Improved Diastolic Function Is Associated With Higher Cardiac Output in Patients With Heart Failure Irrespective of Left Ventricular Ejection Fraction

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Background—Little is known regarding the impact of diastolic function on cardiac output (CO) in patients with heart failure, particularly in patients with lower ejection fraction. This study aimed to evaluate the impact of end-diastolic pressure–volume relationship (EDPVR) on CO and end-diastolic pressure (EDP).

Methods and Results—We retrospectively analyzed 1840 consecutive patients who underwent heart catheterization. We divided patients into 8 groups according to ejection fraction (EF) (35–45%, 46–55%, 56–65%, and 66–75%) and EDP (>16 or ≤16 mm Hg). We estimated EDPVR from single measurements in the catheterization data set. Then, we replaced EDPVRs of high-EDP groups with those of normal-EDP groups and compared CO before and after EDPVR replacement. Normalized EDPVR significantly increased CO at EDP=10 mm Hg regardless of EF (EF 35–45%, from 4.5±1.6 to 4.9±1.0; EF 46–55%, 4.6±1.3 to 5.1±1.1; EF 56–65%, 4.9±1.5 to 5.2±1.0; EF 66–75%, 4.9±1.5 to 5.2±1.1). Changes in CO were similar across EF groups.

Conclusions—Diastolic function normalization was associated with higher CO irrespective of EF. Diastolic dysfunction plays an important role in determining CO irrespective of EF in heart failure patients. (J Am Heart Assoc. 2017;6:e003389. DOI: 10.1161/JAHA.116.003389.)

Key Words: cardiac output • diastolic dysfunction • heart failure

Diastolic dysfunction of the left ventricle is one of the major pathological factors in heart failure (HF). However, evaluation of diastolic dysfunction is insufficient because of methodological difficulty. Annually, 5.1 million people have HF, and the medical cost accounts for $31 billion dollars in the United States. The prevalence of HF with preserved ejection fraction (HFpEF), which accounts for more than 50% of HF cases, has been increasing. The prognosis of HF is devastating. Diastolic dysfunction has been considered a major pathological factor of HFpEF, but because there has been increased focus on several other comorbid conditions that might contribute to HFpEF pathogenesis such as arterial stiffness, diabetes mellitus and anemia, elevated peripheral vessel resistance, left atrial dysfunction, and baroreflex dysfunction, the influence of diastolic dysfunction on pathophysiology in HFpEF patients is not evaluated precisely. Additionally, the impact of diastolic dysfunction on disease pathophysiology is unknown in not only patients with HFpEF but also those with HF with reduced ejection fraction (HFrEF). In HFrEF patients, the combination of systolic dysfunction and diastolic dysfunction makes it more difficult to evaluate the impact of diastolic dysfunction on the hemodynamic pathophysiology. The evaluation of diastolic function in clinical settings is practically limited and mainly depends on echocardiographic examination. Echocardiographic assessment of diastolic function is insufficient to determine the diastolic property of the left ventricle, because heart rate, fluid retention/depletion, and several conditions might change diastolic filling pattern on Doppler echocardiography or annular diastolic velocity pattern on tissue Doppler imaging. While end-diastolic pressure-volume relationship (EDPVR) represents the diastolic property of the left ventricle, measuring EDPVR is not practical in the clinical setting, since it requires perturbing preload or afterload during recording instantaneous left ventricular volume and its

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Methods

Study Design and Patient Selection

The ethics committee of Aso-Iizuka Hospital approved all study protocols; the requirement for informed consent was waived because of the retrospective nature of the study. We retrospectively examined the impact of the diastolic property on hemodynamics in 2417 consecutive patients who underwent cardiac catheter examination on both sides of the heart from January 2003 to December 2013. We analyzed patient etiology, underlying diseases, and sex distribution. End-systolic volume (ESV), end-diastolic volume (EDV), and left ventricular ejection fraction (EF) were derived from left ventriculography. CO was calculated by multiplying (EDV−ESV) by heart rate (HR). We removed incomplete data and the 10 patients who had the largest or smallest systolic aortic pressure, left ventricular pressure, left ventricular EDV, or ESV as outliers. We removed patients with EF <35% or >75% due to the small number of samples. The final number of patients included in the data set was 1840. Then, we classified the patients into 4 groups according to EF: 35% to 45% (n=280), 46% to 55% (n=345), 56% to 65% (n=564), and 66% to 75% (n=651). Then, we divided each group into 2 subgroups according to end-diastolic pressure (EDP): a high-EDP group (EDP ≥16 mm Hg) and normal-EDP group (EDP <16 mm Hg), as previously reported (Figure 1).

