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# Impact of Afterload-Integrated Diastolic Index on Prognosis in Elderly Patients With Heart Failure With Preserved Ejection Fraction With and Without Atrial Fibrillation

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## Abstract

**Objects: We aimed to clarify the differences in the significance of the ratio of diastolic elastance (Ed) to arterial elastance (Ea), [Ed/Ea=(E/e')/(0.9×systolic blood pressure)], an afterload-integrated diastolic index that reflects left atrial pressure overload, on prognosis between patients with heart failure with preserved ejection fraction (HFpEF) with and without atrial fibrillation (AF).**

**Methods: We studied 552 HFpEF patients hospitalized for acute decompensated heart failure (sinus rhythm/AF:352/200). Blood testing and transthoracic echocardiography were performed before discharge. Primary endpoint was all-cause mortality after discharge.**

**Results: During a median follow-up of 508 days, 88 patients (sinus rhythm/AF: 54/34) had all-cause mortality. In the subgroup with sinus rhythm, but not AF, Ed/Ea was significantly higher in patients with than without all-cause mortality. In a multivariate Cox hazard analysis, Ed/Ea was significantly associated with all-cause mortality independent of N-terminal pro-brain natriuretic peptide level in patients with sinus rhythm, but not with AF.**

**Conclusions: Ed/Ea provided lesser important information for predicting all-cause mortality in HFpEF patients with AF than with sinus rhythm. The prognostic risk factors may differ between elderly HFpEF patients with and without AF.**

## Introduction

Assessment of diastolic function using a combination of several indices based on the recommendations for left ventricular (LV) diastolic evaluation by echocardiography is useful for estimating the prognosis of patients with heart failure with preserved ejection fraction (HFpEF) [1-3]. Patients with HFpEF have an increased left atrial volume (LAV), an index of LA volume overload, and an increased E/e', an index of LA pressure overload [4-6]. E/e' is correlated with invasive LV filling pressure and adequate reproducibility even in patients with atrial fibrillation (AF) [7].

## Key Words

Atrial Fibrillation, Diastolic Function, Left Atrial Overload, NT-proB-NP

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LV diastolic elastance (Ed) is expressed as (E/e')/stroke volume (SV)[8] or (E/e')/LV end-diastolic volume [9]. Arterial elastance (Ea) is calculated as (0.9 × systolic blood pressure)/SV [8]. We previously reported the ratio of Ed to Ea as a novel index of the LV diastolic function relative to afterload, which can be calculated as (E/e')/(0.9 × systolic blood pressure) where the Ed is (E/e')/SV [10,11]. Ed/Ea is positively correlated with pulmonary capillary wedge pressure and exhibits an LA pressure relative to the systemic pressure[12]. Thus, the Ed/Ea ratio may be an index reflecting the left-sided heart function including the atrio-ventriculo-arterial interaction under a preserved LV ejection fraction. We recently reported that Ed/Ea may be a useful independent determinant of all-cause mortality in elderly patients with HFpEF[13]. This study aimed to clarify the differences in the role of Ed/Ea on prognosis in patients with HFpEF with and without AF.

