequence of on-going myocardial injury.

Citation: Negi S, Sawano M, Kohsaka S, Inohara T, Shiraishi Y, et al. (2014) Prognostic Implication of Physical Signs of Congestion in Acute Heart Failure Patients and Its Association with Steady-State Biomarker Levels. PLoS ONE 9(5): e96325. doi:10.1371/journal.pone.0096325

Editor: John Calvert, Emory University, United States of America

Received December 17, 2013; **Accepted** April 5, 2014; **Published** May 6, 2014

Funding: The authors have no support or funding to report.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: kohsaka@cpnet.med.keio.ac.jp

Introduction

The evaluation of acute heart failure (AHF) patients starts with careful history taking and physical examination. Signs of congestion and findings related to pulmonary rales, third heart sound (S3), and jugular venous distention (JVD) are known to have important diagnostic importance for AHF patients. However, the association between congestive physical findings in AHF patients and their clinical outcomes has not been well established [1]. In addition, the exact reason why these congestive physical findings are related to adverse clinical outcomes is still unclear.

In the modern management of AHF, biomarkers are used because they are thought to reflect common pathological abnormalities such as acute myocardial injury [2–6] or volume overload in the left ventricle [7–9]. The levels of these biomarkers are measured to obtain "subclinical" pathological and additional prognostic information. Therefore, we sought to examine the association between congestive physical findings upon admission, steady-state biomarker levels at the time of discharge, and long-term outcomes in AHF patients. Clarification of the role of congestive physical findings will aid in risk stratification of AHF patients in a cost-effective manner.

Methods

Study Subjects

This study registered AHF patients admitted to a single-center tertiary hospital between 2006 and 2010, for treatment of AHF, which was diagnosed according to the Framingham criteria. From a total of 339 patients, 110 patients (32.4%) were excluded from the final analysis because of incomplete data about physical findings on admission, biomarker levels on discharge, dates of admission and discharge, outcomes, or underlying conditions; and 96 patients (28.3%) were excluded because of diagnoses other than ischemic cardiomyopathy (ICM) or non-ischemic cardiomyopathy such as dilated cardiomyopathy (DCM) or hypertrophic cardio-

myopathy (HCM). The final study population consisted of 133 patients. Informed consent was obtained from each patient, and written consent was also obtained from all of the participants in the study.

DCM was defined as echocardiographic demonstration of unexplained left ventricular (LV) dilatation (i.e., LV diastolic dimension ≥55 mm) and impaired contraction (i.e., LV ejection fraction <45%) without the presence of obstruction coronary disease. ICM was defined as LV ejection fraction <40% with previously known myocardial infarction or evidence of severe coronary disease on coronary angiography. HCM was defined as presence of increased LV wall thickening ≥15 mm in the absence of identifiable cause for LVH such as hypertension or valvular heart disease. All patients with non-ischemic cardiomyopathy underwent coronary angiography and cardiac biopsy to rule out obstructive coronary disease and infiltrative heart disease. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and the study was approved by Institutional Review Board of Keio University School of Medicine.

Verification of Physical Findings and Measurement of Cardiac Biomarkers

Internal medicine residents obtained all physical findings of patients upon admission and coded the findings in pre-specified case report form. The physical findings were consisted with paroxysmal nocturnal dyspnea, orthopnea, pulmonary rales, JVD, and S3. Cardiology physicians verified these findings subsequently when the patients were transferred to in-patient service.

Plasma brain natriuretic peptide (BNP) levels were measured at the time of admission as well as discharge, using a commercially available assay kit (Shionogi, Tokyo, Japan). Cardiac troponin T (cTnT) level was measured at the time of discharge (Roche Diagnostics, Tokyo, Japan). The lower limit for detection of cTnT was 0.01 ng/mL. Serum creatinine levels were determined by standard laboratory methods. Clinical data were obtained by interviewing patients and from hospital medical records.

Follow-up and Endpoints

The study endpoint was rehospitalization for AHF. The treating physicians made decisions under the usual standard of care. In most cases, patients were readmitted when clinical signs of decompensation such as orthopnea or lower extremity edema were present. The mean length of stay for the index hospitalization was 19 ± 13 days. The mean delay for the initial outpatient follow-up visit upon discharge was 14 ± 10 days (16 patients were transferred to a different hospital, one patient died during hospitalization, one patient was transferred to a different department, and 13 were unknown). The data regarding endpoints were available for all the patients and the mean follow-up period was 726 ± 31 days. Follow-up data were obtained from either the medical records or direct inquiry with the patients or patients' family by mail or phone.

Statistical Analysis

The study population was divided into two groups: readmission group and non-readmission group. Low ejection fraction (EF) was defined as EF <40% and elevated TnT level was defined as a serum TnT concentration of >0.1 ng/mL. Chi-square tests were used to compare categorical variables and student *t*-tests were used for continuous variables. Categorical variables were expressed as numbers (percentages) and continuous variables were expressed as the mean standard deviation.

Kaplan-Meier event curves were constructed and compared using the log-rank test. Multivariable Cox proportional hazards models were constructed using categorical variables that were statistically significant according to univariate analysis. Outcomes were adjusted for age, sex, BNP, and systolic blood pressure on admission. Finally, logistic regression analysis was used to quantify the association between each finding and biomarker level. Statistical analysis was performed using the SPSS software, version 19.0 (SPSS Inc., Chicago, Illinois). Significance was set at a p value of 0.05.

Results

The 133 patients enrolled in this study had a mean age of 65.4 ± 15.2 years, and 22.6% were women. Majority (63.9%) of the patients had non-ischemic etiology: 57.1% had DCM and 6.7% had HCM. At the time of admission, the mean systolic blood pressure (sBP) was 131.8 ± 30.8 mmHg. As for the congestive physical findings, 69.9% had S3, 56.4% had edema, 54.1% had JVD, and 43.6% had pulmonary rales. Details of the characteristics of the study subjects against the presence and absence of each finding are shown in Table 1. Among the patients who were readmitted for AHF, rales were seen in none (0%, no documentation in 21 patients [15.8%]), S3 were ten (21.3%, no documentation in 13 patients [9.7%]), edema were two (4.3%, no documentation in 36 patients [27.1%]).

We performed an additional analysis to see whether patients receiving guideline-based HF medication (e.g., spironolactone, angiotensin-converting enzyme inhibitor, angiotensin II receptor blockers, or β-blocker) prior to admission would have difference in the prevalence of HF-related physical findings compared to those not receiving guideline-based treatment. As shown in Table S1A in Tables S1, there was no significant difference in the readmission rate between patients on each of the optimal guideline based medications before admission and after admission. Individually, patients on beta-blockers had lower percentage of JVD, edema and S3 (p = 0.042, 0.010 and 0.028, respectively). Patients on spironolactone before admission had lower percentage of PND, edema and rales (p = 0.023, 0.004 and 0.002, respectively). We believe that these findings suggest that there might be a possible effect of optimal medical therapy altering physical findings on admission. At the same time, however, we would like to note that these differences did not show significant effect on primary outcome (Table 1B).

