Myocardial Systolic and Diastolic Performance Derived by 2-Dimensional Speckle Tracking Echocardiography in Heart Failure With Normal Left Ventricular Ejection Fraction

Daniel A. Morris, MD; Leif-Hendrik Boldt, MD; Hermann Eichstädt, MD; Cemil Özcelik, MD; Wilhelm Haverkamp, MD

Background—The aim of this study was to investigate the myocardial systolic and diastolic performance of the left ventricle (LV) in patients with heart failure with normal LV ejection fraction (HFNEF) through novel LV myocardial indices, which assess the systolic and diastolic function of the whole myocardium of the LV.

Methods and Results—LV myocardial systolic and diastolic performance were assessed as the average value of peak systolic strain and peak early-diastolic strain rate, respectively, in longitudinal, circumferential, and radial directions from all LV segments using 2-dimensional speckle-tracking echocardiography. We studied patients with HFNEF and a control group consisting of asymptomatic subjects with LV diastolic dysfunction of similar age, sex, and LV ejection fraction. A total of 322 patients were included (92 with HFNEF and 230 with asymptomatic LV diastolic dysfunction). Myocardial systolic and diastolic LV performance were significantly lower in HFNEF (20.13±6.02% and 1.14±0.27 s⁻¹) than in patients with asymptomatic LV diastolic dysfunction (25.33±6.06% and 1.37±0.33 s⁻¹, respectively; all P<0.0001). In addition, patients with HFNEF with low systolic and diastolic LV myocardial performance had significantly higher LV filling pressures (17.1±6.6 and 17.6±6.3 versus 12.0±5.1 and 11.7±4.7, respectively; all P<0.001) and lower cardiac output (4.8±1.0 L/min and 4.9±1.1 L/min versus 5.7±1.2 L/min and 5.8±1.1 L/min, respectively; all P<0.001) than patients with normal LV myocardial performance. In relation to these findings, the symptomatic status (ie, New York Heart Association functional class) was significantly altered in those patients with low systolic and diastolic LV myocardial performance.

Conclusions—In patients with HFNEF, both systolic and diastolic LV myocardial performance are impaired, which is associated with increased LV filling pressures, decreased cardiac output, and worse New York Heart Association functional class. Therefore, the measurement of these myocardial parameters could be of great importance in HFNEF because these echocardiographic indices assess the multidirectional function of the whole myocardium of the LV, thereby allowing detection of an alteration of the global function of the LV which is associated with a worse symptomatic status in these patients. (Circ Heart Fail. 2012;5:610-620.)

Key Words: diastolic heart failure ■ echocardiography ■ systolic dysfunction

Unlike systolic heart failure (HF), HF with normal left ventricular (LV) ejection fraction (HFNEF) is characterized by a normal LV systolic function often evaluated by the biplane Simpson method.1 However, recent studies have shown that, despite a normal LV ejection fraction (LVEF), patients with HFNEF have a significant impairment of the longitudinal systolic function of the LV, suggesting that in these patients the myocardial systolic function of the LV is not preserved.2–5 Furthermore, several investigations have highlighted the key role of the longitudinal diastolic dysfunction of the LV in the pathophysiology of HFNEF.6–9 Nonetheless, despite these studies,2–8 whether a longitudinal systolic and diastolic LV dysfunction is associated with an impairment of the global function or myocardial performance of the LV in patients with HFNEF remains poorly understood. In addition, echocardiographic indices that evaluate the systolic and diastolic myocardial performance of the LV (ie, the average value of the longitudinal, radial, and circumferential function of the LV) have not been investigated in these patients.