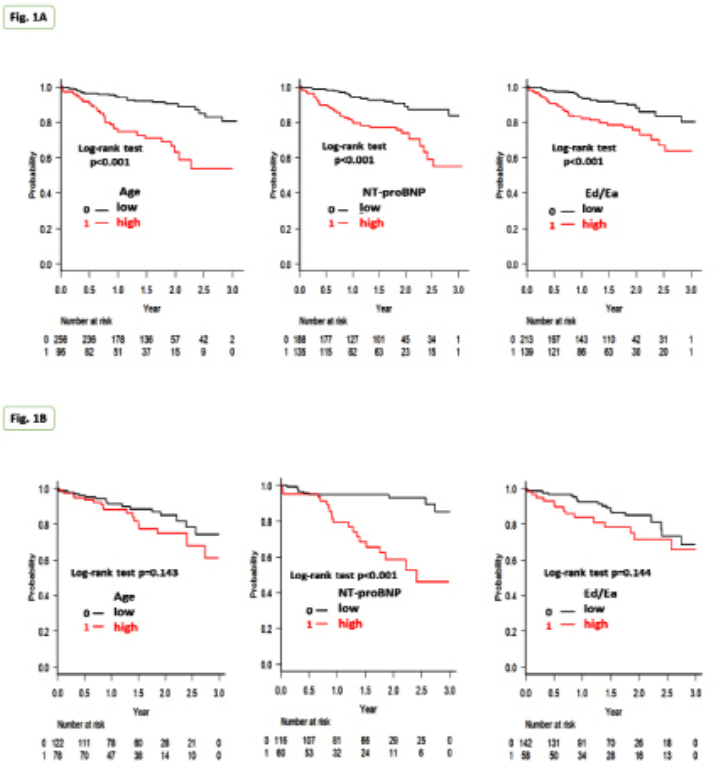


**Figure 1:** **Kaplan–Meier survival curve analysis of patients with heart failure with preserved ejection fraction. (A) Patients with sinus rhythm: Age >86 years, N-terminal pro-brain natriuretic peptide (NT-proBNP) >1,220 pg/mL, and ratio of diastolic elastance (Ed)/arterial elastance (Ea) >0.132 were significant factors for all-cause mortality. (B) Patients with atrial fibrillation: NT-proBNP > 2,081 pg/mL, but not Age >84 years or Ed/Ea >0.144, was a significant factor for all-cause mortality.**

## Methods

### Study subjects

Of 637 patients with prognostic data recruited from the Prospective Multicenter Observational Study of Patients with Heart Failure with Preserved Ejection Fraction (PURSUIT HFpEF) registry, we excluded 85 with missing or poor echocardiographic data. Therefore, we enrolled 552 patients (LV ejection fraction ≥50%; men/women, 255/297; sinus/AF 352/200; mean age, 81 years) at discharge during the index hospitalization for HF. The PURSUIT HFpEF registry is a prospective, multicenter observational registry in which collaborating hospitals in the Osaka region of Japan record clinical, echocardiographic, and outcome data of patients with HFpEF (UMIN-CTR ID: UMIN000021831) [6,14]. This registry is managed in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the ethics committee of each participating hospital and all participants provided written informed consent.

### Echocardiography and laboratory testing

Transthoracic echocardiography was performed when patients were in a stable condition before discharge. Echocardiographic measurements were obtained according to American Society of Echocardiography (ASE) or European Society of Echocardiography guidelines [1,15]. Volumetry was standardized using the modified Simpson's method and the index was calculated as LAV divided by the body surface area. As a marker of LA pressure overload for estimating LV diastolic function, we examined afterload-integrated Ed/Ea [(E/e')/(0.9 × systolic blood pressure)] [6,11,16]. As relative markers of LAV overload, we evaluated LAVI and the ratio of stroke volume (SV) to LAV [12]. Serum N-terminal pro-brain natriuretic peptide (NT-proBNP) and albumin levels, hemoglobin concentration, and estimated glomerular filtration rate (eGFR) were also examined when patients were stable before discharge.

### Follow-up/clinical outcome

After discharge, all patients were followed-up at each hospital. Survival data were obtained by dedicated coordinators and investigators through direct contact with patients and their physicians at the hospital, in an outpatient setting, via telephone interview with their families, or by mail. The primary endpoint of this study was all-cause mortality.