Combined endpoint of rehospitalization and death was met in 37.0% of the patients, and the overall mortality rate was 11.6%. With regard to the congestive physical findings, patients who presented with JVD, pulmonary rales, and S3 had worse readmission rates than those without these findings (Figure 1; log-rank p = 0.024, p < 0.001 and p = 0.011, respectively). Predictors of readmission rate are listed in Table 2. Notably, the presence of pulmonary rales (hazard ratio [HR] 2.03, 95% confidence interval [CI] 1.09–3.79; p = 0.026) and S3 (HR 2.05, 95%CI 1.12–3.75; p = 0.019) at the time of admission were related to readmission even after adjustment for age, sex, BNP, and sBP.

Table 3 shows the association between biomarker levels at the time of discharge and AHF physical findings. The presence of pulmonary rales was associated with high BNP levels (≥150 pg/mL) at the time of discharge (OR 2.208, 95%CI 1.077–4.525; p = 0.031), although this association was found to be insignificant after adjustment for age and sex. Presence of edema (OR 3.758, 95%CI 1.719–8.212; p = 0.001), rales (OR 3.990, 95%CI 1.869–8.516; p < 0.001), and S3 (OR 2.939, 1.206–7.159; p = 0.018) were

Table 1. Characteristics of the study subjects.

		Readmission for ADHF (+) (n = 47)	Readmission for ADHF (−) (n = 86)	P value
Age, yrs		70.21 ± 1.76	62.78 ± 1.73	0.001
Women, %		21.3 (n = 10)	23.3 (n = 20)	0.366
Comorbidities	Ischemic heart disease, %	36.2 (n = 17)	36.0 (n = 31)	0.931
	Dilated cardiomyopathy, %	57.4 (n = 27)	57.0 (n = 49)	0.958
	Hypertrophic cardiomyopathy, %	6.4 (n = 3)	7.0 (n = 6)	0.892
AF, %		36.2 (n = 17)	27.1 (n = 23)	0.655
Systolic Blood Pressure, mmHg		132.80 ± 4.98	131.27 ± 3.16	0.530
NYHA functional class	on admission	3.07 ± 0.11	3.02 ± 0.08	0.705
	on discharge	2.07 ± 0.04	1.98 ± 0.02	0.031
BNP, pg/mL	on admission	770.36 ± 98.26	682.62 ± 79.61	0.030
	on discharge	395.51 ± 49.90	331.59 ± 60.96	0.055
BUN, mg/dL	on admission	24.59 ± 10.42	20.75 ± 9.30	0.041
	on discharge	28.80 ± 14.09	23.35 ± 12.02	0.031
Left ventricular ejection fraction ≤40%, %		48.9 (n = 23)	41.9 (n = 36)	0.541
Troponin T level on discharge >0.10 ng/mL, %		37.2 (n =16)	22.1 (n = 17)	0.004
Death, %		18.2 (n = 8)	4.7 (n = 4)	0.001
Physical signs on admission	PND, %	40.4 (n = 19)	30.2 (n = 26)	0.488
	Orthopnea, %	34.0 (n = 16)	35.3 (n = 30)	0.624
	JVD, %	61.7 (n = 29)	50.6 (n = 43)	0.088
	Edema, %	53.2 (n = 25)	58.1 (n = 50)	0.982
	Rales, %	56.5 (n = 26)	37.6 (n = 32)	0.003
	S3, %	80.9 (n = 38)	64.0 (n = 55)	0.054
Physical signs on discharge	Edema, %	4,3 (n = 2)	4.7 (n = 4)	0.989
	Rales, %	0.0 (n = 0)	2.3 (n = 2)	0.316
	S3, %	21.3 (n = 10)	25.6 (n = 22)	0.800
Medicine on admission	Spironolactone, %	34.0 (n = 16)	36.0 (n = 31)	0.862
	ACE inhibitor, %	29.8 (n = 14)	23.3 (n = 20)	0.245
	ARB inhibitor, %	25.5 (n = 12)	32.6 (n = 28)	0.620
	β-blocker, %	57.4 (n = 27)	50.0 (n = 43)	0.156

Patients readmitted for ADHF were significantly younger and had higher NYHA class on discharge, BNP levels on admission, BUN levels on admission and discharge, TnT levels on discharge, and death rates than those not readmitted for ADHF (p = 0.001, 0.031, 0.030, 0.041, 0.031, 0.004 and 0.001, respectively). The proportion of patients with rales was significantly higher in the readmission group than in the non-readmission group (p = 0.003). Missing values were considered to be negative about physical signs on discharge (missing values of patients with rales were 21, S3 were 13, edema were 36).

ADHF = acute decompensated heart failure, AF = atrial fibrillation, NYHA = New York Heart Association, BNP = brain natriuretic peptide, BUN = blood urea nitrogen, PND = paroxysmal nocturnal dyspnea, JVD = jugular venous distention, S3 = the third heart sound, ACE = angiotensin-converting enzyme, ARB = angiotensin II receptor blockers

doi:10.1371/journal.pone.0096325.t001

related to high TnT levels (>0.10 ng/mL). Pulmonary rales (OR 2.874, p = 0.017) and S3 (OR 2.614, p = 0.050) were significantly associated with high TnT levels after adjustment for age, sex, sBP, and BNP on admission.

Discussion

In our single-institution based HF registry, the presence of pulmonary rales and S3 on admission was associated with HF readmission rate and high TnT levels on discharge. These physical findings are harbingers for difficulty achieving adequate decongestion during AHF treatment, suggesting the involvement of underlying complex mechanisms such as on-going inflammation during the acute phase of AHF.