Estimated Diastolic Pressure From a Single Data Set of EDV and EDP

We estimated EDPVR by referring to previous articles employing a single set of EDV and EDP data. Briefly, EDPVR is considered generally invariant among subjects after normalization of volumes. EDPVR after normalizing LV volume axis was expressed by the following equation,

\[ \text{EDP} = A_n \cdot \text{EDV}_n^{B_n} \]

where \( \text{EDV}_n \) is normalized EDV and \( A_n \) and \( B_n \) are coefficient values of 27.8 mm Hg and 2.76 (no units), respectively. Then we calculated EDV at EDP=0, 15, and 30 mm Hg (\( V_0 \), \( V_{15} \), and \( V_{30} \)) based on previous reports as follows:

\[ V_u = V_m \cdot (0.6 - 0.0006 \cdot P_m) \]
\[ V_{30} = V_u + \frac{(V_m - V_u)}{(P_m/A_n)^{b_n}} \]
\[ V_{15} = 0.8 \cdot (V_{30} - V_u) + V_u \]

where \( V_m \) and \( P_m \) are the measured EDV and EDP. Then, coefficients of diastolic properties \( \beta \) and \( \alpha \) were calculated according to the following equations:

\[ \beta = \frac{\log(P_m/30)}{\log(V_m/V_{30})}, \quad \alpha = \frac{30}{V_{30}^\beta} \]

Finally, we estimated each EDPVR as

\[ \text{EDP} = \alpha \cdot \text{EDV}^\beta \]

where \( \alpha \) and \( \beta \) represent coefficients of diastolic properties. We compared EDV at EDP=0, 15, and 30 mm Hg between the high-EDP and normal-EDP subgroups in each EF group (Figures 2 and 3).

Calculation of Cardiac Output

CO is theoretically determined by the following formula:

\[ \text{CO} = \frac{E_{es}}{E_{es} + E_a} \cdot (\text{EDV} - V_0) \cdot \text{HR} \]

where \( E_{es} \) is left ventricular end-systolic elastance, \( E_a \) is the effective arterial elastance, and \( V_0 \) is the theoretical volume at zero pressure. To simplify the calculation, we considered \( V_0 \) as zero and used 0.9 times peak systolic arterial pressure as the arterial end-systolic pressure as the arterial end-systolic pressure, which is required to determine \( E_{es} \) and \( E_a \). Thus, combining those 2 equations, CO is expressed as follows using \( \alpha \) and \( \beta \):

\[ \text{CO} = \frac{E_{es}}{E_{es} + E_a} \cdot \left( \frac{\text{EDP}}{\alpha} \right)^{\beta} \cdot \text{HR} \]

First, we calculated mean diastolic parameters (ie, \( \alpha \) and \( \beta \)) of the normal-EDP subgroup in each EF group and replaced the diastolic parameters of the high-EDP subgroup with those of the normal diastolic group. Thus, we mathematically restored diastolic properties to clarify the impact on the hemodynamics. We then compared COs at EDP=10 mm Hg between before and after changing diastolic parameters in the high-EDP group.

Statistical Analysis

Statistical analyses were performed using SAS statistical software version 9.2 (SAS Institute, Inc., Cary, NC) and Microsoft Excel 2010 (Microsoft Corp., Redmond, WA). We
compared hemodynamic variables of the 8 groups by using Kruskal–Wallis analysis of variance. We used the Wilcoxon rank–sum test to analyze data among the same EF groups. Categorical variables are expressed as numbers and percentages. The \( \chi^2 \) test was used for comparisons of categorical variables. Data are expressed as mean±SD in Table and mean±SE in Figure 4.

