breakthrough phenomenon. In contrast with PRA, plasma aldosterone was not a risk factor for worse prognosis in the present patients (data not shown), as in past studies.[7] The precise reason for the discrepancy in prognostic ability between PRA and plasma aldosterone concentration in patients with ADHF treated with RAS inhibitors is unclear. One intriguing hypothesis is that renin itself may play a role in the development of HF via renin receptor-mediated pathways independent of the classical RAS.[27,28]

Some earlier studies reported the clinical significance of plasma active renin concentration (PARC) instead of PRA in HF patients. One study showed that PARC was superior to PRA in predicting outcome. In that study, patients with preserved EF (≥45%) or renal failure (serum creatinine >2.0mg/dl) were excluded, but such patients were included in the present study. In the present study we did not measure PARC. Therefore, further studies are needed to investigate whether PRA or PARC is a better biomarker for survival.

In the NARA-HF 2 study, as described here, PRA >2.0 $ng \cdot ml^{-1} \cdot h^{-1}$ was not significantly associated with poor prognosis in patients who had not been treated with RAS blockers, not consistent with previous work reported in the 1970s–1990s. At that time therapy with β-blockers as well as RAS blockers was not accepted as an effective therapy for HF. In the present study approximately 20% of patients had been treated with β-blocker, although they had not been treated with RAS blockers. Moreover the RAS blocker and β-blocker treatment was started during hospitalization and continued after discharge. It is possible that these factors more strongly affect the prognosis.

Study Limitations

There are several limitations to this study. The major limitation is that the sample size was moderate, the study was retrospective in nature, and it was based at a single center. We did not collect data on variables that can potentially influence prognosis in ADHF, such as respiratory function and QRS complex width on admission. We could not compare the doses of ACEI or ARB between the 2 groups because there are no official dose conversion formulas for RAS inhibitors.

With respect to PRA, there were also some limitations. First, it is generally recommended that PRA is measured while in the supine position for >30min, but the supine position might have exacerbated HF in the present patients with emergency admission for ADHF. Therefore, most blood samples were not obtained after 30min at rest. Second, we did not collect data on factors that could influence PRA, such as sympathetic activity and intravascular volume depletion, because we had no data on catecholamine level or serum osmolality.

Conclusions

PRA is associated with increased risk for all-cause and cardiovascular mortality in ADHF patients on RAS inhibitors, suggesting that PRA is a useful biomarker in ADHF.

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Disclosures

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Supplementary Files

Supplementary File 1

Figure S1. Kaplan-Meier event-free survival curves for (**A**) all-cause death and (**B**) cardiovascular death in patients with plasma renin activity (PRA) ≥2.0 ng·ml^{-1}·h^{-1} (blue line, high PRA group; n=180) compared with patients with PRA <2.0 ng·ml^{-1}·h^{-1} (red line, low PRA group; n=113).

Figure S2. Kaplan-Meier event-free survival curves for (**A**) all-cause death and (**B**) cardiovascular death in patients with plasma renin activity (PRA) ≥8.2 ng·ml^{-1}·h^{-1} (blue line, high PRA group; n=90) compared with patients with PRA <8.2 ng·ml^{-1}·h^{-1} (red line, low PRA group; n=203).

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ORIGINAL ARTICLE
Heart Failure

Left Ventricular Ejection Fraction (EF) of 55% as Cutoff for Late Transition From Heart Failure (HF) With Preserved EF to HF With Mildly Reduced EF

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Background: Heart failure (HF) with preserved (HFpEF) left ventricular ejection fraction (LVEF) is a syndrome with complex pathophysiology. Little is known about changes in LVEF that occur over time in HFpEF patients. A fundamental clinical question about HFpEF is whether HFpEF is an early manifestation of HF with reduced LVEF (HFrEF). If so, which patients with HFpEF are likely to show a decline in LVEF to less than 50%? The aim of the present study was to examine longitudinal changes in LVEF in patients with HFpEF.

Methods and Results: Among 279 consecutive HFpEF patients admitted as emergencies, we examined 100 who underwent echocardiography at least 1 year after discharge. EF >50% was used as the definition of HFpEF. During a mean duration from hospitalization to follow-up echocardiography of 31.5 months, 11% of patients had LVEF ≤50% (mildly reduced LVEF), known as mildly reduced (HFmrEF). The utility of LVEF during hospitalization to predict HFmrEF was assessed with receiver-operating characteristic curve analysis. A cutoff value of 55% had sensitivity of 90.9% and specificity of 97.7%. Logistic regression analysis indicated that LVEF ≤55% and ischemic etiology were strong predictors of progression from HFpEF to HFmrEF (odds ratio [OR] 435, 95% confidence interval [CI] 52.65–10,614, P<0.0001 and OR 10.9, 95% CI 2.60–74.80, P=0.0007, respectively).

Conclusions: The present study suggests that HFpEF patients with LVEF ≤55% may progress to HFmrEF in the future. (*Circ J* 2015; **79:** 2209–2215)

Key Words: Cutoff value; Echocardiography; Heart failure; Left ventricular ejection fraction

Heart failure (HF) is an important public health issue worldwide. Until now, most large clinical studies have targeted HF with reduced (HFrEF) left ventricular ejection fraction (LVEF).[1–4] However, HF with preserved LVEF (HFpEF) has recently gained attention because many large clinical studies have demonstrated that half of HF patients have HFpEF[5–7] and they have a similar poor prognosis as those with HFrEF,[8–11] even though various lines of evidence suggest that the pathophysiology of HFpEF is different from that of HFrEF.

Editorial p2108

HFpEF is a complex syndrome, of which the molecular mechanisms and clinical characteristics remain unclear. Recently, some studies[12,13] have reported changes in LVEF that occur over time in patients with HFpEF; a substantial number of patients with HFpEF showed a decline to LVEF <50%. However, it is unclear which patients with HFpEF are more likely to show such a decline. In this context, we performed a longitudinal assessment of LVEF based on echocardiography in patients with acute decompensated HF (ADHF) in the Nara Registry and Analyses for Heart Failure 2 (NARA-HF 2 Study) cohort study.

Methods

Study Population and Data Collection

The NARA-HF 2 Study recruited 611 consecutive patients admitted as emergencies with documented ADHF (either acute new-onset or acute-on-chronic HF) between January 2007 and December 2012.[14–16] The diagnosis of HF was based on the Framingham criteria.[17] The study population included both HFrEF and HFpEF patients, but patients with acute myocar-

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Table 1. Baseline Characteristics of Patients Admitted With Acute Decompensated HF in the NARA-HF 2 Study

	Total (n=100)	50%<LVEF≤55% (n=13)	LVEF >55% (n=87)	P value
Demographic				
Age, years	70.3±12.1	69.2±12.8	70.5±12.0	0.8056
Female, %	48.0	38.5	49.4	0.4605
Body mass index, kg/m^2	24.2±4.0	25.5±4.3	24.0±3.9	0.2699
Etiology of HF, %				
Ischemic	35.0	84.6	27.6	<0.0001
Valvular	15.0	7.7	16.1	0.4289
Hypertensive	10.0	0.0	11.5	0.1976
Hypertrophic cardiomyopathy	6.0	0.0	6.9	0.3288
Medical history, %				
Hypertension	85.0	84.6	85.1	0.9668
Diabetes mellitus	53.0	61.5	51.7	0.5084
Dyslipidemia	40.0	38.5	40.2	0.8528
Old myocardial infarction	19.0	53.9	13.8	0.0006
Atrial fibrillation	33.0	23.1	34.5	0.4146
Procedures, %				
PCI	23.0	53.9	18.4	0.0046
CABG	3.0	0.0	3.5	0.4966
NYHA class on admission, %				
III or IV	78.0	76.9	78.2	0.9200
Vital signs at discharge				
SBP, mmHg	121.5±17.0	117.1±11.2	122.2±17.7	0.3563
Heart rate, beats/min	68.9±9.4	71.2±5.9	68.6±9.8	0.2435
Laboratory data at discharge				
Hemoglobin, g/dl	11.0±1.9	10.9±1.4	11.1±2.0	0.8922
eGFR, ml/min/1.73 m^{2*}	32.5 (12.4–58.3)	25.6 (11.0–46.2)	35.4 (12.4–58.4)	0.3822
Sodium, mEq/L	138.9±3.4	139.1±4.9	139.8±3.5	0.5005
Plasma BNP, pg/ml*	191 (131–348)	347 (206–536)	184 (122–324)	0.0524
Medication at discharge, %				
ACE inhibitor or ARB	80.0	69.2	81.6	0.2980
β-blocker	39.0	46.2	37.9	0.5707
MR blocker	20.0	15.4	20.7	0.6466
Diuretic	78.0	76.9	78.2	0.9203

*Data are shown as percentage, mean±standard deviation, or median (interquartile range). ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MR, mineralocorticoid receptor; NARA-HF 2 Study, the Nara Registry and Analyses for Heart Failure 2; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.

dial infarction (AMI), acute myocarditis, and acute HF with acute pulmonary embolism were excluded.

The NARA-HF Study 2 included 279 patients with LVEF >50%. We analyzed data from 100 patients who underwent follow-up with echocardiography at least 1 year after discharge. The remaining 179 patients were not enrolled in the present investigation: 15 patients died in the hospital during the emergency admission, 55 patients died within 1 year of discharge, 7 patients were lost to follow-up, and 102 patients were not able to undergo follow-up echocardiography in at the study hospital. None of the 100 patients had severe valvular disease (aortic or mitral stenosis or regurgitation) or developed new-onset AMI during the follow-up period. For each patient, baseline data included age, sex, body mass index (BMI), HF etiology, medical history, as well as vital signs, laboratory data, medications, and echocardiography results during hospitalization and at follow-up.