The prognostic implications of signs and symptoms for HF patients have been previously reported. Devroey et al reported that the presence of pulmonary rales was significantly associated with HF ($p < 0.001$) [10]. Drazner et al reported that the presence of S3 was associated with increased risk of rehospitalization in the Studies of Left Ventricular Dysfunction (SOLVD) trial [1]. These results implying that the left-sided signs of HF are associated with rehospitalization, are consistent with the results of our current study. On the other hand, right-sided HF physical findings such as JVD or edema did not show any statistical significant association with adverse outcomes, and this finding is in contrast with those of previous studies such as the SOLVD or ESCAPE trial [11], probably because of the difference in patient characteristics between the studies; the SOLVD and the ESCAPE trials examined chronic HF patients in the outpatient setting, whereas this study examined AHF patients at the time of admission. Patients with chronic HF who present with JVD have either residual secondary pulmonary hypertension or isolated pulmonary

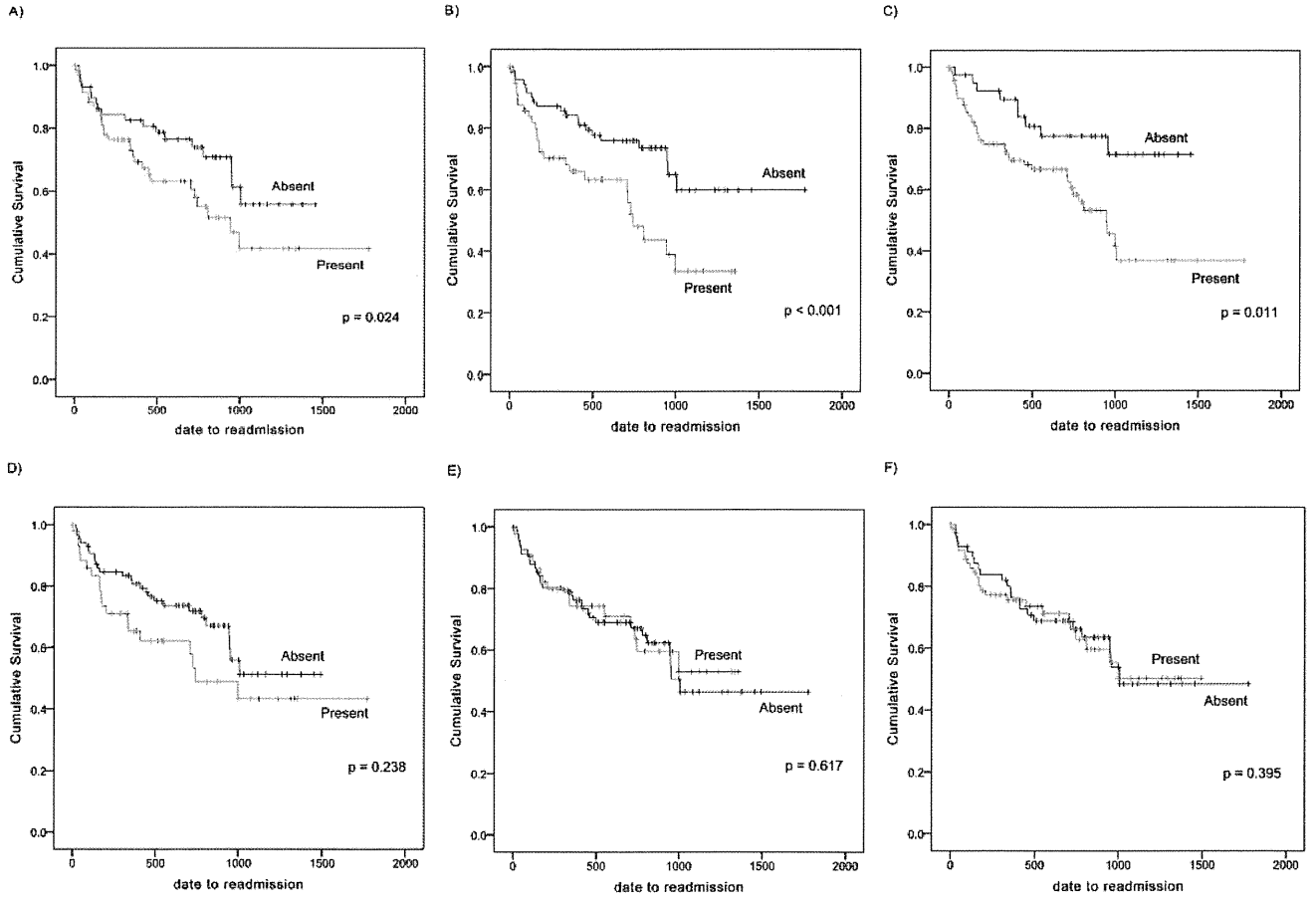

Figure 1. Kaplan Meier analysis of event-free survival according to the presence or absence of physical findings. Jugular venous distension (JVD) (A), rales (B), third heart sound (S3) (C), paroxysmal nocturnal dyspnea (D), orthopnea (E), and edema (F). Patients with JVD, pulmonary rales, or S3 had worse readmission rates that those without these findings (log-rank $p = 0.024$, $p < 0.001$, $p = 0.001$, respectively).
doi:10.1371/journal.pone.0096325.g001

hypertension, both being signs of inadequate compensation. These signs may be of low significance when predicting adverse outcomes in AHF patients.

In our study, the left-sided physical signs of AHF were also related to elevated biomarker levels at the time of discharge. TnT is a sensitive and specific marker for myocyte injury [12] and has been studied in acute and chronic HF patients previously. Missov et al [13] found increased levels of circulating cTnT in patients with HF but no clinically significant signs of ischemia. This phenomenon is thought to be caused by coronary microvascular dysfunction [14]. The findings of previous studies highlight that increased TnT levels are independent markers of mortality in HF patients [4]. In the ADHERE trial, AHF patients who tested positive for elevated troponin levels had lower systolic blood pressure on admission, lower ejection fraction, and higher in-hospital mortality rates than those who tested negative [15]. BNP is another well-known and frequently used biomarker for HF diagnosis and treatment. It is a neurohormone specifically secreted from the cardiac chambers in response to hemodynamic stress. The BNP level is elevated in situations where the ventricles are dilated, hypertrophic, or subject to increased wall tension [16,17]. The clinical validity of brain natriuretic peptide (BNP) measurements has been previously reported. Nishii M et al. reported that a high BNP level was a predictor of long-term risk in patients with non-ischemic dilated cardiomyopathy who were asymptomatic for more than six months after admission for AHF [18]. Januzzi and Troughton reported that BNP-guided therapy resulted in superior medical management compared to traditional care, mostly because of frequent and sophisticated drug adjustment [19]. In addition, BNP-guided therapy might be particularly attractive in older patients who are less physically active and in those whom symptoms are less reliable [20]. In our study, there were few patients with high BNP levels without significant physical findings before discharge. As the reviewer commented, these patients may benefit from BNP measurement to predict their long-term outcome such as readmission or death. However, caution is needed since other studies have suggested that BNP-guided HF management may have little or even a negative impact on elderly patients because of increased risk of drug-drug interactions and worsening organ failure secondary to polypharmacy [21]. Obviously, treatment strategies should be based on both physical signs and biomarkers. Physical signs are safe, cost-efficient non-invasive methods to assess the state of patients with HF. At times, physical signs may serve as unclear indices because of interobserver variation. In such situations, biomarkers could prove to be strong prognostic indices. The precise relationship between physical signs and biomarkers should be studied further.