**Results**

**Comparison of EDPVR Between High-EDP and Normal-EDP Subgroups**

The characteristics of the study population and hemodynamic variables are detailed in Table. There was no significant difference in age and sex. Mean age was around 70 years old, and 28% to 38% of patients were female. The prevalence of ischemic heart disease was not significantly different among EF groups. The prevalence of ischemic heart disease was more than 60% in all EF groups. The percentages of patients with diabetes mellitus, mitral regurgitation, and diastolic cardiomyopathy were lower in higher EF groups. Percentage of patients with hypertrophic cardiomyopathy showed a reverse trend.

Higher EF groups tended to have higher left ventricular (LV) peak systolic pressure, lower HR, smaller LV ESV, and smaller LV EDV. Within the same EF groups, high-EDP groups tended to have higher LV pressures and volumes. Estimated \( V_{15} \), \( V_{30} \), and \( V_{30} \) were smaller in the high-EDP subgroup than in normal-EDP subgroup regardless of EF. The lower EF groups tended to have greater \( V_{15} \), \( V_{30} \), and \( V_{30} \). Figure 3 shows mean EDV and EDP and the estimated EDPVR of each EF group. EDPVR shifted toward the right, which indicated enlarged LV volume as EF was reduced. Within the same EF groups, EDPVRs in high-EDP groups (dashed line) were steeper than those in normal-EDP groups (solid line). The calculated coefficients \( \alpha \) and \( \beta \) values were higher in patients in the EDP-elevated group than in patients in the normal-EDP group.

**Change in Cardiac Output Before and After Normalizing EDPVR**

COs at EDP=10 mm Hg before and after changing diastolic properties are shown in Figure 4. Normalizing diastolic properties in high-EDP groups significantly increased CO in all EF groups (4.5±1.6 to 4.9±1.0 L/min in EF 35–45% group, 4.6±1.3 to 5.1±1.1 L/min in EF 46–55% group, 4.9±1.5 to 5.2±1.0 L/min in EF 56–65% group, and 4.9±1.5 to 5.2±1.1 L/min in EF 66–75% group) (Figure 4A). The degrees of increase in CO were similar among all EF groups (Figure 4B).
Discussion

This study revealed that diastolic dysfunction plays a similar role in the pathophysiology of HF in patients with high EDP irrespective of EF. In addition, this study demonstrates that the mathematical estimation of EDPVR is feasible and may be an attractive tool for evaluating the contribution of diastolic function to hemodynamics.

Hemodynamic Characteristics and EDPVR According to EF and EDP Subsets

The present study demonstrated that CO was consistently preserved even in HF patients with lower EF. Borlaug et al also reported that CO was preserved even in HFP EF patients. Moreover, Schwartzenberg et al reported that CO was increased in HFP EF patients. These findings support our results and suggest that the mathematical CO estimation is adequate for clinical use. Meanwhile, within each EF group, EDPVRs of the high-EDP subgroup were shifted left and steeper compared with the normal-EDP subgroup (Figure 3). This report is the first to reveal how EDPVR differs according to EDP.

Change in Cardiac Output After EDPVR Normalization in the High-EDP Group

Diastolic dysfunction, which is the key pathophysiological mechanism in HFP EF, is also considered a potential pathophysiological factor of HFrEF. In the present study, EDPVR normalization was significantly associated with higher CO regardless of EF in high-EDP patients. Furthermore, there were no differences in the degree of change in CO among EF groups, suggesting that diastolic dysfunction exerts a similar hemodynamic effect regardless of EF. Although several previous articles have mentioned the importance of diastolic dysfunction in HFrEF, this study is the first to demonstrate its quantitative impact on CO. This finding highlights the profound impact of diastolic dysfunction on hemodynamics in patients with HFrEF.

Previous studies used the same single-point EDPVR estimation method as we used in the current study. In those studies, α and β were defined as the diastolic curve fitting constant and stiffness constant, respectively. Those studies reported that the both α and β values were significantly different between HFP EF and HFrEF. It is difficult to distinguish the effect of each specific coefficient on diastolic function. Therefore, we changed both coefficients in the current study to clarify the effect of diastolic properties.