### Statistical analysis

Continuous variables are expressed as means ± standard deviations, whereas categorical variables are presented as frequencies and

**Table 1:** **Clinical characteristics before discharge in patients with heart failure with preserved ejection fraction with and without all-cause mortality**

| | Sinus rhythm | | P value (- vs. +) | Atrial fibrillation | | P value (- vs. +) |
|---|---|---|---|---|---|---|
| | All-cause mortality | | | All-cause mortality | | |
| | - (n = 298) | + (n = 54) | | - (n = 166) | + (n = 34) | |
| Age, years | 79 ± 10 | 86 ± 8 | <0.001 | 82 ± 7 | 84 ± 7 | 0.043 |
| Male sex, n (%) | 132 (44) | 22(41) | 0.628 | 84 (51) | 17 (50) | 0.949 |
| Systolic blood pressure, mmHg | 122 ± 17 | 123 ± 20 | 0.713 | 116 ± 16 | 116 ± 17 | 0.879 |
| Diastolic blood pressure, mmHg | 65 ± 11 | 66 ± 11 | 0.819 | 66 ± 12 | 64 ± 11 | 0.411 |
| Heart rate, bpm | 70 ± 12 | 73 ± 14 | 0.217 | 72 ± 15 | 75 ± 14 | 0.254 |
| Coronary artery disease, n (%) | 65 (22) | 12 (22) | 0.946 | 31 (19) | 10 (29) | 0.157 |
| Diabetes mellitus, n (%) | 107 (36) | 20 (37) | 0.873 | 58(35) | 9 (26) | 0.341 |
| Dyslipidemia, n (%) | 138 (46) | 18 (33) | 0.077 | 65 (39) | 13 (38) | 0.920 |
| Hypertension, n (%) | 256 (86) | 50 (93) | 0.261 | 147 (89) | 24 (71) | 0.007 |
| N-terminal pro-brain natriuretic peptide, pg/mL | 2,479 ± 5,566 | 4,842 ± 13,163 | 0.034 | 1,995 ± 3,003 | 3,826 ± 2,817 | 0.002 |
| Echocardiographic data | | | | | | |
| LAD, mm | 42 ± 7 | 41 ± 8 | 0.797 | 48 ± 9 | 48 ± 7 | 0.656 |
| LAVI, mL/m² | 48 ± 21 | 57 ± 32 | 0.014 | 62 ± 26 | 61 ± 20 | 0.768 |
| SV/LAV | 0.80 ± 0.37 | 0.78 ± 0.56 | 0.709 | 0.56 ± 0.31 | 0.56 ± 0.28 | 0.926 |
| LVEF, % | 60 ± 8 | 59 ± 9 | 0.269 | 61 ± 7 | 61 ± 7 | 0.789 |
| Ed/Ea | 0.125 ± 0.052 | 0.150 ± 0.057 | 0.001 | 0.125 ± 0.045 | 0.141 ± 0.054 | 0.071 |
| Medications | | | | | | |
| Beta-blockers, n (%) | 159 (53) | 29 (54) | 0.962 | 93 (56) | 22 (65) | 0.420 |
| Calcium-channel blockers, n (%) | 167 (56) | 32 (59) | 0.661 | 75 (45) | 16 (47) | 0.841 |
| Diuretics, n (%) | 238 (80) | 44 (81) | 0.784 | 147 (89) | 32 (94) | 0.335 |
| RAAS inhibitors, n (%) | 212 (71) | 39 (72) | 0.871 | 132 (80) | 25 (74) | 0.438 |
| Statins, n (%) | 108 (36) | 19 (35) | 0.881 | 50 (30) | 10 (29) | 0.934 |

Values are mean ± standard deviation or number (%).
LAD, left atrial diameter; LAVI, left atrial volume index; SV, stroke volume; LAV, left atrial volume; LVEF, left ventricular ejection fraction; Ed, diastolic elastance; Ea, arterial elastance.