The study was approved by the Ethics Committee of Nara Medical University, and written informed consent was given by all patients according to the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.

Definitions

Using echocardiography, we measured LVEF at admission and at follow-up at least 1 year after discharge. We adopted the generally accepted criteria of LVEF >50%[6,12,18] as the definition for HFpEF in this study. Receiver-operating characteristic (ROC) curve analysis was performed on LVEF data obtained during hospitalization to define a cutoff for predicting LVEF ≤50% at follow-up.

Echocardiography

All echocardiography was performed at Nara Medical University Hospital. For each patient, echocardiograms obtained

during hospitalization and at follow-up (at least 1 year after discharge) included measurements of LV end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD), LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), left atrial dimension (LAD), interventricular septal (IVS) and LV posterior wall (LVPW) thickness by 2D echocardiography or M-mode. LVEF assessment was based on 2D echocardiography using the quantitative 2D biplane volumetric Simpson method from 4- and 2-chamber views. LV hypertrophy (LVH) was defined as IVS and LVPW thicknesses >12 mm. If there echocardiography was performed multiple times during the hospitalization, we used the data from the examination performed closest to discharge, because data immediately after admission might be incorrect because of tachycardia or inadequate positioning. All measurements were calculated separately by 1 echocardiologist and 1 expert sonographer. The variation in measurements between the 2 investigators was 3.1% in the present study.

Statistical Analysis

Continuous variables are expressed as mean±standard deviation or median (interquartile range [IQR]), and between-group differences were compared using Student's t-test. Categorical variables were summarized as percentages and analyzed using the chi-square test. To evaluate the progression from HFpEF to HFrEF, results are reported as odds ratio (OR), 95% confidence interval (CI), and P values using logistic regression. JMP version 10 for Windows (SAS Institute Inc, Cary, NC, USA) was used for all statistical analyses. P<0.05 was considered statistically significant.

Results

Baseline Characteristics of the Study Patients

The mean duration between echocardiography during hospitalization for ADHF and follow-up echocardiography was 31.5 months. During this interval, LVEF fell to <50% in 11.0% (n=11) of patients. The mean age at hospital admission was 70.3±12.1 years, and 48.0% of the patients were women. Regarding the etiology of HF, 35.0 % of patients had ischemic causes, 15.0% had valvular causes, 10.0% had hypertensive heart disease, and 6.0% had hypertrophic cardiomyopathy. The New York Heart Association (NYHA) function class on admission was III or IV in 78.0% of patients. The median (IQR) plasma B-type natriuretic peptide concentration at discharge was 191 (131–348) pg/ml (**Table 1**).

Changes in LVEF

The mean LVEF was 67.0±9.2% during hospitalization and 67.4±11.1% at follow-up. During the follow-up period, LVEF decreased in 50.0% of patients (n=50), increased in 45.0% (n=45), and did not change in 5.0% (n=5). The median annual change in LVEF was –0.1%, with 25% and 75% percentiles of –1.9% and +2.6%, respectively. Among patients with a decline in LVEF from hospitalization to follow-up, LVEF decreased to below 50% in 11 patients. Based on ROC curve analysis for LVEF ≤50% at follow-up, the area under the ROC curve was 0.9893. The LVEF cutoff value was 55%, with sensitivity of 90.9% and specificity of 97.7% (**Figure 1**).

As shown by the distribution of LVEF during hospitalization and follow-up (**Figure 2**), 10 of 11 patients with LVEF <50% at follow-up had LVEF between 50% and ≤55% during hospitalization. Consequently, the proportion of patients with 50%<LVEF≤55% decreased dramatically, from 13.0% during hospitalization to 4.0% at follow-up. Only 1 of 87 patients with LVEF>55% during hospitalization had a follow-up LVEF <50%.

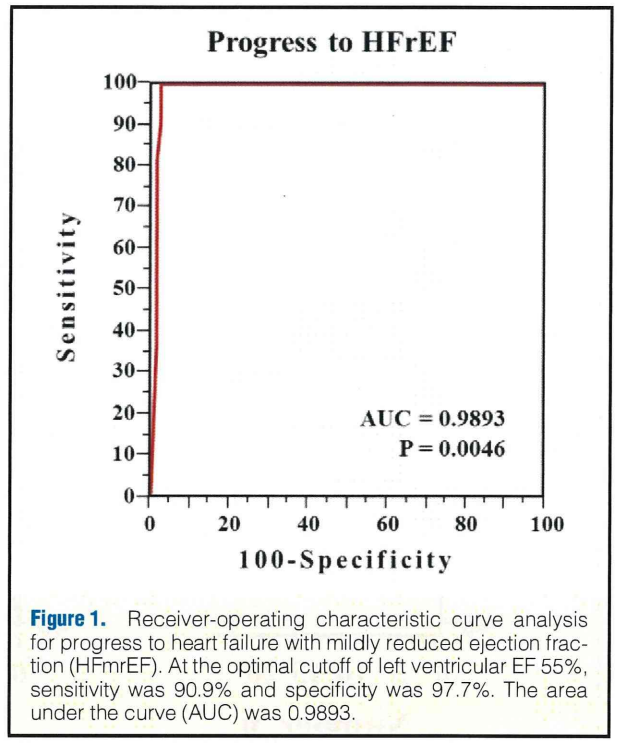

Figure 1. Receiver-operating characteristic curve analysis for progress to heart failure with mildly reduced ejection fraction (HFmrEF). At the optimal cutoff of left ventricular EF 55%, sensitivity was 90.9% and specificity was 97.7%. The area under the curve (AUC) was 0.9893.

Comparison of Clinical Characteristics of Patients With 50%<LVEF≤55% and LVEF >55%

To identify other clinical predictors of LVEF <50% during follow-up, we compared the baseline clinical characteristics of patients with 50%<LVEF≤55% with those with LVEF >55% (**Table 1**). Age, BMI, and the proportion of females were similar in both groups. With regards to HF etiology, the proportion of patients with ischemic causes was significantly higher in patients with 50%<LVEF≤55% compared with patients with LVEF>55%. The prevalence of old MI was significantly higher in patients with 50%<LVEF≤55% than in patients with LVEF>55%. There were no significant differences in the prevalence of comorbidities other than old MI between the 2 groups. NYHA functional class was similar. Systolic blood pressure and heart rate at discharge were similar in both groups. There were also no significant differences in laboratory findings or medications at discharge.

Table 2 shows the echocardiographic parameters. The mean follow-up duration in both groups was similar. There was a significant difference in the annual change in LVEF between patients with 50%<LVEF≤55% and LVEF >55%. LVEDD and LVESD were significantly higher in patients with 50%<LVEF≤55% than in patients with LVEF >55% at both measurement points. Regarding LV volume, both LVEDV and LVESV were significantly larger in patients with 50%<LVEF≤55% than in patients with LVEF >55% during hospitalization as well as at follow-up. In patients with LVEF >55%, LVEDV and LVESV were unchanged during hospitalization to follow-up, but LVEDV increased by 10.1% and LVESV by 28.6% in patients with 50%<LVEF≤55%. LAD and the prevalence of LVH were similar between the 2 groups (data not shown).

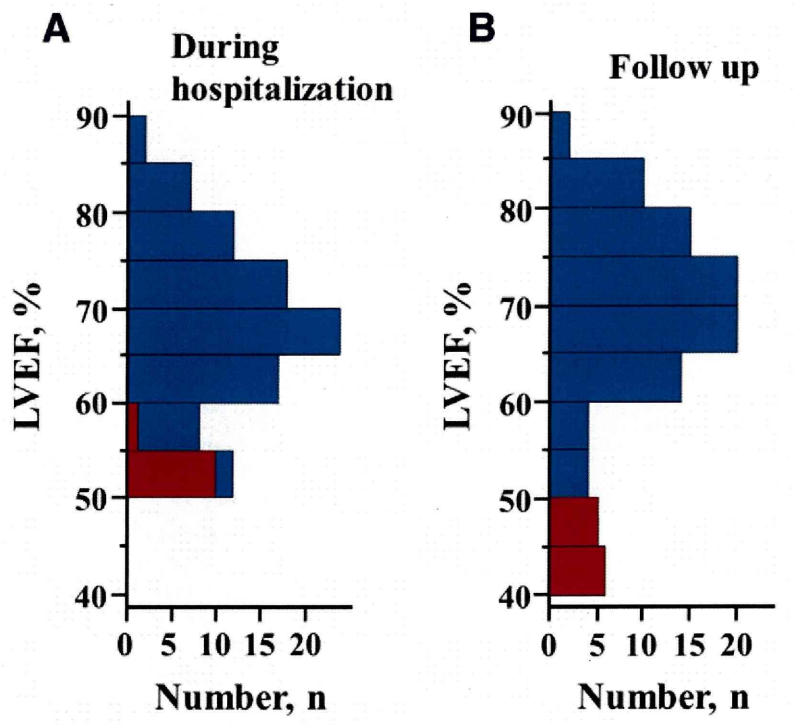

Figure 2. Distribution of left ventricular ejection fraction (LVEF) (**A**) during hospitalization for acute decompensated heart failure and (**B**) at follow-up. Red represents patients with LVEF <50% at follow-up and the identical subjects in (**A**) and (**B**).