Clinical Perspective on p 620

We hypothesized that in patients with HFNEF a significant alteration in the longitudinal function of the LV, and to a lesser extent in the circumferential and radial LV function, could lead...
to an impairment in the systolic and diastolic global function or myocardial performance of the LV, with consequent increase in LV filling pressures, decrease in cardiac output (CO), and worsening of the symptomatic status in these patients. With the aim of validating this hypothesis, we analyzed the myocardial performance of the LV in patients with HFNEF by means of 2 novel LV myocardial indices (ie, the myocardial systolic and diastolic index or performance), which evaluate the systolic and diastolic multidirectional function of the whole myocardium of the LV using 2-dimensional speckle-tracking echocardiography.

Methods

Study Population

We included and analyzed consecutive patients ≥18 years of age with signs or symptoms of HF, evidence of LV diastolic dysfunction (LVDD), and LVEF >50% by transthoracic echocardiography, according to the diagnostic criteria of HFNEF and LVDD of the American Society of Echocardiography (ASE) and the European Association of Echocardiography (EAE).1,9 We also studied a control group consisting of asymptomatic subjects with LVDD (in accordance with the diagnostic criteria of LVDD of the ASE and the EAE,9 ie, septal e’ mitral annular peak velocity <8 cm/s, or lateral e’ mitral annular peak velocity <10 cm/s, or maximal left atrial volume index ≥34 mL/m² without history of HFNEF and of similar age, sex, and LVEF. Three conditions were necessary for the diagnosis of HFNEF: (1) presence of signs or symptoms of congestive HF (dyspnea [New York Heart Association [NYHA] class ≥II], pulmonary rales, pulmonary edema, bilateral lower extremity edema, hepatomegaly, or fatigue); (2) presence of normal LV systolic function (LVEF >50% by the Simpson method); and (3) evidence of LVDD (septal e’ mitral annular peak velocity <8 cm/s, or lateral e’ mitral annular peak velocity <10 cm/s, or maximal left atrial volume index ≥34 mL/m²).1,9 We included consecutive in- and outpatients admitted in the Department of Cardiology (Campus Virchow-Klinikum) of the Charité University Hospital from August 2009 until August 2010 (some of these patients were also included in previous studies of our research group).4,10,11 The Charité institutional review board approved this research project, and informed consent was obtained from all subjects.

The selection of exclusion criteria in this study was based on the consensus of experts on HFNEF and on LV diastolic function of the ASE and EAE.1,9 To avoid reversible causes of myocardial dysfunction, patients with active coronary artery disease were excluded from this study (ie, patients with unstable angina or non–ST-segment elevation myocardial infarction without revascularization or with revascularization within the last 72 hours, patients with ST-segment elevation acute myocardial infarction within the last 30 days, subjects waiting for coronary artery bypass graft or within 90 days postoperatively, subjects with chronic stable angina, and patients with evidence of myocardial ischemia assessed by stress echocardiography). Furthermore, with the purpose of excluding causes of dyspnea or myocardial dysfunction other than HFNEF, patients with the following characteristics were excluded from this study: (1) primary or secondary pulmonary hypertension of causes other than isolated LVDD or HFNEF; (2) severe pulmonary disease defined as pulmonary pathology with supplemental oxygen requirement; (3) severe kidney disease defined as estimated glomerular filtration rate <30 mL/min per 1.72 m² for at least 3 months, history of renal transplantation, or severe acute renal failure with dialysis requirement; (4) severe chronic liver disease or history of liver transplantation; (5) congenital heart disease; (6) pericardial disease characterized by moderate or severe pericardial effusion (echo-free space in end diastole ≥10 mm) or constrictive pericarditis; (7) cardiomyopathy; and (8) valvular heart disease defined as mild, moderate, or severe mitral or aortic stenosis; moderate or severe nonfunctional mitral or tricuspid regurgitation; and moderate or severe aortic regurgitation (according to the diagnostic criteria of the guidelines for the management of patients with valvular heart disease of the American College of Cardiology).12

Furthermore, to avoid underestimations of myocardial and mitral annular measurements, patients with valvular heart surgery, mitral annular calcification (≥2 mm), cardiac pacing, and poor 2-dimensional quality in ≥1 segments of the LV (not suitable for analysis by 2-dimensional speckle-tracking echocardiography in apical 4-chamber, 2-chamber, long-axis, and short-axis views) were also excluded from this study. Finally, to avoid mistakes in the myocardial measurements of the LV because of the variability of R-R interval, patients with atrial or ventricular arrhythmias at the time of inclusion in the study were also excluded.