In the guideline of management of HF, it is mentioned that abnormalities of systolic and diastolic dysfunction

Figure 2. Estimated entire EDPVR and end-diastolic volumes (EDVs) at end-diastolic pressure (EDP) of 0, 15, and 30 mm Hg (V_u, V_15, and V_30, respectively). V_u, V_15, and V_30 are plotted in blue dots. Measured (EDV, EDP) is plotted in red dot. EDPVR values superimposed. EDP = α EDV^β, where α and β represent coefficients of diastolic properties. EDPVR, end-diastolic pressure–volume relationship.

Figure 3. Calculated EDPVRs and single sets of (mean EDV, mean EDP). Calculated EDPVRs and single sets of (mean EDV, mean EDP) are plotted (squares) in (A through D). Solid lines indicate EDPVRs of normal EDP subgroups and dashed lines indicate EDPVRs of elevated EDP subgroups. In lower EF groups, EDVs are larger than that of higher EF groups. EDPVRs from elevated EDP subgroups are shifted upward compared to EDPVRs from normal EDP subgroups. EDP indicates end-diastolic pressure; EDPVR, end-diastolic pressure–volume relationship; EDV, end-diastolic volume; EF, ejection fraction; LV, left ventricular.
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independently of EF. Although specific therapies for diastolic dysfunction are lacking, the guideline\textsuperscript{28} recommends systolic and diastolic blood pressure control, correcting volume overload status, coronary revascularization for patients with coronary artery disease, and atrial fibrillation management. These recommendations also might be beneficial for HF patients with low EF.

The previous studies reported that diastolic function is impaired in the female\textsuperscript{29} and aged\textsuperscript{30} patients. Other studies showed that diabetes mellitus\textsuperscript{31} and hypertension\textsuperscript{32} were the

Table. Characteristics of Study Population and Hemodynamic Variables

|                        | EF=40% | EF=50% | EF=60% | EF=70% | P Value* |
|------------------------|--------|--------|--------|--------|----------|
| EDP elevation          | -      | +      | -      | +      | -        |
| N                      | 167    | 113    | 219    | 126    | 406      |
| Age, y                 | 69.0±11.4 | 69.6±11.9 | 69.8±10.9 | 68.9±13.3 | 66.8±12.9 |
| Female sex, n (%)      | 65 (38.9) | 32 (28.3) | 62 (28.3) | 49 (38.9) | 137 (33.7) |
| Body weight, kg        | 552±11.7 | 577.7±11.1 | 568.8±11.4 | 585.5±12.1 | 581.1±11.6 |
| Heart rate, bpm        | 73±17  | 73±15  | 72±17  | 71±16  | 69±15  |
| LV peak systolic pressure, mm Hg | 120±25  | 130±28\textsuperscript{T} | 124±25  | 140±31\textsuperscript{T} | 130±25 |
| LV end-diastolic pressure, mm Hg | 10±4  | 21±5\textsuperscript{T} | 10±4  | 20±4\textsuperscript{T} | 10±3  |
| LV end-systolic volume, mL | 97±36  | 106±39  | 70±22  | 75±24  | 50±17  |
| LV end-diastolic volume, mL | 164±58  | 177±61  | 140±43  | 150±46  | 128±41  |
| Underlying diseases    |        |        |        |        |          |
| Hypertension, n (%)    | 86 (51.5) | 53 (46.9) | 124 (56.6) | 72 (57.1) | 214 (52.7) |
| Diabetes mellitus, n (%) | 49 (29.3) | 32 (28.3) | 47 (21.5) | 31 (24.6) | 83 (20.4) |
| Etiology               |        |        |        |        |          |
| Ischemic heart disease, n (%) | 107 (64.1) | 93 (82.3) | 152 (69.4) | 102 (81.0) | 243 (59.9) |
| Mitral valve regurgitation, n (%) | 18 (10.8) | 9 (8.0) | 9 (4.1) | 5 (4.0) | 26 (6.4) |
| Aortic valve regurgitation, n (%) | 7 (4.2) | 8 (7.1) | 3 (1.4) | 6 (4.8) | 24 (5.9) |
| Aortic valve stenosis, n (%) | 2 (1.2) | 7 (6.2) | 7 (3.2) | 5 (4.0) | 6 (1.5) |
| Dilated cardiomyopathy, n (%) | 15 (9.0) | 3 (2.7) | 4 (1.8) | 1 (0.8) | 4 (1.0) |
| Hypertrophic cardiomyopathy, n (%) | 1 (0.6) | 1 (0.9) | 3 (1.4) | 2 (1.6) | 8 (2.0) |
| Calculated values      |        |        |        |        |          |
| \(\alpha\) (10\textsuperscript{−11} mm Hg) | 1.2±5.9 | 13.5±82\textsuperscript{T} | 1.4±3.1 | 17.6±59 | 2.8±8.6 |
| \(\beta\) (unit less) | 5.8±0.14 | 5.9±0.53 | 5.8±0.14 | 6.0±0.50\textsuperscript{T} | 5.8±0.13 |
| \(V_{15}\), mL | 89±31 | 83±29 | 77±23 | 72±22\textsuperscript{T} | 69±22 |
| \(V_{30}\), mL | 181±64 | 166±57 | 156±49 | 142±43\textsuperscript{T} | 141±44 |
| \(V_{90}\), mL | 204±72 | 187±64 | 176±56 | 160±49\textsuperscript{T} | 158±50 |