Table 2. Comparison of Echocardiographic Parameters Between HF Patients With 50%<LVEF≤55% or LVEF >55%

Echocardiographic parameter	Total (n=100)	50%<LVEF≤55% (n=13)	LVEF >55% (n=87)	P value
Time to follow-up echocardiography, months	31.5±17.0	37.3±16.6	30.6±17.0	0.1426
LVEF during hosp, %	67.0±9.2	51.9±1.9	69.2±7.5	<0.0001
LVEF at follow-up, %	67.4±11.1	46.0±4.1	70.6±7.7	<0.0001
LVEF change per year, %*	−0.1 (−1.9 to +2.6)	−4.3 (−6.0 to −1.5)	+0.5 (−1.4 to +2.7)	<0.0001
LVEDD during hosp, mm	49.6±7.7	55.4±6.1	48.8±7.5	0.0031
LVEDD at follow-up, mm	49.4±6.5	57.3±6.3	48.3±5.7	<0.0001
LVEDD change per year, ml	0.0 (−1.4 to +1.6)	+0.3 (−0.4 to +2.9)	0.0 (−1.5 to +1.6)	0.1987
LVESD during hosp, mm	33.1±7.2	40.4±5.6	32.0±6.7	<0.0001
LVESD at follow-up, mm	32.4±6.6	42.8±5.6	30.9±5.2	<0.0001
LVESD change per year, ml	0.0 (−1.6 to +1.2)	0.0 (−1.1 to +2.2)	0.0 (−1.7 to +1.0)	0.2500
LVEDV during hosp, ml	71.9±31.4	100.8±30.7	67.5±29.2	0.0006
LVEDV at follow-up, ml	70.3±34.4	111.4±48.9	64.2±27.2	<0.0001
LVEDV change per year, ml	−0.5 (−5.6 to +8.0)	+3.0 (−7.0 to +10.4)	−0.5 (−5.4 to +8.0)	0.5610
LVESV during hosp, ml	24.9±15.3	49.3±16.1	21.2±11.3	<0.0001
LVESV at follow-up, ml	24.9±20.3	62.1±28.4	19.3±11.0	<0.0001
LVESV change per year, ml	+0.1 (−2.7 to +2.9)	+3.4 (−2.0 to +8.6)	0.0 (−2.8 to +2.5)	0.0614

*Data are shown as percentage, mean±standard deviation or median (interquartile range). LVEF/LVEDV/LVESV change=change between hosp and follow-up. EDD, end-diastolic dimension; EDV, end-diastolic volume; EF, ejection fraction; ESD, end-systolic dimension; ESV, end-systolic volume; hosp, hospitalization; LV, left ventricular.

Next, we examined which factors were associated with the transition of LVEF from >55% to ≤55%. As shown in **Table 3**, 50%<LVEF≤55% during hospitalization and ischemic etiology were strong predictive factors (OR 435, 95% CI 52.65–10,614, P<0.0001 and OR 10.9, 95% CI 2.60–74.80, P=0.0007, respectively). Other than these 2 factors, LVEDD, LVESD, LVEDV and LVESV were significantly associated with progression to HF with mildly reduced EF (HFmrEF). Regarding the change in LV volume from baseline to follow-up, the annual change in LVESV was a predictor (OR 1.12, 95% CI 1.02–1.26, P=0.0232) but the change in LVEDV was not. In contrast, none of age, sex and medications was associated with progression to HFmrEF (**Table 3**).

Table 3. Predictors of Progression From HF With Preserved EF to HF With Reduced EF

	OR	95% CI	P value
50%<LVEF≤55%	435.0	52.65–10,614	<0.0001
Age, years	0.98	0.93–1.03	0.3696
Female sex	0.89	0.24–3.17	0.8577
HF of ischemic etiology	10.9	2.60–74.80	0.0007
LVEDD during hosp, mm	1.14	1.04–1.28	0.0066
LVESD during hosp, mm	1.15	1.05–1.28	0.0018
LVEDV during hosp, ml	1.04	1.01–1.06	0.0007
LVEDV change per year, ml	1.02	0.98–1.06	0.4224
LVESV during hosp, ml	1.16	1.09–1.28	<0.0001
LVESV change per year, ml	1.12	1.02–1.26	0.0232
ACE inhibitor or ARB at discharge	0.63	0.16–3.10	0.5368
β-blocker at discharge	1.35	0.36–4.81	0.6442
MR blocker at discharge	0.88	0.13–3.79	0.8717
Diuretic at discharge	1.35	0.36–4.81	0.6442

LVEDV/LVESV change=change between hosp and follow-up. CI, confidence interval; OR, odds ratio. Other abbreviations as in Tables 1,2.

Discussion

HF is classified simply by LVEF into 2 (HFrEF and HFpEF) or 3 (HFrEF, HF-borderline EF, and HFpEF) categories.[3,12,19,20] As for HFpEF, both the European Society of Cardiology (ESC) and the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines state that HFpEF is defined as LVEF >50%,[18,21] but large clinical trials on HFpEF have enrolled patients with LVEF >40% or 45%. Therefore, the definition of HFpEF is not still strictly fixed, so we used LVEF >50% as the cutoff for HFpEF in the present study. The present study results indicated that approximately 10% of patients with HFpEF at baseline had a decline in LVEF to less than 50% but above 40% after a mean follow-up of 31.5 months. Thus, approximately 10% of patients change from HFpEF to HFmrEF, or HF-borderline EF. It is unclear from the present study whether these patients will further progress to HFrEF over a longer period of time.

The present study found LVEF of 55% as a cutoff for the transition from HFpEF to HFmrEF with high sensitivity and specificity based on ROC curve analysis. Although HFpEF is commonly thought to represent diastolic dysfunction with normal systolic function, through a more sensitive method, LV strain, subtle impairment of LV systolic contractility was recently already demonstrated in some patients with HFpEF.[22,23] However, given that normal LVEF as measured is 64.9±4.9%[24] by echocardiography and 61% in women and 55% in men by MRI,[25] systolic function with LVEF<55% on echocardiography is moderately reduced rather than normal. The ESC guidelines propose that patients with LVEF in the range of 35–50% are in a "grey area" and most likely have primary mild systolic dysfunction.[18] However, this "grey area" might be wider.

The clinical syndrome of acute HF diagnosed by Framingham criteria occurs in patients with any level of LVEF. Earlier studies have demonstrated that there is a bimodal distribution of LVEF among patients with acute HF, with a lower proportion of patients with 40%<LVEF≤55%.[12,26] Because the present study enrolled only patients with LVEF >50%, LVEF at baseline did not show a bimodal distribution, but in the overall NARA-HF Study 2 there was a similar a bimodal distribution (**Figure S1**).

The clinical characteristics of patients with 50%≤LVEF<55% were different from those with LVEF >55%. Consistent with prior studies,[6,12,13] there was a much higher proportion of patients with ischemic etiology among patients with 50%<LVEF≤55%. Ischemic etiology was a strong predictor for transition from HFpEF to HFmrEF in the present study, as reported previously.[12,13] In fact, the rate of LVEF decline was much higher among patients with ischemic etiology than in those with non-ischemic etiology (**Figure 3**). In addition, in patients with 50%<LVEF≤55%, LVEDV and LVESV during hospitalization were larger than in patients with LVEF >55%, and the percent increment of LVESV between the 2 echocar-

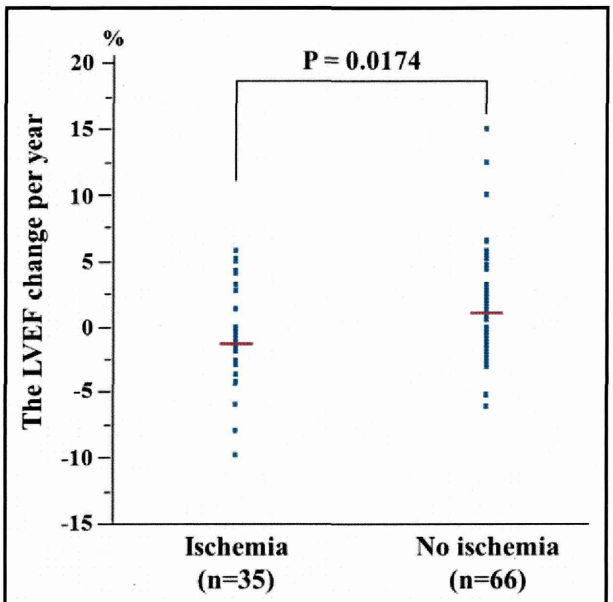

Figure 3. Change in left ventricular ejection fraction (LVEF) from hospitalization to follow-up. The median change (interquartile range) was −1.40% (−3.03 to +2.23) in patients with ischemia and +0.90% (−1.31 to +2.65) in patients with heart failure of non-ischemic etiology (P=0.0174).

diography examinations was much greater than that of LVEDV. Thus, decline of LVEF in patients with 50%<LVEF≤55% was probably related to the increase in LVESV. These findings all suggest that there are qualitative differences in the pathophysiology and time course of LV dysfunction between patients with LVEF >55% and those with LVEF ≤55%.

Patients whose LVEF had fallen to below 50% at follow-up were not confirmed as having a clinical episode of ischemic disease during follow-up. Moreover, the proportion of readmission for worsening of HF during follow-up was similar in patients with LVEF <50% at follow-up and those with LVEF ≥50% at follow-up (45% and 36%, respectively, P=0.5427). Also, in the univariate logistic regression analysis, readmission for worsening of HF was not a predictor of the decline in LVEF. Therefore, it is unlikely that additional ischemic events or worsening of HF during follow-up was the cause of the decline in LVEF in this study.

Recently, some large randomized clinical trials in HFpEF patients with various therapeutic agents such as angiotensin-receptor blockers (CHARM-preserved, I-preserved),[7,27] and mineralocorticoid receptor blocker (TOPCAT),[28] failed to show beneficial effects of these drugs in HFpEF, although these agents have been proven to effectively reduce cardiovascular events in HFrEF. Of note, the inclusion criteria was LVEF >40% for the CHARM-preserved study and LVEF >45% for the I-preserved and TOPCAT studies; because a substantial number of patients with "grey area" LVEF were included, further analyses or subanalyses should be conducted with consideration of this.