In our cohort, higher readmission rates were seen in AHF patients with increased TnT levels but not in those with elevated BNP levels. This may be related to relatively high number of DCM patients included in our study. These patients are known to have high BNP levels even after they reach compensated state.

Table 2. Predictors associated with readmission rate.

Predictors		HR (95% CI)	P value	HR Adjusted for Age and Sex (95% CI)	P value	HR Adjusted for Age, Sex, BNP level, and sBP on admission (95% CI)	P value
Age		1.026 (1.010–1.043)	0.002	–	–	–	–
Women, %		1.348 (0.795–2.287)	0.268	–	–	–	–
Comorbidities	Ischemic heart disease, %	0.982 (0.604–1.596)	0.982	–	–	–	–
	Dilated cardiomyopathy, %	1.002 (0.792–1.268)	0.986	–	–	–	–
	Hypertrophic heart disease, %	1.021 (0.729–1.430)	0.905	–	–	–	–
AF, %		1.191 (0.714–1.987)	0.502	–	–	–	–
Systolic Blood Pressure, mmHg		0.997 (0.989–1.006)	0.503	–	–	–	–
Systolic Blood Pressure ≥140, mmHg		0.811 (0.483–1.364)	0.430	–	–	–	–
NYHA functional class	on admission	1.113 (0.816–1.518)	0.499	–	–	–	–
	on discharge	3.064 (1.141–8.232)	0.026	–	–	–	–
BNP, pg/mL	on admission	1.001 (1.000–1.001)	<0.001	–	–	–	–
	on admission ≥150	8.936 (2.185–36.555)	0.002	–	–	–	–
	on discharge	1.001 (1.001–1.001)	<0.001	–	–	–	–
	on discharge ≥150	2.610 (1.440–4.731)	0.002	–	–	–	–
Left ventricular ejection fraction ≤40%, %		1.166 (0.729–1.866)	0.522	–	–	–	–
Troponin T on discharge >0.10 ng/mL, %		2.404 (1.449–3.986)	0.001	–	–	–	–
PND		1.351 (0.819–2.228)	0.239	1.174 (0.706–1.952)	0.535	1.167 (0.668–2.037)	0.587
Orthopnea		0.867 (0.496–1.517)	0.618	0.727 (0.408–1.294)	0.278	0.690 (0.378–1.260)	0.227
JVD		1.819 (1.074–3.078)	0.026	1.513 (0.869–2.632)	0.143	1.396 (0.783–2.488)	0.258
Edema		1.246 (0.750–2.069)	0.396	1.077 (0.634–1.830)	0.783	1.055 (0.597–1.863)	0.855
Rales		2.489 (1.479–4.191)	0.001	1.951 (1.096–3.474)	0.023	2.034 (1.090–3.794)	0.026
S3		2.077 (1.165–3.700)	0.013	1.908 (1.064–3.419)	0.030	2.056 (1.126–3.754)	0.019

Predictors associated with readmission rate according to multivariable Cox proportional hazards models. Even after adjusting for age, sex, BNP level, and sBP on admission, the presence of rales and S3 were significantly related to the readmission rate (p = 0.026 and 0.019, respectively).

HR = hazard ratio, sBP = systolic blood pressure, AF = atrial fibrillation, NYHA = New York Heart Association, BNP = brain natriuretic peptide, PND = paroxysmal nocturnal dyspnea, JVD = jugular venous distention, S3 = the third heart sound

doi:10.1371/journal.pone.0096325.t002

Table 3. Logistic regression analysis.

			A. Predictors of BNP level on discharge ≥150 pg/mL			
Variables	OR (95% CI)	P value	OR Adjusted for Age and Sex (95% CI)	P value	OR Adjusted for Age, Sex, BNP level, and sBP on admission (95% CI)	P value
PND	0.901 (0.448–1.811)	0.770	0.732 (0.352–1.521)	0.403	0.545 (0.237–1.252)	0.153
Orthopnea	1.023 (0.492–2.125)	0.952	0.963(0.456–2.036)	0.922	0.757 (0.330–1.735)	0.511
JVD	1.488 (0.767–2.889)	0.240	1.237 (0.617–2.479)	0.548	0.559 (0.242–1.288)	0.172
Edema	1.397 (0.717–2.725)	0.326	1.235 (0.622–2.454)	0.546	0.841 (0.379–1.870)	0.671
Rales	2.208 (1.077–4.525)	0.031	1.689 (0.790–3.609)	0.176	1.473 (0.625–3.473)	0.376
S3	1.852 (0.940–3.650)	0.075	1.677 (0.836–3.364)	0.146	1.656 (0.741–3.702)	0.219
			B. Predictors of troponin T on discharge >0.10 ng/mL			
Variables	OR (95% CI)	P value	OR Adjusted for Age and Sex (95% CI)	P value	OR Adjusted for Age, Sex, BNP level, and sBP on admission (95% CI)	P value
PND	1.368 (0.663–2.822)	0.397	1.119 (0.521–2.406)	0.773	1.054 (0.475–2.337)	0.897
Orthopnea	0.870 (0.394–1.919)	0.730	0.750 (0.325–1.729)	0.499	0.654 (0.273–1.567)	0.340
JVD	1.773 (0.854–3.678)	0.124	1.155 (0.522–2.553)	0.722	1.043 (0.449–2.424)	0.922
Edema	3.758 (1.719–8.212)	0.001	3.019 (1.333–6.838)	0.008	3.134 (1.302–7.546)	0.011
Rales	3.990 (1.869–8.516)	<0.001	2.548 (1.127–5.760)	0.025	2.583 (1.097–6.082)	0.030
S3	2.939 (1.206–7.159)	0.018	2.547 (1.000–6.490)	0.050	2.459 (0.941–6.421)	0.066

Logistic regression analysis quantifying the association between biomarkers on discharge and physical findings and symptoms. Although the level of BNP on discharge (A) were not related to any physical findings and symptoms, the findings of edema, rales, and S3 were related to TnT levels on discharge (B) after adjusting for age, sex, BNP level, sBP on admission.

BNP = brain natriuretic peptide, OR = odds ratio, sBP = systolic blood pressure, PND = paroxysmal nocturnal dyspnea, JVD = jugular venous distention, S3 = the third heart sound

doi:10.1371/journal.pone.0096325.t003

The lack of statistical differences could have resulted from this unique cohort. On the contrary, AHF patients with elevated TnT level at discharge were those that required early readmission. Elevated TnT may be a more sensitive biomarker compared to BNP in identifying vulnerable AHF patients who require close monitoring post discharge.