Transthoracic Echocardiography

All patients were examined at rest in the left lateral decubitus position using a Vivid-7 ultrasound system (GE-Healthcare, Horten, Norway), followed by an offline analysis using EchoPac version 110.1.0 workstation (namely, measurements by 2-dimensional speckle-tracking echocardiography). The echocardiographic measurements and analyses were performed by experienced echocardiographers blinded to each other’s results. LV diameters, LV volumes, LV mass and grading of LV hypertrophy, LVEF (Simpson method), LV relative wall thickness, LA volume, LV diastolic function, and grading of LVDD were assessed as recommended by the ASE and EAE.8,11 In that regard, severe LV hypertrophy was defined as LV mass ≥122 g/m² in women or ≥149 g/m² in men, and concentric LV hypertrophy was determined as relative wall thickness >0.42 or LV mass ≥109 g/m² in women or relative wall thickness >0.42 or LV mass ≥116 g/m² in men.13 Furthermore, in accordance with the guidelines for the evaluation of LV diastolic function by echocardiography of the ASE and EAE,8 the noninvasive estimation of LV filling pressures was assessed by the mitral E/e’ average septal-lateral ratio (ie, ratio of early-diastolic mitral inflow peak velocity by pulsed-wave Doppler [E] to early-diastolic mitral annular [average septal-lateral] peak velocity using spectral tissue Doppler imaging [e’]) and estimated as elevated when the mitral E/e’ average septal-lateral ratio was ≥13.3 Furthermore, in agreement with the consensus of experts for quantification of Doppler echocardiography of the ASE,1,4 CO was derived as the product of LV stroke volume (SV) and heart rate (namely, SV was calculated as the product of the velocity time integral and the cross-sectional area of the LV outflow tract using pulsed-wave Doppler and 2-dimensional echocardiography).14 In addition, we defined low CO as a CO ≤2.2 L/min per m² or ≤5 L/min and low SV as an SV ≤35 mL/m², according to previously validated studies.10,11 All echocardiographic measurements using speckle-tracking (mean frame rates of 67.2±4.8 frames/s), Doppler, and conventional 2-dimensional echocardiography were calculated as the average of 3 measurements.

2-Dimensional Speckle-Tracking Echocardiography

The analyses by 2-dimensional speckle-tracking echocardiography were performed offline and blinded to the clinical characteristics of the patients. The measurements of LV longitudinal systolic strain and early-diastolic strain rate (SRe) were performed at basal, mid, and apical levels in the apical 4-chamber, 2-chamber, and long-axis views (ie, 18 segments of the LV).4,10,11,14 The average values of the peak systolic strain (during LV systole) and the peak early-diastolic SRe (during LV diastole) in longitudinal direction from 18 LV segments were named LV global longitudinal systolic strain and LV global longitudinal early-diastolic SRe, respectively.4,10,11,14 The measurements of LV circumferential and radial systolic strain and early-diastolic SRe were performed at the 3 short-axis views of the LV (basal, midventricular, and apical levels).15,16 The average values of the peak systolic strain (during LV systole) and the peak early-diastolic SRe (during LV diastole) in circumferential and radial directions from 18 LV segments were called LV global circumferential and radial systolic strain and early-diastolic SRe, respectively.1,8,19 LV systolic and diastolic rotations were performed in the basal (identified by the mitral valve) and apical (smallest LV cavity achievable distal to the papillary muscles) short-axis views, and the differences between apical and basal rotations were calculated as twist (peak systolic rotation) and untwist rate (peak early-diastolic rotation rate).20
Myocardial Systolic and Diastolic Performance of the LV