Study Limitations

The major limitations are that the sample size was small, the study was retrospective in nature, and based at a single center. Approximately half of potentially eligible subjects were excluded for lack of echocardiography at follow-up, which might be a potential source of bias. Furthermore, we did not collect information on medications after discharge that can potentially affect LVEF. These factors underscore the need for future prospective studies of greater power, ideally controlled for medication regimens, that could further elucidate the natural history of HFpEF.

Conclusions

The present study showed that HFpEF patients with LVEF ≤55% were more likely to progress to HFmrEF in the future than those with LVEF >55%. This finding provides insights to the pathophysiology of HFpEF and suggests that patients with ischemic disease, who show 50%≤LVEF<55%, may actually have HFrEF and not HFpEF. A large-scale prospective study is necessary to confirm this hypothesis.

Founding Source

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Conflicts of Interest

Y.S. has conflicts of interest to disclose as follows.

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Other authors have no financial conflicts of interest to disclose.

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Supplementary Files

Supplementary File 1

Figure S1. Distribution of left ventricular ejection fraction (LVEF).

Please find supplementary file(s);
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Sex differences in clinical characteristics and long-term outcome in acute decompensated heart failure patients with preserved and reduced ejection fraction

Yasuki Nakada, Rika Kawakami, Tomoya Nakano, Akihiro Takitsume, Hitoshi Nakagawa, Tomoya Ueda, Taku Nishida, Kenji Onoue, Tsunenari Soeda, Satoshi Okayama, Yukiji Takeda, Makoto Watanabe, Hiroyuki Kawata, Hiroyuki Okura, and Yoshihiko Saito

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Nakada Y, Kawakami R, Nakano T, Takitsume A, Nakagawa H, Ueda T, Nishida T, Onoue K, Soeda T, Okayama S, Takeda Y, Watanabe M, Kawata H, Okura H, Saito Y. Sex differences in clinical characteristics and long-term outcome in acute decompensated heart failure patients with preserved and reduced ejection fraction. *Am J Physiol Heart Circ Physiol* 310: H813–H820, 2016. First published January 8, 2016; doi:10.1152/ajpheart.00602.2015.—In patients with acute decompensated heart failure (ADHF), sex differences considering clinical and pathophysiologic features are not fully understood. We investigated sex differences in left ventricular (LV) ejection fraction (LVEF), plasma B-type natriuretic peptide (BNP) levels, and prognostic factors in patients with ADHF in Japan. We studied 748 consecutive ADHF patients of 821 patients registered in the ADHF registry between January 2007 and December 2014. Patients were divided into four groups based on sex and LVEF [reduced (ejection fraction, or EF, <50%, heart failure with reduced EF, or HFrEF) or preserved (EF ≥50%, heart failure with preserved LVEF, or HFpEF)]. The primary endpoint was the combination of cardiovascular death and heart failure (HF) admission. The present study consisted of 311 female patients (50% HFrEF, 50% HFpEF) and 437 male patients (63% HFrEF, 37% HFpEF). There was significant difference between sexes in the LVEF distribution profile. The ratio of HFpEF patients was significantly higher in female patients than in male patients (P = 0.0004). Although there were no significant sex differences in median plasma BNP levels, the prognostic value of BNP levels was different between sexes. Kaplan-Meier analysis revealed that the high BNP group had worse prognosis than the low BNP group in male but not in female patients. In multivariate analysis, log transformed BNP at discharge predicted cardiovascular events in male but not in female HF patients (female, hazard ratio: 1.169; 95% confidence interval: 0.981–1.399; P = 0.0806; male, hazard ratio: 1.289; 95% confidence interval: 1.120–1.481; P = 0.0004). In patients with ADHF, the distribution of LV function and the prognostic significance of plasma BNP levels for long-term outcome were different between the sexes.

acute decompensated heart failure; B-type natriuretic peptide; sex differences; preserved ejection fraction

NEW & NOTEWORTHY

In acute decompensated heart failure patients, plasma B-type natriuretic peptide (BNP) levels, hemodynamics, renal function, and cardiovascular event rates were similar between sexes. However, the left ventricular ejection fraction distribution and etiology of heart failure differed between sexes. Additionally, the present study is the first to demonstrate sex differences in the prognostic significance of plasma BNP levels for long-term outcome.

GENERALLY, WOMEN HAVE LOWER incident rates of cardiovascular events and longer lifespans than men. In addition, it has been reported that the prevalence and mortality rates of ischemic heart disease were higher in male than in female patients (24, 25). Recently, as is the case with heart failure (HF) patients, the impact of sex difference has received considerable attention. Several studies have reported cases of HF with preserved left ventricular (LV) ejection fraction (HFpEF) in as many as half of all HF patients (3, 18, 20). To date, patients with HFpEF are older, mostly women, and more likely to have hypertension.

Plasma B-type natriuretic peptide (BNP) levels are elevated in HF patients and are believed to be predictive of mortality (10, 19, 29). Plasma BNP levels were higher in female than in male HF patients with similar LV functions. However, plasma BNP levels were lower in HFpEF than in HF with reduced EF (HFrEF) patients (7, 26). Previous studies have suggested that there were no significant differences in the ability of plasma BNP levels to predict in-hospital mortality despite sex and ejection fraction (EF) differences (4, 6). It remains to be fully elucidated, however, whether sex differences exist in patients with acute decompensated HF (ADHF). We therefore investigated sex differences in LVEF, plasma BNP levels, and prognostic factors in patients with ADHF.

MATERIALS AND METHODS

Patient population. The present study recruited ADHF patients from the NARA-HF 2 study (23). The NARA-HF 2 study recruited 821 consecutive patients with emergency admission to our department for ADHF between January 2007 and December 2014. The diagnosis of HF was based on the criteria of the Framingham study (16). Patients with acute myocardial infarction, acute myocarditis, and acute HF with acute pulmonary embolism were excluded from this registry.

Among the 821 enrolled patients, we excluded 37 who died during the current hospitalization, 15 who were lost to follow-up, and 21 with missing LVEF reports. Thus we analyzed 748 patients with ADHF. Patients were divided into four groups based on sex and LVEF: *1*) female patients with reduced EF (EF <50%); *2*) male patients with reduced EF; *3*) female patients with preserved EF (EF ≥50%); and *4*)

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male patients with preserved EF. We divided the patients according to high and low BNP groups based on the median plasma BNP levels in each group.

The present study was approved by the Nara Medical University Institutional Ethics Committee and was performed in accordance with the 1975 Declaration of Helsinki rules for clinical research protocols. Written, informed consent was obtained from all patients.

Outcomes. The primary endpoint was the combination of cardiovascular death and HF admission. Cardiovascular death was defined as death due to HF, myocardial infarction, sudden death, stroke, or vascular disease. We checked patient medical records to determine vital status and the cause of death. When this information was unavailable in the medical records, we telephoned the patients or their families.

Measurement of BNP. Plasma samples for BNP measurements were collected on admission and at discharge. Plasma BNP levels were measured using a chemiluminescent immunoassay kit (Siemens Healthcare diagnostics, Tokyo, Japan). Intra- and interassay coefficients of variation for measurements were 1.8–4.3% and 0.5–2.1%, respectively.

Estimated glomerular filtration rate calculation. The Modification of Diet in Renal Disease (MDRD) study equation is commonly used for glomerular filtration rate (GFR) estimation worldwide, but the equation is less accurate for Japanese populations. In this study, the estimated GFR (eGFR) was calculated according to the published equation for Japanese persons: $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times (0.739 \text{ for women})$ (15).

Echocardiography. Ultrasound examinations were performed using the Sonos 7500 systems (Philips, Best, the Netherlands) and Acuson Sequoia systems (Siemens, Erlangen, Germany). LVEF was calculated by using the modified Simpson's method. The LV end-diastolic diameter (LVDd) and LV end-systolic diameter were measured by using the M-mode echocardiography. LV end-diastolic