**Table 2: Analytical data of prognostic factors for all-cause mortality in patients with heart failure with preserved ejection fraction showing sinus rhythm**

| | | | Cox hazard analysis | | | | | |
|---|---|---|---|---|---|---|---|---|
| | ROC curve analysis | | Univariate | | | Multivariate | | |
| | Cutoff point | AUC | Ratio | 95% CI | P value | Ratio | 95% CI | P value |
| Age | 86 years | 0.721 | 3.812 | 2.228-6.523 | <0.001 | 3.491 | 1.948-6.257 | <0.001 |
| Sex | - | - | 0.919 | 0.533-1.582 | 0.761 | 1.191 | 0.659-2.149 | 0.562 |
| NT-proBNP | 1,220 pg/mL | 0.681 | 3.322 | 1.859-5.936 | <0.001 | 2.755 | 1.512-5.021 | <0.001 |
| LAVI | 46 mL/m$^2$ | 0.578 | 1.407 | 0.804-2.46 | 0.231 | 0.884 | 0.485-1.612 | 0.689 |
| Ed/Ea | 0.132 | 0.642 | 2.517 | 1.456-4.351 | <0.001 | 1.835 | 1.019-3.305 | 0.043 |

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; NT-proBNP, N-terminal pro-brain natriuretic peptide; LAVI, left atrial volume index; Ed, diastolic elastance; Ea, arterial elastance.

percentages. Differences in categorical variables between the groups were assessed using chi-square tests, while those in continuous variables were assessed using Student's t- or Welch's t-tests, as appropriate. Correlations were assessed using Pearson or Spearman coefficients and p-values were examined using regression analysis. Cutoff points of prognostic factors for all-cause mortality were evaluated using receiver operating characteristic (ROC) curve analysis. Survival curves were estimated using the Kaplan–Meier survival analysis and the groups were compared using log-rank test. The Cox hazard ratio was evaluated in univariate and multivariate analyses. P-values <0.05 were considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

## Results

### Clinical and laboratory characteristics of patients with HFpEF

During a median follow-up of 508 days, 88 patients (sinus rhythm/AF 54/34) had all-cause mortality. We observed significant differences between patients showing sinus rhythm with and without all-cause mortality in terms of age (p<0.001) and serum NT-proBNP level(p=0.034) (Table 1). We observed no significant differences in medications or the incidence of hypertension, diabetes mellitus, dyslipidemia, and coronary artery disease between the two groups. In contrast, the incidence of hypertension was significantly lower in AF patients with than without all-cause mortality. We observed no significant differences in age, NT-proBNP level, incidence of coronary artery disease, diabetes mellitus and dyslipidemia, or medication use between AF patients with and without all-cause mortality.

With respect to echocardiographic parameters, LAVI (p=0.014) and Ed/Ea (p=0.001)—but not SV/LAV, or LV ejection fraction—at discharge differed significantly between patients with and without all-cause mortality showing sinus rhythm (Table 1). In contrast, patients with AF showed no significant differences in LAVI and Ed/Ea between those with and without all-cause mortality (Table 1). Although the data are not shown, the deceleration time of the E wave, septal e', lateral e', and E/A did not differ significantly between the groups.

In patients with sinus rhythm, the NT-proBNP log-transformed level was modestly correlated with echocardiographic indices such as LAVI (r=0.244, p<0.001), SV/LAV (r=0.224, p<0.001), and Ed/Ea (r=0.182, p<0.001). In contrast, the NT-proBNP log-transformed level was more modestly correlated with LAVI (r=0.203, p=0.011) and Ed/Ea (r=0.148, p=0.049) in those with AF. Evaluations of the correlations between the indices of LA pressure and volume overload showed that Ed/Ea was modestly correlated with LAVI in patients with sinus rhythm (r=0.231, p<0.001), but not with AF (r=0.009, p=0.905).