Our study has several limitations. First, this study was conducted in a single-center tertiary university hospital. Therefore, a multicenter study with a large study population is needed to determine the correlation between physical findings and biomarker levels. Second, despite adjusting for known risk factors, according to the results of the Cox hazards models, residual confounding may have been caused by unmeasured and measured variables. Third, there were no standardized instructions for obtaining physical findings and this may have led to some degree of misclassification depending on the physicians. The physical examination results could have been inaccurate to some extent, and no confirmatory tests such as phonocardiography for S3 were performed during this study.

The significance of physical examination cannot be underestimated. A strong relationship has been shown between left-sided HF symptoms and elevated TnT levels. Therefore, focused bedside assessment is vital and our findings add to the prognostic importance of physical findings in AHF patients.

Supporting Information

Tables S1 This file includes Table S1 and S2. Table S1. Presence of physical signs by the use of guideline-based heart failure medications on admission. All the data in the table are percentages. There was no significant difference in the readmission rate between patients receiving each of the optimal guidelinebased medications before and after admission. Individually, patients on beta-blockers had a lower percentage of jugular venous distention, edema, and S3 (P = 0.042, 0.010, and 0.028, respectively). Patients receiving spironolactone before admission had a lower percentage of paroxysmal nocturnal dyspnea, edema, and rales (P = 0.023, 0.004, and 0.002, respectively). Table S2. Readmission rate according to the use of guidelinebased heart failure medication at the time of admission.
(DOC)

Acknowledgments

The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Author Contributions

Conceived and designed the experiments: SN SK TI. Analyzed the data: SN MS SK. Contributed reagents/materials/analysis tools: YS TK YM MS TY KF. Wrote the paper: SN MS SK.

References

1. Drazner MH, Rame JE, Stevenson LW, Dries DL (2001) Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. N Engl J Med 345: 574–581.

2. Miller WL, Hartman KA, Burritt MF, Grill DE, Rodeheffer RJ, et al. (2007) Serial biomarker measurements in ambulatory patients with chronic heart failure: the importance of change over time. Circulation 116: 249–257.

3. Del Carlo CH, O'Connor CM (1999) Cardiac troponins in congestive heart failure. Am Heart J 138: 646–653.
4. Sato Y, Yamada T, Taniguchi R, Nagai K, Makiyama T, et al. (2001) Persistently increased serum concentrations of cardiac troponin t in patients with idiopathic dilated cardiomyopathy are predictive of adverse outcomes. Circulation 103: 369–374.
5. Perna ER, Macin SM, Canella JP, Augier N, Stival JL, et al. (2004) Ongoing myocardial injury in stable severe heart failure: value of cardiac troponin T monitoring for high-risk patient identification. Circulation 110: 2376–2382.
6. Latini R, Masson S, Anand IS, Missov E, Carlson M, et al. (2007) Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. Circulation 116: 1242–1249.
7. Bettencourt P, Azevedo A, Pimenta J, Frioes F, Ferreira S, et al. (2004) N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. Circulation 110: 2168–2174.
8. Cheng V, Kazanagra R, Garcia A, Lenert L, Krishnaswamy P, et al. (2001) A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. J Am Coll Cardiol 37: 386–391.
9. Januzzi JL, van Kimmenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, et al. (2006) NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. Eur Heart J 27: 330–337.
10. Devroey D, Van Casteren V (2011) Signs for early diagnosis of heart failure in primary health care. Vasc Health Risk Manag 7: 591–596.
11. Drazner MH, Hellkamp AS, Leier CV, Shah MR, Miller LW, et al. (2008) Value of clinician assessment of hemodynamics in advanced heart failure: the ESCAPE trial. Circ Heart Fail 1: 170–177.
12. Fonarow GC, Peacock WF, Phillips CO, Givertz MM, Lopatin M (2007) Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. J Am Coll Cardiol 49: 1943–1950.
13. Missov E, Calzolari C, Pau B (1997) Circulating cardiac troponin I in severe congestive heart failure. Circulation 96: 2953–2958.
14. Takashio S, Yamamuro M, Izumiya Y, Sugiyama S, Kojima S, et al. (2013) Coronary microvascular dysfunction and diastolic load correlate with cardiac troponin T release measured by a highly sensitive assay in patients with nonischemic heart failure. J Am Coll Cardiol 62: 632–640.
15. Fonarow GC, Peacock WF, Horwich TB, Phillips CO, Givertz MM, et al. (2008) Usefulness of B-type natriuretic peptide and cardiac troponin levels to predict in-hospital mortality from ADHERE. Am J Cardiol 101: 231–237.
16. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, et al. (2010) Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. Eur J Heart Fail 12: 423–433.
17. Daniels LB, Maisel AS (2007) Natriuretic peptides. J Am Coll Cardiol 50: 2357–2368.
18. Nishii M, Inomata T, Takehana H, Naruke T, Yanagisawa T, et al. (2008) Prognostic utility of B-type natriuretic peptide assessment in stable low-risk outpatients with nonischemic cardiomyopathy after decompensated heart failure. J Am Coll Cardiol 51: 2329–2335.
19. Januzzi JL, Troughton R (2013) Are serial BNP measurements useful in heart failure management? Serial natriuretic peptide measurements are useful in heart failure management. Circulation 127: 500–507; discussion 508.
20. Pfisterer M, Buser P, Rickli H, Gutmann M, Erne P, et al. (2009) BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial. JAMA 301: 383–392.
21. Gaggin HK, Mohammed AA, Bhardwaj A, Rehman SU, Gregory SA, et al. (2012) Heart failure outcomes and benefits of NT-proBNP-guided management in the elderly: results from the prospective, randomized ProBNP outpatient tailored chronic heart failure therapy (PROTECT) study. J Card Fail 18: 626–634.