Continuous variables are expressed as mean±SD. Categorical variables are expressed as numbers and percentages. bpm indicates beats per minute; EDP, end-diastolic pressure; EF, ejection fraction; LV, left ventricular; \(V_{15}\), \(V_{30}\), and \(V_{90}\), end-diastolic volumes at which end-diastolic pressure is 0 (\(V_{15}\)), 15 (\(V_{30}\)), and 30 (\(V_{90}\)) mm Hg.

*\(P\) values obtained from Kruskal–Wallis test for continuous variables and from the \(x^2\) test for categorical variables.

†\(P<0.05\) vs normal/EDP subgroup in same EF group using Wilcoxon rank-sum test.

Continuous variables are expressed as mean±SD. Categorical variables are expressed as numbers and percentages. bpm indicates beats per minute; EDP, end-diastolic pressure; EF, ejection fraction; LV, left ventricular; \(V_{15}\), \(V_{30}\), and \(V_{90}\), end-diastolic volumes at which end-diastolic pressure is 0 (\(V_{15}\)), 15 (\(V_{30}\)), and 30 (\(V_{90}\)) mm Hg.

*\(P\) values obtained from Kruskal–Wallis test for continuous variables and from the \(x^2\) test for categorical variables.

†\(P<0.05\) vs normal/EDP subgroup in same EF group using Wilcoxon rank-sum test.
Limitations

First, we estimated EDPVR from a single point based on the previously reported mathematical model that hypothesized EDPVR as a simple nonlinear curve. This limited the accuracy of estimating true EDPVR. However, perturbation of volume load to measure EDPVR during catheterization is ethically unacceptable in HF patients. Therefore, estimating EDPVR from a single data set is considered the best method to determine EDPVR at this time. Second, LV volume was measured from left ventriculography, although the “gold standard” for LV volumetry is computed tomography or magnetic resonance imaging. However, left ventriculography is still widely performed and often used as a reference value to evaluate other volumetric methods. It is reasonable to think that our results would not differ substantially with the use of computed tomography or magnetic resonance imaging to evaluate LV volume.

Conclusions

Although diastolic dysfunction is one of the major pathophysiological causes of HFrEF, our results revealed that diastolic dysfunction also plays a key role in the pathogenesis of HFrEF. The mathematical estimation of EDPVR can provide clinicians with detailed information about the role of diastolic dysfunction in individual patients and thus appears to be an attractive tool for practical applications.

Disclosures

None.

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Figure 4. Cardiac output changes and cardiac output increment. In the high-EDP subgroup, changing diastolic properties (α and β) to those of the normal-EDP group significantly increased CO (A). There were no significant differences in the increment of CO among EF groups (B). CO indicates cardiac output; EDP, end-diastolic pressure; EF, ejection fraction. *P<0.05 vs normal-EDP subgroup of the same EF group using the paired t test. #P values obtained from Kruskal–Wallis test.
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