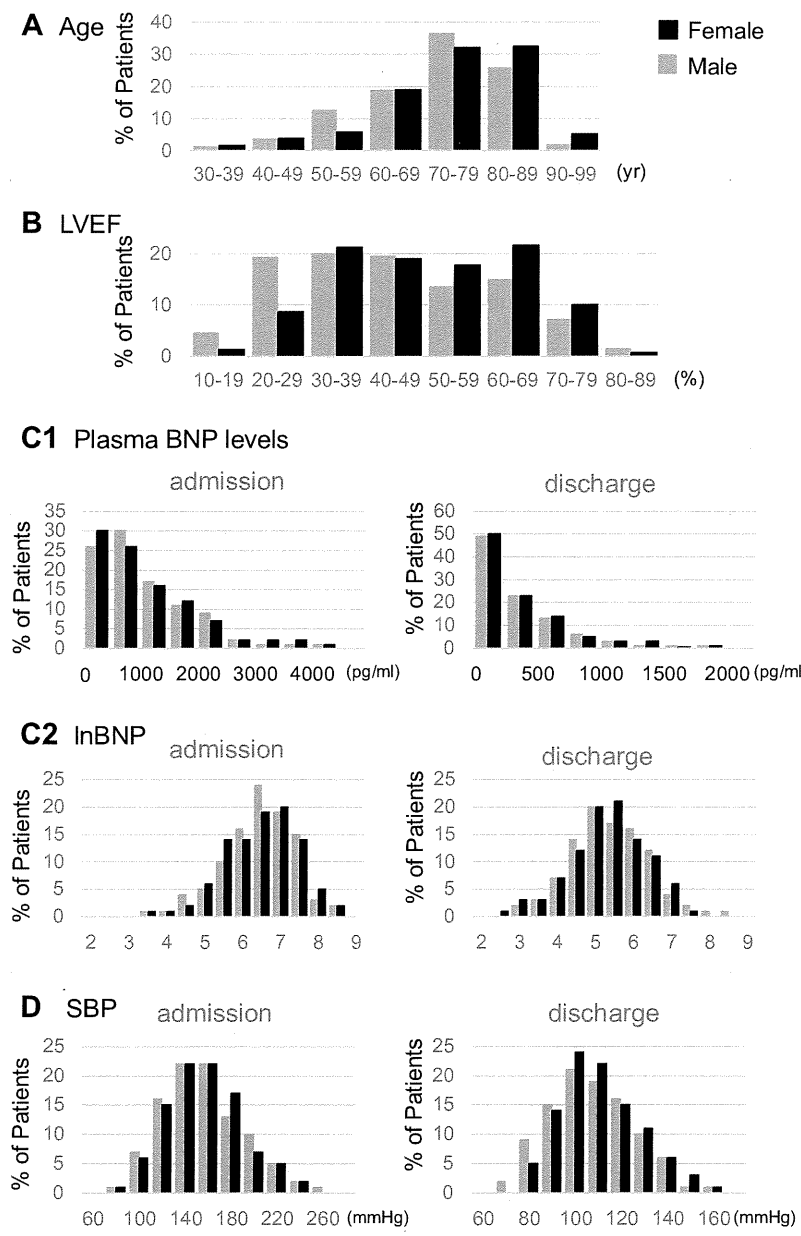

Fig. 1. Sex differences in the distribution of age, left ventricular ejection fraction (LVEF), plasma B-type natriuretic peptide (BNP) levels, log transformed BNP (lnBNP), and systolic blood pressure (SBP). Female patients and male patients are shown. *A*: plot of age distribution. *B*: plot of LVEF distribution. *C1*: plots of plasma BNP levels on admission and at discharge. *C2*: plots of lnBNP on admission and at discharge. *D*: plots of SBP on admission and at discharge.

volume was calculated according to the formula by Teichholz et al. (21): end-diastolic volume (ml) = [7/(2.4 + LVDd)]·LVDd^3.

Statistical analysis. Normally distributed data are presented as means ± SD and nonnormally distributed data as the median and interquartile range. Natural log transformation was performed for plasma BNP levels owing to nonlinear distribution. Differences between the groups were compared using the χ^2-square test for categorical variables. The Student *t*-test (normally distributed data) or Wilcoxon rank sum test (nonnormally distributed data) was used for the comparison of continuous variables between the two groups. Cumulative event-free rates during follow-up were assessed using the Kaplan-Meier method. Univariate and multivariate analyses of event-free survival were examined using the Cox proportional hazard models. $P < 0.05$ was considered statistically significant. We used JMP software for Windows version 11 (SAS Institute, Cary, NC) for all statistical analyses.

RESULTS

Baseline characteristics. The present study consisted of 311 female patients (HFrEF: 156, HFpEF: 155) and 437 male patients (HFrEF: 276, HFpEF: 161). The ratio of HFpEF patients was significantly higher in female patients than in male patients ($P = 0.0004$). Figure 1 shows the distribution of age, LVEF, plasma BNP levels, log transformed BNP (lnBNP), and systolic blood pressure (SBP) in female and male patients. There were apparent differences in the age and LVEF distri-

Table 1. *Comparison of sex-specific baseline characteristics for HF patients with rEF and pEF*

	LVEF <50% (rEF)			LVEF ≥50% (pEF)			rEF vs. pEF, *P* Value	
	Female	Male	*P* Value	Female	Male	*P* Value	Female	Male
n	156	276		155	161			
Demographic								
Age, y	72.9 ± 12.5	70.6 ± 12.1	0.0327	75.0 ± 12.0	73.2 ± 11.5	0.1077	0.1321	0.0377
BMI, kg/m^2	22.7 ± 4.1	23.7 ± 3.9	0.0033	23.4 ± 4.7	23.8 ± 3.9	0.2370	0.1691	0.7260
Causes of HF, %			0.0131			0.0484	<0.0001	<0.0001
Ischemic heart disease	40.4	55.8		17.5	30.6			
Dilated cardiomyopathy	26.9	25.0		2.0	3.8			
Hypertensive heart disease	2.6	2.2		14.9	13.8			
Valvular heart disease	11.5	8.3		32.5	19.4			
Medical history, %								
Previous HF hospitalization	21.2	25.7	0.2866	17.4	27.3	0.0352	0.4053	0.7140
Hypertension	69.9	76.1	0.1586	84.5	82.0	0.5488	0.0021	0.1498
Diabetes mellitus	37.8	44.6	0.1733	34.8	47.8	0.0194	0.5857	0.5100
Atrial fibrillation	36.5	31.9	0.3259	37.4	36.0	0.7980	0.8730	0.3768
Vital sign on admission								
Heart rate, beats/min	101.5 ± 25.9	98.8 ± 26.2	0.2375	89.8 ± 26.3	90.3 ± 26.6	1.0000	<0.0001	0.0004
SBP, mmHg	138.1 ± 35.1	140.8 ± 35.1	0.6824	152.0 ± 37.9	152.5 ± 37.8	0.8907	0.0013	0.0010
DBP, mmHg	80.2 ± 22.6	84.0 ± 22.6	0.1032	79.6 ± 21.5	82.0 ± 23.8	0.3608	0.6858	0.3951
Vital sign at discharge								
Heart rate, beats/min	72.8 ± 10.9	70.7 ± 10.9	0.0778	68.8 ± 10.3	71.6 ± 11.1	0.0720	0.0066	0.4584
SBP, mmHg	109.1 ± 17.8	108.0 ± 17.8	0.3842	118.3 ± 17.5	117.7 ± 18.8	0.9060	<0.0001	<0.0001
DBP, mmHg	61.5 ± 10.9	61.6 ± 10.9	0.9804	63.4 ± 11.0	64.1 ± 10.6	0.4459	0.2003	0.0097
Echocardiographic parameters								
LVDd, mm	55.6 ± 8.2	60.1 ± 9.2	<0.0001	47.1 ± 7.0	50.8 ± 7.5	<0.0001	<0.0001	<0.0001
LVDs, mm	45.6 ± 8.6	50.0 ± 10.4	<0.0001	31.0 ± 6.2	33.6 ± 7.4	0.0027	<0.0001	<0.0001
LVEDVi	106.8 ± 35.9	110.3 ± 39.3	0.5254	73.1 ± 25.9	75.6 ± 24.8	0.2882	<0.0001	<0.0001
LVEF, %	35.4 ± 8.5	33.2 ± 9.2	0.0134	63.1 ± 18.0	62.8 ± 8.7	0.5272		
Laboratory data on admission								
BNP, pg/ml	1,210 [652–1925]	1,043 [616–1817]	0.2716	584 [296–1295]	637 [312–1046]	0.9303	<0.0001	<0.0001
Laboratory data at discharge								
BNP, pg/ml	307 [168–591]	295 [153–582]	0.9193	196 [103–420]	176 [108–391]	0.5691	0.0040	0.0001
Hemoglobin (g/dl)	11.3 ± 1.7	12.0 ± 2.3	0.0013	10.6 ± 1.6	11.0 ± 2.2	0.2784	0.0011	<0.0001
eGFR, ml·min·1.73 m^2	43.3 ± 26.6	44.2 ± 23.7	0.2847	39.5 ± 26.5	38.7 ± 27.4	0.7448	0.2137	0.0067
BUN, mg/dl	31.9 ± 18.2	33.5 ± 18.5	0.4019	34.9 ± 17.5	35.9 ± 19.4	0.9349	0.0747	0.2365
Creatinine, mg/dl	1.6 ± 1.8	2.0 ± 1.9	<0.0001	2.1 ± 2.3	2.7 ± 2.8	0.0002	0.3184	0.0151
BUN/Cre ratio	25.5 ± 10.7	21.2 ± 8.7	<0.0001	25.4 ± 12.2	18.9 ± 8.9	<0.0001	0.8727	0.0094
Sodium, mEq/l	138.4 ± 4.0	137.6 ± 3.8	0.0422	138.5 ± 4.0	137.7 ± 3.7	0.0245	0.5928	0.7073
Medication at discharge, %								
β-Blockers	69.7	72.5	0.5396	35.5	46.0	0.0586	<0.0001	<0.0001
ACE-I/ARBs	95.3	95.9	0.7702	87.9	90.1	0.5507	0.0238	0.0202
Diuretics	85.2	86.2	0.7604	80.6	76.4	0.3596	0.2922	0.0090
Loop diuretics dose, mg	23.1 ± 22.8	25.8 ± 25.4	0.5432	22.1 ± 23.7	20.8 ± 27.6	0.3400	0.6099	0.0251
Loop diuretics dose, mg/BSA	15.7 ± 15.6	15.3 ± 14.8	0.5325	15.0 ± 15.7	12.3 ± 16.5	0.0860	0.7740	0.0209
Follow-up period								
The length of follow-up, mo	18.3 [8.3–43.9]	14.4 [5.3–37.9]	0.0252	24.3 [8.4–48.1]	20.3 [6.8–43.3]	0.2595	0.4998	0.1034

Values are means ± SD for continuous normally distributed variables, the median (25th to 75th interquartile range [IQR]) for continuous nonnormally distributed variables, or *n* (%). BMI, body mass index; HF, heart failure; EF, ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVDd; left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular EF; pEF, preserved EF; rEF, reduced EF; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; BSA, body surface area; BUN, blood urea nitrogen; BUN/Cre ratio, BUN-to-creatinine ratio; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

bution profile between sexes. The distributions of plasma BNP levels, lnBNP, and SBP were quite similar between the sexes.