### Prognostic analysis

The areas under the curve and cutoff points of each parameter were evaluated in ROC curve analysis for the prediction of all-cause mortality. The cutoff point for age was lower but those of NT-proBNP, Ed/Ea and LAVI were higher in patients with AF than those with sinus rhythm (Tables 2, 3). Although NT-proBNP level was a significant prognostic factor in patients with sinus rhythm (p<0.001) or AF (p<0.001) by Kaplan–Meier survival analysis, age (p<0.001) and Ed/Ea (p<0.001) were significant only in those with sinus rhythm (Figure 1). Although not shown, Ed/Ea was a modest prognostic factor even in patients with AF, when the prognosis was evaluated for the first year after enrollment by Kaplan-Meier survival analysis (p=0.050). In a multivariate Cox hazard analysis, Ed/Ea and NT-proBNP were independent predictors of prognosis in sinus rhythm after adjusting for age, sex, and LAVI (Table 2). However, NT-proBNP, but not Ed/Ea, was independently associated with prognosis in AF patients after adjusting for age and sex (Table 3).

### Differences in clinical characteristics between patients with and without AF

Although we observed no differences in all-cause mortality, age, and male sex between patients with and without AF, systolic blood pressure (p<0.001) was significantly lower and albumin level (p=0.008) and hemoglobin concentration (p<0.001) were significantly higher in patients with AF as compared to those in patients without AF (Table 4). In echocardiographic findings, the indices of LA volume overload such as left atrial dimension, LAVI, and SV/LAV differed significantly between patients with and without AF (p<0.001 for all).

**Table 3: Analytical data of prognostic factors for all-cause mortality in patients with heart failure with preserve dejection fraction showing atrial fibrillation**

| | | | Cox hazard analysis | | | | | |
|---|---|---|---|---|---|---|---|---|
| | ROC curve analysis | | Univariate | | | Multivariate | | |
| | Cutoff point | AUC | Ratio | 95% CI | P value | Ratio | 95% CI | P value |
| Age | 84 years | 0.600 | 1.646 | 0.839-3.227 | 0.146 | 1.108 | 0.488-2.511 | 0.806 |
| Sex | - | - | 0.956 | 0.488-1.875 | 0.897 | 1.009 | 0.463-2.193 | 0.982 |
| NT-proBNP | 2,081 pg/mL | 0.755 | 5.545 | 2.514-12.23 | <0.001 | 5.651 | 2.374-13.45 | <0.001 |
| LAVI | 55 mL/m$^2$ | 0.528 | 0.897 | 0.436-1.845 | 0.767 | 0.916 | 0.422-1.986 | 0.825 |
| Ed/Ea | 0.144 | 0.589 | 1.659 | 0.835-3.298 | 0.148 | 1.388 | 0.622-3.094 | 0.423 |

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; NT-proBNP, N-terminal pro-brain natriuretic peptide; LAVI, left atrial volume index; Ed, diastolic elastance; Ea, arterial elastance.

**Table 4: Differences in patient characteristics with and without atrial fibrillation**

| | Atrial fibrillation | | P value (- vs. +) |
|---|---|---|---|
| | - (n = 352) | + (n = 200) | |
| All-cause death, n (%) | 54 (15) | 34 (17) | 0.608 |
| Age, years | 81 ± 10 | 82 ± 7 | 0.057 |
| Male sex, n (%) | 154 (44) | 101 (51) | 0.126 |
| Systolic blood pressure, mmHg | 122 ± 18 | 116 ± 16 | <0.001 |
| Diastolic blood pressure, mmHg | 65 ± 11 | 66 ± 12 | 0.825 |
| Heart rate, bpm | 71 ± 13 | 73 ± 15 | 0.075 |
| Laboratory data | | | |
| Albumin, g/dL | 3.4 ± 0.5 | 3.5 ± 0.4 | 0.008 |
| eGFR, mL/min/1.73 m² | 42.2 ± 20.8 | 43.4 ± 15.2 | 0.507 |
| Hemoglobin, g/dL | 11.1 ± 1.9 | 11.8 ± 2.0 | <0.001 |
| N-terminal pro-brain natriuretic peptide, pg/mL | 2,860 ± 7,392 | 2,296 ± 3,050 | 0.335 |
| Echocardiographic data | | | |
| LAD, mm | 42 ± 7 | 48 ± 9 | <0.001 |
| LAVI, mL/m² | 50 ± 23 | 62 ± 25 | <0.001 |
| SV/LAV | 0.79 ± 0.40 | 0.56 ± 0.31 | <0.001 |
| LVEF, % | 60 ± 8 | 61 ± 7 | 0.235 |
| Ed/Ea | 0.129 ± 0.053 | 0.127 ± 0.047 | 0.652 |