2．　委託業務成果報告（吉川 勉）

別刷

(1) Significance of AT_1 Receptor Independent Activation of Mineralocorticoid Receptor in Murine Diabetic Cardiomyopathy

(2) Presence of Autoantibody Directed Against β1-Adrenergic Receptors Is Associated With Amelioration of Cardiac Function in Response to Carvedilol: Japanese Chronic Heart Failure (J-CHF) Study

(3) Presence of ventricular aneurysm predicts poor clinical outcomes in patients with cardiac sarcoidosis

(4) Takotsubo cardiomyopathy, a new concept of cardiomyopathy: Clinical features and pathophysiology

厚生労働科学研究委託費（循環器疾患・糖尿病等生活習慣病対策実用化研究事業）
委託業務成果報告

急性心不全におけるガイドラインベースの治療実施状況と予後因子規定に関する国際共同多施設レジストリ研究

研究分担者：　榊原記念病院　副院長　吉川　勉

研究要旨

慶應義塾大学病院、榊原記念病院、杏林大学病院に入院した急性増悪期心不全(ADHF)患者を前向きに登録した。入院時腎機能及びその変化が臨床転帰に及ぼす影響と急性期血圧・急性期フロセミド静注の使用との関連について検討した。ADHF の予後予測において、入院時 eGFR と収縮期血圧(SBP)は密な関連を有することが明らかとなった。eGFR 別に異なった至適血圧維持を設定する必要があることが示唆された。ADHF 患者においてフロセミド静注は入院中の腎機能悪化および入院中死亡と関連するが、その意義は入院時 eGFR 値で異なることが明らかとなった。

A. 研究目的

ADHF 患者における入院時腎機能及び入院中の変化に及ぼす諸因子について明らかにする。

B. 研究方法

慶應義塾大学病院、榊原記念病院、杏林大学病院に入院した ADHF 患者を前向きに登録した。入院時腎機能及びその変化が臨床転帰に及ぼす影響と急性期血圧・急性期フロセミド静注の使用との関連について検討した。

（倫理面への配慮）

各施設の倫理委員会で本研究に関する審査を受け、承認を得た。臨床疫学倫理指針に基づき、各施設で本研究に関する情報を広く公開し、包括同意を得た。

C. 研究結果

入院時 eGFR 高値群・低値群のいずれも入院時 SBP 低値が院内予後および退院後予後不良と関連した。多変量解析では両群とも入院時 SBP が独立した予後予測因子となったが、Cut off 値は eGFR 高値群で 100mmHg 未満、eGFR 低値群で 120mmHg 未満と、eGFR 低値群でより高い値であった。

ADHF 患者においてフロセミド静注を行った群では、急性期腎機能増悪(WRF)および入院中死亡のいずれもが増加した。多変量ロジスティック回帰では ADHF 患者に対するフロセミド静注は WRF の予測因子となったが、院内

予後の予測因子とはならなかった。

入院時 eGFR 高値群および低値群で解析すると、eGFR 高値群で WRF はフロセミド静注群で有意に多かったが、入院中死亡に有意差はなかった。一方 eGFR 低値群では WRF の頻度はフロセミド静注の有無で差はなかったが、入院中死亡はフロセミド静注群で有意に多かった。これは静注変力薬の使用が関連している可能性がある。多変量ロジスティック回帰では eGFR 高値群ではフロセミド静注は WRF の予測因子となったが、eGFR 低値群ではならなかった。いずれの群でもフロセミド静注は院内予後の予測因子とはならなかった。

D. 考察

ADHF で血管拡張薬などにより SBP を下げると WRF が増加する。SBP を下げた群での WRF は予後を悪化させなかったが、SBP を下げなかった群での WRF は予後を悪化させた(Jeffrey M, et al: Eur J Heart Fail;13:877-884, 2011)。今回のレジストリーにおける先行研究では WRF は院内死亡の独立した予後予測因子で、eGFR 低値群で WRF は多かった(21.8% vs. 15.9%, p=0.03)。eGFR 低値群での入院時 SBP 低値は WRF と関連して予後を悪化させている可能性がある。

心不全患者に対するフロセミド投与では特に投与量が増大すると予後が悪化する(Eshaghian et al: Am J Cardiol 97: 1759-1764, 2006)。しかし ADHF 患者では急性期に体液貯留を来していることが多く、中心静脈圧上昇による腎うっ血を介して腎灌流圧を低下させ、腎機能悪化を来すことがある。この腎機能悪化は可逆性である(Inohara T et al; ATTEND Investigators: PLoS One. 8;9:e105596, 2014, 柏原ほか: Heart View 16(9): 906-911, 2012)。

少数例の心不全患者での検討では、著明な体液貯留を認め有効循環血漿量が保たれていれば、フロセミド投与は腎機能を悪化させなかった(De Vecchis et al: Minerva Cardioangiol. 59: 543-54, 2011)。入院時腎機能障害を有する心不全患者は体液貯留傾向にあると考えられ、静注変力薬を要さないような有効循環血漿量が保たれている状態での適切なフロセミド投与は腎機能悪化および予後悪化を来さないと考えられる。

E. 結論

ADHF の予後予測において、入院時 eGFR と SBP は密な関連を有することが明らかとなった。eGFR 別に異なった至適血圧維持を設定する必要があることが示唆された。

ADHF 患者においてフロセミド静注は入院中の腎機能悪化および入院中死亡と関連するが、その意義は入院時 eGFR 値で異なることが明らかとなった。

F. 研究発表

1. 論文発表

Murakami T, Yoshikawa T, Maekawa Y, Ueda T, Isogai T, Konishi Y, Sakata K, Nagao K, Yamamoto T, Takayama M: Characterization of predictors of in-hospital cardiac complications of takotsubo cardiomyopathy: multi-center registry from Tokyo CCU Network. J Cardiol 2014;63:269-73

Nagatomo Y, Meguro T, Ito H, Koide K, Anzai T, Fukuda K, Ogawa S, Yoshikawa T: Significance of AT_1 Receptor Independent Activation of Mineralocorticoid Receptor in Murine Diabetic Cardiomyopathy. PLOS ONE 2014;9:e93145

Negi S, Sawano M, Kohsaka S, Inohara T, Shiraishi Y, Kohno T, Maekawa Y, Sano M, Yoshikawa T, Fukuda K: Prognostic implication of physical signs of congestion in acute heart failure patients and its association with steady-state biomarker levels. PLOS ONE 2014;9:e96325

Nagatomo Y, Yoshikawa T, Okamoto H, Kitabatake A, Hori M: Presence of Autoantibody Directed against β1-Adrenergic Receptors is Associated with Amelioration of Cardiac Function in Response to Carvedilol: Japanese Chronic Heart Failure (J-CHF) Study. J Card Fail (in press)

Asakura M, Yamamoto H, Asai K, Hanatani A, Hirata K, Hirayama A, Kimura K, Kobayashi Y, Momomura S, Nakagawa Y, Nishi Y, Saito Y, Satoh Y, Yamada T, Yamashina A, Yasuda S, Yoshikawa T, Kada A, Uesaka H, Kitakaze M, on behald of the EARLIER investigators and coordinators: Rationale and design of the double-blind, randomized, placebo-controlled multicenter trial on efficacy of early initiation of eplerenone treatment in patients with acute heart failure (EARLIER). Cardiovasc Drugs Ther (online publication)