Table 1 summarizes the characteristics of the ADHF patients according to sex and LVEF. Female patients were significantly older than male patients in the HFrEF group and tended to be older in the HFpEF group. In both the EF groups, female patients were more likely to have valvular heart disease and were less likely to have ischemic heart disease. Heart rate, SBP, and diastolic blood pressure on admission and at discharge were similar in both groups. There were no significant sex differences in the median plasma BNP levels on admission and at discharge for both patient groups. The blood urea nitrogen to creatinine (BUN/Cre) ratio and sodium levels were significantly higher in female than in male patients in both EF groups. Table 1 also shows the statistical information between HFpEF and HFrEF within the same sex. The HFpEF group has lower plasma BNP levels and higher SBP than the HFrEF group in both sexes. In male patients, the average dose of loop diuretics was smaller in the HFpEF group than in the HFrEF group. However, in female patients it is similar in both the HFpEF and HFrEF groups.

Sex differences in long-term outcome. There were 376 cardiovascular events during a median follow-up of 18.5 (7.1–42.2) mo. Out of them 72 were cardiovascular deaths (28 in women and 44 in men) and 274 were admissions due to HF (108 women and 166 men). The incidence of cardiovascular death and admission due to HF tended to be lower in female than in male groups, but the difference was not statistically significant [Cox regression analysis, hazard ratio (HR): 0.809; 95% confidence interval (CI): 0.651–1.002; Log rank P = 0.0531; Fig. 2*A*]. As shown in Fig. 2*B*, the Kaplan-Meier event-free survival curves were similar between patients with HFrEF and HFpEF (Log rank P = 0.3113).

Figure 3 shows the Kaplan-Meier analysis for each subgroup based on the median BNP levels on admission and at discharge. Plasma BNP levels on admission were not a predictive factor for cardiovascular events in four groups of patients by sex and EF (Fig. 3, a, b, e, and f). The plasma BNP levels at discharge were a prognostic marker in male patients with HFrEF and HFpEF groups (Cox regression analysis, HR: 1.454; 95% CI: 1.021–2.077; Log rank P = 0.0381 in HFrEF; and Cox regression analysis HR, 1.650; 95% CI: 1.010–2.731; Log rank P = 0.0454 in HFpEF). However, in female patients, plasma BNP levels higher than the median level were not associated with cardiovascular events in either the HFrEF or HFpEF groups (Cox regression analysis, HR: 1.217; 95% CI: 0.730–2.041; Log rank P = 0.4506 in HFrEF; and Cox regression analysis, HR: 1.335; 95% CI: 0.796–2.257; Log rank P = 0.2732 in HFpEF).

The results of the multivariate analysis are exhibited in Table 2. The history of HF hospitalization was a predictive marker in both sex groups. In female HF patients, taking angiotensin-converting enzyme inhibitor and/or angiotensin II receptor blocker, eGFR, and BUN/Cre ratio was significant prognostic factors, but these were not in male patients. However, lnBNP at discharge predicted cardiovascular events in male HF patients but not in female HF patients.

DISCUSSION

The present study focused on sex difference in clinical characteristics and prognosis of patients with ADHF and demonstrated three sex differences, that is, EF distribution pattern, prognostic significance of plasma BNP levels, and clinical factors that predict cardiovascular events.

Although some cohorts of HFpEF reported that the female sex is dominant in patients with HFpEF (13, 27), in the present study the proportion of female and male in the patients with HFpEF was almost the same. The proportions of the females were 42% in the Japanese Diastolic Heart Failure Study (J-DHF) (30) and 45% in the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) (5), both of which enrolled Japanese patients. However, the proportion of HFpEF in female HF patients was significantly higher than that in male HF patients in the present study. The predominance of HFpEF in females is observed in every cohort. One possible explanation for this would be the difference of etiology of HF between the sexes. An earlier work speculated that reactive oxygen species would be more easily produced in the female (31), which may lead to high frequency of HFpEF in females. To investigate the molecular mechanism of HFpEF, the development of animal models, which are similar to human HFpEF, would be needed.

Generally, BNP is accepted as the most useful prognostic biomarker of HF (1, 9, 22). van Veldhuisen et al. (26) also documented that BNP was a prognostic factor for outcome

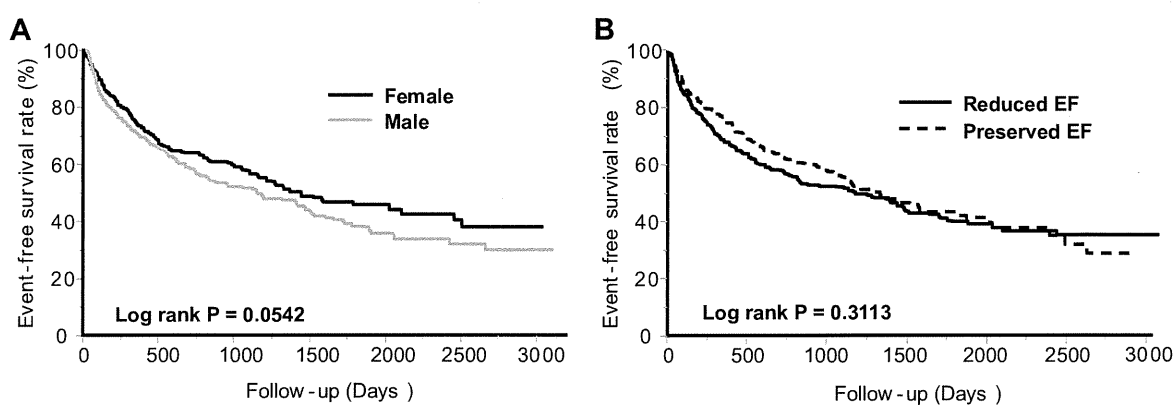

Fig. 2. *A*: sex-stratified Kaplan-Meier curves for cardiovascular events. *B*: Kaplan-Meier curves for cardiovascular events according to LVEF. EF, ejection fraction.

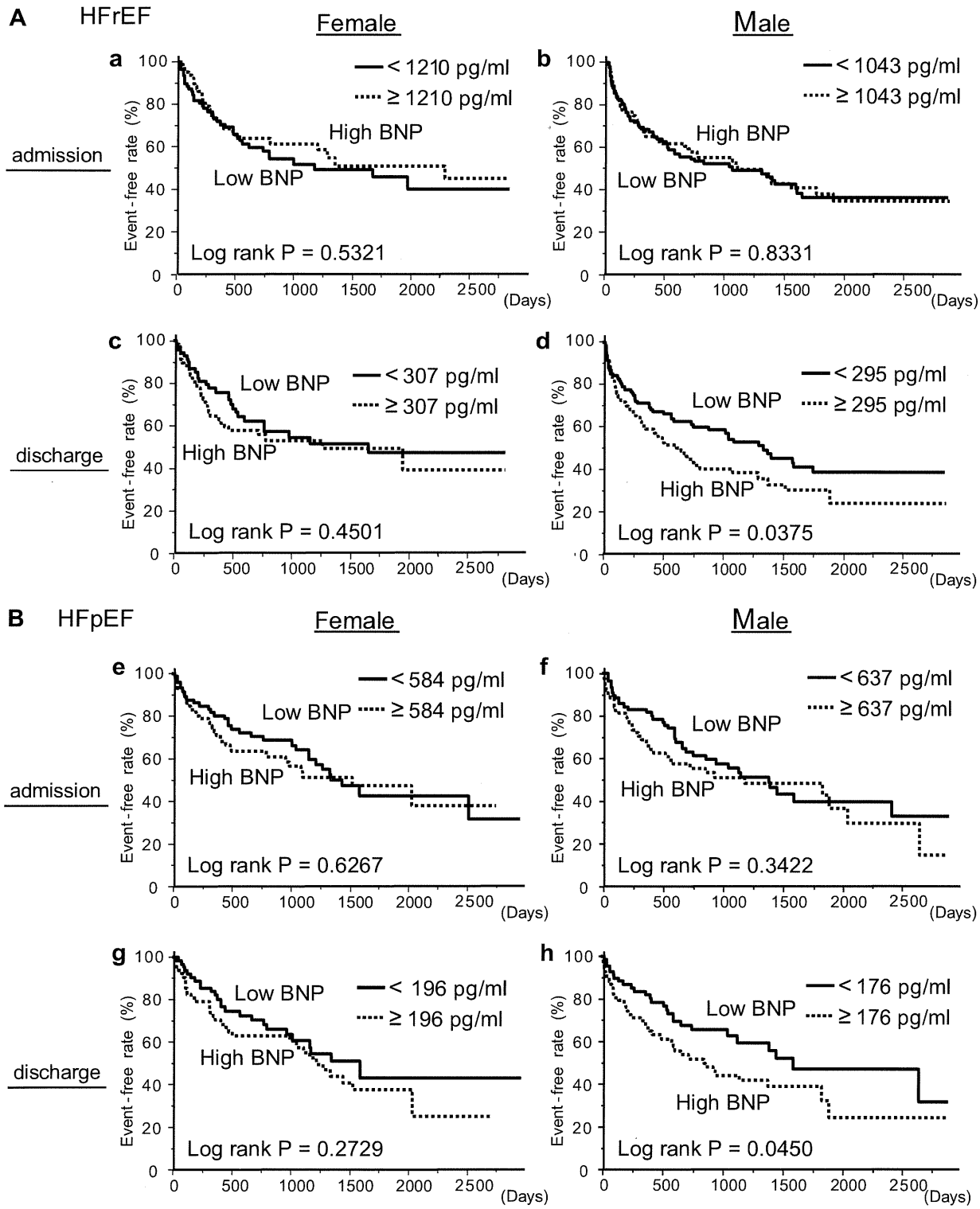

Fig. 3. *A*: sex-stratified Kaplan-Meier curves for cardiovascular events in the heart failure with reduced left ventricular ejection fraction (HFrEF) group. This was based on the median BNP levels on admission for female (a) and male (b) patients, as well as on the median BNP levels at discharge for female (c) and male (d) patients, respectively. *B*: sex-stratified Kaplan-Meier curves for cardiovascular events in the heart failure with preserved left ventricular ejection fraction (HFpEF) group. This was based on the median BNP levels on admission for female (e) and male (f) patients, as well as on the median BNP levels at discharge for female (g) and male (h) patients.