Values are mean ± standard deviation.
eGFR, estimated glomerular filtration rate; LAD, left atrial diameter; LAVI, left atrial volume index; SV, stroke volume; LAV, left atrial volume; LVEF, left ventricular ejection fraction; Ed, diastolic elastance; Ea, arterial elastance.

However, the indices of LA pressure overload such as Ed/Ea did not differ between the two groups. The incidence of coronary artery disease, hypertension, diabetes mellitus and dyslipidemia was not significantly different between the two groups (data not shown).

## Discussion

The Ed/Ea, an afterload-integrated diastolic index that reflects LA pressure overload, provided lesser additional prognostic information to the serum NT-proBNP level for predicting all-cause mortality in HFpEF patients with AF than in those without AF. The prognostic risk factors may differ between elderly HFpEF patients with and without AF.

Since albumin level and hemoglobin concentration were significantly higher, and systolic blood pressure was significantly lower in patients with AF than those in patients without AF, volume reducing therapy may be more prominent in patients with AF than that of those without AF at recruitment. This issue would be related to the lack of difference in all-cause mortality between patients with and without AF. As a matter of cause, the indices of LA volume overload were significantly higher in patients with AF than those in patients without AF.

Notably, we observed no significant differences in the indices of LA pressure overload such as Ed/Ea between the patients with and without AF, and between AF patients with and without all-cause mortality. In patients with AF, the variability of the LA enlargement could bring a compensatory mechanism to maintain LA pressure. Accordingly, further increase in LA volume may not elevate LA pressure when the hemodynamic state worsens after enrollment in patients with AF. In other words,the alterations of LA pressure overload accompanying with hemodynamic changes would be different between the patients with and without AF. Therefore, indices of LA pressure overload such as Ed/Ea would be less prominent as a determinant factor of prognosis in patients with AF. Furthermore, LV diastolic dysfunction may be already related to the occurrence of AF per se in HFpEF patients with AF.The prognostic role of LA pressure overload resulting from LV diastolic dysfunction, was offset in the patients with AF, but not without AF, resulting in less prognostic role of Ed/Ea in patients with AF. These issues were reflected in the higher cutoffs of NT-proBNP and LAVI for prognosis in patients with AF than in those in patients without AF. Because there was a significant difference in the incidence of hypertension between AF patients with and without all-cause mortality, but not between those showing sinus rhythm with and without all-cause mortality, the genesis of death may differ between HFpEF patients with and without AF. Thromboembolic events may be important in the causes of death in patients with AF.

## Limitations

We examined all-cause mortality rather than cardiac death because the determination of cardiac death can be difficult in elderly patients. One must pay attention to measure E/e' by echocardiography in patients with AF [14]. The factors affecting the reproducibility of echocardiographic measurements included the ratio of preceding to pre-preceding cycle length and heart rate during image acquisition. The mean heart rate in our AF patients was 73 beats/min, which is optimal for guideline recommendation of cycle lengths equivalent to a heart rate range of 60–80 beats/min.

## Conclusions

The Ed/Ea [(E/e')/(0.9 × systolic blood pressure)], an afterload-integrated diastolic index that reflects LA pressure overload, provided lesser important information for evaluating all-cause mortality in HFpEF patients with AF than with sinus rhythm. The prognostic risk factors may differ between elderly HFpEF patients with and without AF.

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