Inohara T, Kohsaka S, Shiraishi Y, Goda A, Sawano M, Yagawa M, Mahara K, Fukuda K, Yoshikawa T; West Tokyo Heart Failure Registry Investigators: Prognostic impact of renal and hepatic dysfunction based on the MELD-XI score in patients with acute heart failure. Int J Cardiol (letter) 2014;176:571-3

Miyazawa K, Yoshikawa T, Takamisawa I, Mahara K, Inoue K, Iguchi N, Takayama M, Umemura J, Sumiyoshi T, Tomoike H: Presence of ventricular aneurysm predicts poor clinical outcomes in patients with cardiac

sarcoidosis. Int J Cardiol (letter) (in press)

Mizuno A, Kohsaka S, Shiraishi Y, Goda A, Yoshikawa T: Seasonal changes in systemic volume overload are to be considered. Circ J (letter) in press

Yoshikawa T: Takotsubo cardiomyopathy, a new concept of cardiomyopathy: clinical feaures and pathophysiology. Int J Cardiol (in press)

吉川勉:たこつぼ型心筋症　日内会誌 2014;103(2):309-15

吉川勉:未治療心不全患者はβ遮断薬からですか、ACE 阻害薬からですか。それとも同時ですか。　Heart View 2014;18(12):180-3

吉川勉:COPD を合併する慢性心不全にβ遮断薬を投与してよいですか。使うとすればどのβ遮断薬ですか。COPD に対してもβ遮断薬は有効ですか。Heart View 2014;18(12):184-7

2.　学会発表

吉川勉:拡張型心筋症に対する免疫吸着療法　第 18 回日本心不全学会シンポジウム「重症心不全の診断および治療戦略」　2014 年 10 月 11 日、大阪

Shiraishi Y, Dicken B, Kohsaka S, Rigby A, Koshy A, Inohara T, Goda A, Nagai T, Yoshikawa T, Cleland JGF: Differences in guideline-based medical therapy of patients with heart failure in Japan and Great Britain. Euro Heart Failure, May 18, 2014, Athens

ShiraishiY, Dicken B, Kohsaka S, Rigby A, Rasool R, Inohara T, Goda A, Nagai T, Yoshikawa T, Cleland JGF: Patient characteristics and outcomes in Japanese and British patients admitted with heart failure; the West Tokyo - Kingston-upon-Hull collaboration. Euro Heart Failure, May 19, 2014, Athens

Dicken B, Shiraishi Y, Kohsaka S, Rigby A, Inohara T, Goda A, Nagai T, Yoshikawa T, Cleland JGF: Patient characteristics and outcomes in Japanese and British patients admitted with heart failure; West Tokyo - Kingston upon Hull collaboration. European Scoeity of Cardiology Congress 2014, Balcerona, Dec 1, 2014

Nagatomo Y, Yoshikawa T, Okamoto H, Kitabatake A, Hori M: Autoantibody titer directed against b1-adrenergic receptors is a predictor of reverse remodeling

during carvedilol therapy for chronic heart failure: Japanese Chronic Heart Failure (J-CHF) Study. American Heart Association Meeting 2014, Chicago, Nov 19, 2014

Takei M, Kohsaka S, Inohara T, Shiraishi Y, Sawano M, Goda A, Yoshikawa T, Fukuda K: Is Plasma Volume Reduction Related to Worsening Renal Function in Heart Failure with/without Preserved Ejection Fraction? 78th Annual Scientific Meeting of the Japanese Circulation Society Mar 22, 2014, Tokyo

Inohara T, Kohsaka S, Shiraishi Y, Sawano M, Yagawa M, Mahara K, Goda A, Yoshikawa T, Fukuda K: The Prognostic Impact of Hepatic Dysfunction Based on the MELD-XI Scoring System in Patients with Acute Decompensated Heart Failure. 78th Annual Scientific Meeting of the Japanese Circulation Society Mar 22, 2014, Tokyo

Murakami T, Yoshikawa T, Maekawa Y, Ueda T, Isogai T, Konishi Y, Sakata K, Nagao K, Yamamoto T, Takayama M: Poor Clinical Outcomes during Hospitalization in Patients with Takotsubo Cardiomyopathy with Chronic Kidney Disease: Multi-Center Registry from Tokyo CCU Network. 78th Annual Scientific Meeting of the Japanese Circulation Society Mar 21, 2014, Tokyo

Sakata K, Yoshikawa T, Murakami T, Maekawa Y, Isogai T, Konishi Y, Nagao K, Yamamoto T, Takayama M: Echocardiographic Evaluation of Cardiac Dysfunction in Patients with Takotsubo Cardiomyopathy—Results from Tokyo CCU Network Scientific Committee—78th Annual Scientific Meeting of the Japanese Circulation Society Mar 23, 2014, Tokyo

Utanohara Y, Iguchi N, Yoshikawa T, Takayama M, Umemura J, Sumiyoshi T, Tomoike K: Evaluation of Left Atrium Wall Motion by Using 5D-Computed Tomography. 78th Annual Scientific Meeting of the Japanese Circulation Society Mar 21, 2014, Tokyo

Uesugi Y, Goda A, Inohara T, Shiraishi Y, Yagawa M, Mahara M, Matsushita K, Kohsaka S, Yoshikawa T, Sato T, Yoshino H: Difference in the Impact of Left Atrium Size by Presence/Absence of LV Systolic Dysfunction among Acute Heart Failure Patients. 78th Annual Scientific Meeting of the Japanese Circulation Society Mar 21, 2014, Tokyo

Utanohara Y, Iguchi N, Yoshikawa T, Takayama M, memura J, Sumiyoshi T, Tomoike H: Utility of Dual Myocardial SPECT in Hypertrophic Cardiomyopathy Using D-SPECT Comparison with Conventional SPECT Imaging. 78th Annual Scientific Meeting of the Japanese Circulation Society Mar 21, 2014, Tokyo

Isogai T, Yoshikawa T, Ueda T, Maekawa Y, Sakata K, Murakami T, Nagao K, Yamamoto T, Takayama M: Comparison of Electrocardiographic Findings among Three Ballooning Forms of Takotsubo Cardiomyopathy: A Multi-Center Study of Tokyo CCU Network Scientific Committee. 78th Annual Scientific Meeting of the Japanese Circulation Society Mar 23, 2014, Tokyo

Izumi Y, Yagawa M, Mahara K, Tomoike H, Kohsaka S, Inohara T, Goda A, Yoshikawa T: Impaired Renal Function Predicts Adverse Clinical Outcomes in Relation to Abnormal Erythropoiesis in Patients with Acutely Decompensated Heart Failure. 78th Annual Scientific Meeting of the Japanese Circulation Society Mar 23, 2014, Tokyo