Table 2. *Predictors of cardiac event with cardiovascular death and HF admission*

	Female						Male					
	Univariate			Multivariate			Univariate			Multivariate		
Covariate	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95%CI	*P* Value
Age, per 1 y	1.032	(1.016–1.049)	<0.0001	1.015	(0.996–1.033)	0.1189	1.009	(0.997–1.020)	0.1345			
BMI, per 1 kg/m^2	0.986	(0.925–1.043)	0.6390				0.987	(0.923–1.050)	0.6873			
Previous HF hospitalization	2.175	(1.476–3.142)	0.0001	1.549	(1.012–2.323)	0.0442	2.081	(1.557–2.759)	<0.0001	1.814	(1.330–2.454)	0.0002
Hypertension	1.710	(1.099–2.799)	0.0164	1.555	(0.954–2.683)	0.0778	1.125	(0.815–1.588)	0.4814			
Diabetes mellitus	0.972	(0.681–1.371)	0.8719				1.199	(0.913–1.573)	0.1918			
Atrial fibrillation	1.321	(0.932–1.857)	0.1165				1.149	(0.859–1.524)	0.3453			
Heart rate, per 1 beat/min	0.996	(0.981–1.012)	0.6369				1.004	(0.990–1.017)	0.5855			
SBP, per 10 mmHg	0.911	(0.823–1.007)	0.0675				0.946	(0.878–1.017)	0.1351			
LVEF, per 1 %	1.000	(0.989–1.010)	0.9586				0.996	(0.988–1.004)	0.3552			
Log transformed BNP at discharge	1.169	(0.981–1.399)	0.0806				1.343	(1.173–1.535)	<0.0001	1.289	(1.120–1.481)	0.0004
Hemoglobin, per 1 g/dl	0.922	(0.831–1.020)	0.1149				0.923	(0.869–0.979)	0.0072	0.943	(0.883–1.006)	0.0776
Sodium, per 1 mEq/l	0.958	(0.920–1.000)	0.0504				0.993	(0.956–1.032)	0.7053			
eGFR, per 1 ml·min·1.73 m^2	0.994	(0.987–1.000)	0.0484	0.986	(0.976–0.995)	0.0032	0.998	(0.993–1.003)	0.4437			
BUN/Cre ratio	1.035	(1.020–1.051)	< 0.0001	1.044	(1.023–1.064)	< 0.0001	1.015	(1.000–1.029)	0.0539			
β-Blockers	1.137	(0.810–1.597)	0.4570				1.130	(0.857–1.501)	0.3893			
ACE-I/ARBs	0.483	(0.281–0.904)	0.0247	0.413	(0.233–0.789)	0.0092	0.827	(0.471–1.617)	0.5518			
Diuretics	2.257	(1.345–4.108)	0.0014	1.607	(0.875–3.252)	0.1315	1.237	(0.862–1.835)	0.2563			

HR, hazard ratio; CI, confidence interval.

both in the patients with HFpEF and HFrEF. However, we showed that prognostic significance of BNP is differential between the sexes in patients with ADHF, although median levels of BNP were similar in both sexes. BNP levels at discharge were a significant predictor for cardiovascular events in whole patients or in male patients in the present study, but BNP levels were not in female patients, suggesting the prognostic power of BNP is weaker in females than in males in certain populations. The reasons why BNP levels were not significantly associated with cardiovascular events in female patients are not clear, but there would be several possible reasons. First, the sample size is small to reach statistical significance, because the *P* value is 0.0806 in female patients by the univariate Cox regression analysis. Second, the range of plasma BNP levels was small. Even in female patients, when we set 300 pg/ml for a cutoff value, high BNP group had a significantly worse prognosis than the low BNP group in female patients (Log rank $P = 0.0438$), which cannot explain the sex difference of predictive significance of BNP. Third, there existed the difference in medication, especially diuretics, between the sexes. Although absolute dose of loop diuretics was similar in both sexes; the dose of loop diuretics corrected by body surface area tended to be higher in females than in males. In male patients the dose of loop diuretics was lower in HFpEF than in HFrEF, but in female patients the dose of loop diuretics was not changed between HFrEF and HFpEF. Moreover, the ratio of BUN to creatinine was significantly higher in female than in male patients, indicting more hemoconcentration in females. In all these findings, there was a relatively higher overdose of loop diuretics used in female patients than in male patients, which might affect BNP levels at discharge.

In this study, there was no significant difference in plasma BNP levels between the sexes. Until today, some reported the sex difference in plasma levels of BNP or relating peptides in certain populations, but it is still uncertain. Lam et al. (8) reported that NT-proBNP levels in females was higher than those in males in the Framingham Heart study, but Meyer et al. (17) reported that NT-proBNP levels were similar between the sexes in heart failure patients. Masson et al. (14) also reported the higher NT-proBNP levels but similar BNP levels in females than in males in the Valsartan Heart Failure Trial (Val-HeFT) study.

In the present study of either male or female patients, BNP levels on admission were not associated with cardiovascular events. Some earlier reports (12, 28) showed that BNP levels even in the acute phase predict cardiovascular events; others did not (2, 11). In the acute phase of HF, BNP levels are influenced by multifactor compared with those in the chronic phase. Some HF patients suffered from infection at the same time, which may stimulate BNP production through inflammatory cytokine productions, such as IL-6 or IL-1β. Other HF patients were associated with worsening of renal function, which affects BNP levels.

GFR values in this study were lower than those in previous reports (4, 26). We included a relatively large number of hemodialysis patients (6.4%) and slightly higher average age (72.6 years). These may be related to the difference.

The multivariate Cox regression analysis indicates the sex difference in predictive factors, specific to the sex of each patient. In male patients, cardiac factors (i.e., plasma BNP levels and the history of HF admission) were strongly associated with cardiovascular events, rather than in female patients, as were renal factors (i.e., eGFR and BUN/Cre ratio). Given that male patients more likely have HFrEF than HFpEF, it may be plausible that cardiac factors are significant predictors. As above mentioned, a relatively higher overdose of loop diuretics used in female patients rather than in male patients might be related to this difference.

Clinical implication and future direction. Women and men have different clinical courses, and in this study we revealed

sex differences in EF distribution pattern, prognostic significance of plasma BNP levels, and clinical factors that predict cardiovascular events. In the management of ADHF patients, it is necessary to pay attention to sex differences and LV function (reduced EF or preserved EF).

As patients with HF become elderly, the prevalence of HFpEF increases. Because of the widespread primary prevention of ischemic heart disease, the incidence of ischemic heart disease is becoming lower in not only the United States but also Japan. Given these findings, future baseline characteristics of HF will be changed to those similar to current female patients. Thus better understanding of the complex pathophysiology of the sex-oriented difference of HF is one way to make the prognosis of HF better.

Limitations. The present study had following limitations. First, this was a single-center study involving a relatively small number of ADHF patients that included both HFrEF and HFpEF patients. Second, this study was designed as a dynamic cohort and had a relatively short follow-up period than those in previous reports. Third, this study was performed in Japan with Japanese patients, and so we did not assess Western populations.

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AUTHOR CONTRIBUTIONS

Author contributions: Y.N. and T.U. conception and design of research; Y.N. and R.K. performed experiments; Y.N., R.K., T. Nakano, A.T., H.N., and T.U. analyzed data; Y.N. interpreted results of experiments; Y.N. prepared figures; Y.N. and Y.S. drafted manuscript; R.K., T. Nakano, A.T., H.N., T.U., T. Nishida, K.O., T.S., S.O., Y.T., M.W., H.K., H.O., and Y.S. edited and revised manuscript; Y.S. approved final version of manuscript.

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◆Summary
Healthcare Information System. Considerations on existing systems and on the systems in the future
Electronic health records have been widely adopted and they are implemented without special abilities and efforts. In the meantime, state of the art systems in the past have become nuisance in hospitals towards the end of the life cycle. In this article, changing environment and problems of hospital information systems over the past several years were examined. The future of the systems were discussed.

提言

真にあるべきHIS像を示す

HIS―既存システムの考察と今後あるべき姿を考える

真に役立つHIS像とは

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要旨：電子カルテシステムは普及期に入っており、特別な要件を必要とせず導入が可能となっている。一方で、過去に新技術・新システムとして導入されたものが、そのライフサイクルを終えるに際してさまざまな悩みの種となることは少なくない。本稿では、ここ数年間で変化してきた病院情報システムを取り巻く状況と課題に触れ、今後あるべき姿について考察する。

ひところは大病院の先端的取り組みであった電子カルテシステムの導入も、ここ数年のうちに一般化してきた感がある。システム導入手法も院内の知恵を結集させた一大プロジェクトという位置づけから、ベンダーに対価を払ってお任せするのが安心、との認識も増えてきている。「新技術」を使いこなして医療の質を向上させるのか、それとも「新技術」に翻弄され金食い虫として手を焼くのか、新しいものには2つの道が待っている。

本稿では、ここ数年間で変化してきた病院情報システムを取り巻く状況と課題に触れ、今後あるべき姿について考えてみたい。

今、最も気になること

読者の皆さんが、病院情報システムについて最も気になることは何であろうか。医事会計は当然のこと、オーダリングシステムやPACSも、既に数年間は稼働している施設がかなり多いであろう。そのような施設の管理者や経営者が最も気になっているのは、PACSがデータで一杯になりそうだ、だが納得のいく次の手がない、ではないだろうか。

ベンダーの提案は、PACSの容量を現在の1・5倍、あるいは、2倍に増やすこと、ただし、価格も購入した当時の1・5倍である、などであろう。「この先、5年ごとに同様の出費をしなければならないのだろうか？」、「昔は不要なフィルムを廃棄したり倉庫に預けていたのに、PACS内の全てのデータは本当に必要なのだろうか？」など、気になっている方が多いのではないだろうか。

まずは、PACSの価格について考察する。少々乱暴な議論になるが、PACSの購入費用を全データ量で割り算し、1TB当たりの費用を計算していただきたい。どのくらいになるであろうか。1TB当たり100万円程度であろうか。数年前ではそれ以上かもしれない。PACSには画像を管理しているデータベースや画像のビューワ機能があるとはいえ、大雑把な計算である程度の費用感が実感できるであろう。

一方で、市販のNAS（Network Attached Storage）であれば2～3万円／TB、ハードディスク単品なら5000円／TBといったところであろうか。

そもそも放射線画像は、広く標準化が進んでいるDICOM規格であり、画像ファイルはNASにでもハードディスクにでも保存が可能なはずである（電子保存の要件を満たす必要があるが）。画像ファイルを保存して置いておくだけなら、桁の違う費用を払う必要はあるのだろうか。工夫の余地はないのだろ

うか。

この問題は、データ保存手段の決定権が病院にはない、と捉えることもできる。とすると、もう1つの課題である「PACS内の全てのデータは本当に必要なのか?」は、データの要・不要を決定する術が病院にない、と捉えることができる。厳密に言えば、画像ファイルごとの選別は可能であるが、1つひとつ手作業ではデジタル化した意味がない。かといって、ベンダーが「病院が望むように」画像を選別してくれるはずもなく、病院の側も画像データはフィルムのような物理体ではないだけに、手を付け難い。

このようにPACSのような電子化の先鞭となったシステムであっても医療施設の意のままに管理、とはなっていないのが現状である。このことは、新技術を購入しただけでは期待する効果は得られないことを示している。この状況を打破するにはハードウェアを含むシステムのレベル、そして、データのレベルで深い知識と技術を持つ医療者の必要性と医療側の取り組みが必要であろう。

EOLという便利な口実

一番気になることが既存システムにおけるデータ増加への対応であるなら、一番の悩みの元はEOL（End Of Life：販売終了、保守終了）ではないだろうか。EOLは、ハードウェアやソフトウェアといったIT製品であればどの製品にも関係するが、特に医療施設を悩ませるのは、ネットワークインフラやサーバ系のハードウェア・ミドルウェアではなかろうか。

EOLを言い渡す立場は2種類ある。1つは対象の製品を製造している製造企業、もう1つはその製品を販売する、あるいは、その製品を組み込んだ自社製品を販売する企業である。

後者から検討しよう。特に部門システムベンダーが対象となるが、これら企業はサーバハードウェアやデータベースソフトウェアを自社製造していることはまずない。したがってハードウェアやデータベースなど製品の基礎となるものがEOLを迎えると、自ずとそれを利用する部門システムもEOLとなる。

このような構造であるから、部門システムベンダーは病院にEOLを告げることになる。これは自社製品を更新してもらうビジネスチャンスにもつながり、かつ、自分たちが原因ではないので、EOLは格好の口実となっている。告げるベンダーもどことなく嬉しそうに見えるのだが、決まり文句が、「弊社も何とかしたいのですが、製造元のEOLですのでどうすることもできません」である。

もう1つのEOLの宣告者である製造企業はどうであろうか。一般的に企業規模が大きく（通常は世界規模）、EOLの宣告はメール等でやってくる。仮に、担当者がやってきたとしても、「EOLを告げる」以上の機能はないのが通常である。メールや問い合わせ窓口に連絡をしたとしても、EOLの内容を再確認するのみで、機械的に取り扱われるだけである。

さて、EOLへの対策はあるだろうか。我々ユーザーは製造企業ではないので直接のコントロール権はないが、短期的、長期的な対応がいくつか考えられる。短期的なものは部品の供給がある限り、製品の保守を請け負ってくれる企業の存在である。医療に限らずこの手の悩みは世界中にあるので、大小さまざまな企業がこれに参入している。長期的には、理想論になるかもしれないが、自らのシステムに対する理解の向上と部門ベンダーの協力も必要である。

デスクトップPCを例に挙げよう。デスクトップPCにもEOLはある。しかし、このEOLは怖くはない。なぜだろうか。PCに対する知識とその対応策が医療施設のスタッフでも思いつくからである。PCと同じとは言わないが、システムインフラもその延長線上にある。部門ベンダーも基盤製品のEOLを不可避な事項と扱うのではなく、IT・エンジニアリングの視点で代替策の検討や大規模なリプレイスの回避策などを顧客の立場で検討すべきであろう。

最後は、やはり医療施設でのシステムに対するライフサイクルの考え方である。システムの購入前の段階から製品には必ず終わりがあることを認識し、それに対して5年後、あるいは、それ以上後にどのような対応があるか十分に検討し、製品終息時に診療記録資産、および、ワークフロー資産をどのように継続することができるか、複数のプランを練った後に製品を購入すべきである。

「新技術」との付き合い方

IT市場に限らず、どの製品市場もそうな

のかもしれないが、「最新」＝「最良」の方程式が崩れてきている。派手なセールスプロモーションや絵に描いたような事例紹介を鵜呑みにすると後で手痛い目に遭うことになる。ここでは、個別の製品に言及するというよりは「新技術」を採用した製品に対する筆者の考え方を示したい。

まず第一に、システムに「一点豪華主義」はない。システムは定義からして複数の要素が複雑に相互作用する全体構成を指す。したがって、新技術を採用した製品をポンと既存システムに投入しても大きな効果は見込めないどころか、既存機能とのバランスを崩すことにもつながる。

次に、「既存技術との比較」は常に欠かせない。例えば、ハードウェアの仮想化技術はここ数年でかなり普及してきている。ひところは及び腰だった部門ベンダーも、今では積極的に提案に盛り込んでいるようだ。一方で、VDI（Virtual Desktop Infrastructure）に代表される端末仮想化技術はサーバ仮想化技術に比較して医療施設に普及していないように見える。

ここで、VDIに対する既存技術は、物理体デスクトップPCであるので、両者を比較しよう。VDIの利点で強調されるのはセキュリティと管理効率だろうか。セキュリティについては、HISはインターネットに通じていない場合が多く、VDIでのセキュリティの発想とは根本が異なり過剰投資となりがちである。

一方の管理効率はどうであろうか。VDIのサーバインフラによる一元管理は、必ずしも正解とはなり得ない。なぜなら、PCは院内のスタッフにて故障個所の確認から交換や修理まで取り扱えるのに対し、VDIインフラの障害時には院内スタッフには手に負えない高度な技術や、場合により製造元までのエスカレーションを必要とすることがある。

そして最後に価格である。PCの価格が10万円台前半、あるいはそれ以下で調達できるのに対し、VDIのライセンスやインフラ構築費用は端末1台当たりに換算すると、数台分のPCに相当してしまうのが現状である。このように新技術の検討では既存技術との比較を欠かすことができないのである。

その他にも、PACSの既存データの扱いで前述したように、自院にてどこまで対象技術や製品を理解し使いこなすことができるかは、運用中盤から後半にかけて影響が出てくる。そして、EOLにて例を挙げて述べたように、「新技術」のライフサイクルの検討なしに採用することは、後に悩みの種を作るだけである。

イノベーションを阻む善意の取り組み

10年ほど前には、オーダリングシステム、あるいは、電子カルテシステムの院内導入を進める際に「抵抗勢力」が誇らしげに出してきた言葉に「キーボードアレルギー」があった。パソコンを触ったことがない、キーボードの入力ができないので専属スタッフが診察室にて入力補助をしなければシステム導入には反対、といった具合である。今では滑稽な言い訳であるが、当時は理解できる論として真剣に議論されていたものである。

そうしたキーボードアレルギーの人々も希少種となり（別な意味でキーボードに触れたことのない若者は増えているが）、「抵抗勢力」という言葉も懐かしい響きを持つと同時に、そうしたエネルギーを費やせる人々も院内には少なくなっているのでなかろうか。

ここ10年ほどでの医療の中心的な考え方、あるいは現代の医療を象徴する考え方に「医療安全」が挙げられる。筆者も医療安全が専門であり、ITと同じくらい、いやそれよりも長期に医療安全に取り組んできた立場なので医療安全を否定するつもりはない。危惧しているのは、過剰な、あるいは、誤った安全対策手法によってイノベーションあるいは「新しいこと」が阻害されている現状である。

医療安全の重要性が認識されるにつれ、安全の管理組織は人員を増してきた。人員が増えると質の維持が困難になる。残念ながら、医療・医学上の意味を考慮せず、あるいは理解できないスタッフが小役人のように「安全」を唱えながら院内を取り締まって歩くようになる。自ずと、医療スタッフは「今日と全く変わらぬ明日」を望むようになり、それが「安全」と信じる者すら出現する。しかもこれらは「善意の取り組み」である点が扱いを困難にする。

「イノベーション」や「新技術」には、必ず「変化」が伴う。そして「変化」は「リスク」を内在する。「リスク」は「管理」することが重要なのである。安全は医療の必要条件ではあるが十分条件でないこと、思考なき「医療安全」は医療の前進を阻害することを「新