田嶋美裕　泉祐樹　矢川真弓子　高見澤格　井口信雄　高山守正　梅村純　住吉徹哉　友池仁暢　吉川勉：心不全を契機に診断されたアミロイドーシス患者における予後予測因子の検討　第62回日本心臓病学会2014年9月27日、仙台

牧野潤　白石泰之　香坂俊　合田あゆみ　猪原拓　矢川真弓子　福田恵一　吉川勉：急性非代償性心不全患者の短期予後予測リスクツリー作成の試み　第62回日本心臓病学会2014年9月27日、仙台

村上力　吉川勉　前川裕一郎　上田哲郎　磯貝俊明　小西裕二　坂田好美　山本剛　長尾健　高山守正：たこつぼ型心筋症における院内心合併症予測因子の検討　第62回日本心臓病学会2014年9月27日、仙台

泉祐樹　矢川真弓子　馬原啓太郎　友池仁暢　白石泰之　猪原拓　合田あゆみ　香坂俊　吉川勉：急性非代償性心不全における急性期フロセミド静注が腎機能悪化および短期予後に及ぼす影響　第62回日本心臓病学会2014年9月28日、仙台

Izumi Y, Yagawa M, Mahara K, Tomoike H, Shiraishi Y, Inohara T, Goda A, Kohasaka S, Yoshikawa T: Clinical scenarios on admission predict different clinical outcomes in relation to renal function in patients with acutely decompensated heart failure. 18th Japanese Heaert Failure Society Meeting, Oct 11,

2014, Osaka

Akita K, Kohno T, Kohsaka S, Shiraishi Y, Sawano M, Inhohara T, Maekawa Y, Sano M, Yoshikawa T, Fukuda K: Clinical features and outcome in octagenarians hospitalized for acute heart failure. 18th Japanese Heaert Failure Society Meeting, Oct 10, 2014, Osaka

G. 知的財産権の出願・登録状況（予定を含む）

1. 特許取得　なし
2. 実用新案登録　なし
3. その他　なし

PLOS ONE

Significance of AT_1 Receptor Independent Activation of Mineralocorticoid Receptor in Murine Diabetic Cardiomyopathy

Yuji Nagatomo[1], Tomomi Meguro[2]*, Hiroyuki Ito[1], Kimi Koide[1], Toshihisa Anzai[1], Keiichi Fukuda[1], Satoshi Ogawa[1], Tsutomu Yoshikawa[1]

1 Cardiology Division, Department of Medicine, Keio University School of Medicine, Tokyo, Japan, **2** Department of Cardiology, KAKEN Hospital, International University of Health and Welfare, Ichikawa, Japan

Abstract

Background: Diabetes mellitus (DM) has deleterious influence on cardiac performance independent of coronary artery disease and hypertension. The objective of the present study was to investigate the role of the renin-angiotensin-aldosterone system, especially angiotensin II type 1a receptor ($AT_{1a}R$) and mineralocorticoid receptor (MR) signaling, in left ventricular (LV) dysfunction induced by diabetes mellitus (DM).

Methods and Results: DM was induced by intraperitoneal injection of streptozotocin (200 mg/kg BW) in wild-type (WT) or $AT_{1a}R$ knockout (KO) male mice, and they were bred during 6 or 12 weeks. Some KO mice were administered the MR antagonist eplerenone (100 mg/kg body weight). At 6 weeks, LV diastolic function was impaired in WT-DM, but preserved in KO-DM. At that time point MR mRNA expression was upregulated, NADPH oxidase subunit (p47phox) and glutathione peroxidase (GPx1) mRNA expression were upregulated, the staining intensities of LV tissue for 4-hydroxy-2-nonenal was stronger in immunohistochemistry, the number of terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) positive cells was increased, Bcl-2 protein expression was significantly downregulated, and the expression of SERCA2a and phosphorylated phospholamban was depressed in WT-DM, while these changes were not seen in KO-DM. At 12 weeks, however, these changes were also noted in KO-DM. Eplerenone arrested those changes. The plasma aldosterone concentration was elevated in WT-DM but not in KO-DM at 6 weeks. It showed 3.7-fold elevation at 12 weeks even in KO-DM, which suggests "aldosterone breakthrough" phenomenon. However, the aldosterone content in LV tissue was unchanged in KO-DM.

Conclusions: DM induced diastolic dysfunction was observed even in KO at 12 weeks, which was ameliorated by minelarocorticoid receptor antagonist, eplerenone. AT_1-independent MR activation in the LV might be responsible for the pathogenesis of diabetic cardiomyopathy.

Citation: Nagatomo Y, Meguro T, Ito H, Koide K, Anzai T, et al. (2014) Significance of AT_1 Receptor Independent Activation of Mineralocorticoid Receptor in Murine Diabetic Cardiomyopathy. PLoS ONE 9(3): e93145. doi:10.1371/journal.pone.0093145

Editor: Sadashiva Karnik, Cleveland Clinic Lerner Research Institute, United States of America

Received November 14, 2013; **Accepted** February 28, 2014; **Published** March 24, 2014

Funding: This work was supported by a grant from the Japanese Ministry of Education, Culture, Sports, Science and Technology (No. 17790500; http://www.mext.go.jp/). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: tmeguro@iuhw.ac.jp

Introduction

Cardiovascular complications including coronary artery disease are a major cause of morbidity and mortality in patients with diabetes mellitus (DM). In addition, the risk of heart failure is two-fold higher in men with DM and five-fold higher in women with DM, according to the Framingham study [1], and DM is an independent risk factor for the occurrence of heart failure (HF) [2]. The presence of DM or even impaired glucose tolerance (IGT) in patients with HF has also been shown to be an independent risk factor for adverse outcome such as rehospitalization for HF [3]. A lot of studies have suggested that DM per se has an adverse effect on cardiac function [4,5]. For example, left ventricular (LV) systolic and diastolic dysfunction occurs in rodents with streptozotocin-induced DM [5]. In patients with DM, diastolic dysfunction characteristically occurs first and is followed by impairment of contractility [6]. The molecular mechanisms underlying cardiac dysfunction related to DM include impaired calcium handling [7], increased oxidative stress [8–10], and an increase of apoptosis [9].

The renin-angiotensin-aldosterone system (RAAS) has an important role in the onset and progression of DM-associated vascular complications and DM-induced cardiac dysfunction, with the detrimental effect of angiotensin II type 1 receptor (AT_1) signaling having attracted much attention [4,11]. On the other hand, angiotensin II potently promotes aldosterone production [12]. Interruption of AT_1 signaling by treatment with angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) results in a reduction of plasma aldosterone concentration (PAC), followed by a return to baseline during *long-term* administration [13,14] that is referred to as "aldosterone