To assess the global function or myocardial performance of the LV, we analyzed the average value of the longitudinal, radial, and circumferential functions of the entire myocardium of the LV. In this regard, using 2-dimensional speckle-tracking echocardiography and the same 18-segment LV model used for the aforementioned measurements of LV global systolic strain and early-diastolic strain rate, we assessed the systolic and diastolic myocardial performance of the LV averaging the value of peak systolic strain and peak early-diastolic SRe in longitudinal, radial, and circumferential direction, namely:

- Myocardial Systolic Performance = (global radial systolic strain - global longitudinal early diastolic SRe - global circumferential systolic strain) / 3
- Myocardial Diastolic Performance = (global longitudinal early diastolic SRe - global circumferential early diastolic SRe - global radial early diastolic SRe) / 3

Examples of how to calculate these indices are available in the online-only Data Supplement.

Echocardiographic Criteria and Range of Values in Healthy Subjects

In a group of healthy subjects, we analyzed the range of values of the systolic and diastolic myocardial performance with the aim to determine the 2.5th percentile of these indices (calculated as −1.96 SDs from the mean of this population), which was used to define a low systolic and diastolic LV myocardial performance (ie, values <2.5th percentile from healthy subjects). Healthy subjects were defined as all those individuals with a normal echocardiogram according to the diagnostic criteria of the ASE[12,13] and without history or presence of ≥1 of the following findings: cardiovascular disease; pathologic with known cardiovascular involvement; kidney, liver, or lung disease; and medications with known cardiovascular effects. A total of 94 healthy subjects (age range, 18–68 years; 57.4% women; LVEF 62.0±5.0%) were included, and the values of the myocardial systolic performance (MSP) and the myocardial diastolic performance (MDP) in this group were as follows: MSP 29.54±5.3% and MDP 1.78±0.29 s⁻¹. In addition, in this group of healthy individuals we determined the range of values of LV global longitudinal, radial, circumferential, and rotational systolic strain and early-diastolic SRe (LV global systolic strain: longitudinal −20.90±2.16%, circumferential −19.82±3.70%, radial 47.92±13.81%; LV global early-diastolic SRe: longitudinal 1.53±0.30 s⁻¹, circumferential 1.56±0.50 s⁻¹, radial −2.26±0.63 s⁻¹; LV twist: 12.98±3.94°; LV untwist rate: −145.3±37.0°/s) to define as LV longitudinal, radial, circumferential, or rotational dysfunction the values <2.5th percentile of these myocardial measurements. Clinical characteristics and conventional echocardiographic assessments of this cohort of healthy subjects are shown in more detail in online-only Data Supplement Table I.

Statistical Analysis

Continuous data are presented as mean±SD and dichotomous data in percentage. Differences in continuous variables between groups were assessed using Student t test. Categorical variables were compared by χ² test and Fisher exact test, as appropriate. Comparisons among ≥3 groups were assessed using 1-way ANOVA. Correlation between continuous variables was evaluated using a Pearson correlation analysis. Association of independent variables with low systolic and diastolic LV myocardial performance, elevated LV filling pressures, and an NYHA functional class ≥3 was analyzed using a logistic regression analysis. With the purpose of determining the reproducibility of the indices of myocardial systolic and diastolic performance, we analyzed the intra- and interobserver variability on 48 randomly selected patients using a Bland-Altman analysis. All statistical analyses were performed with Statview 5.0 (SAS Institute) and SPSS 15.0 (IBM). Differences were considered statistically significant when P<0.05.

Results

Patient Clinical Characteristics

A total of 450 patients met the eligibility criteria (ie, inclusion criteria) during the study period (178 with HFNEF and 272 with asymptomatic LVDD). However, 88 patients (51 with HFNEF and 37 with asymptomatic LVDD) could not be analyzed because of a poor 2-dimensional quality in ≥1 segments of the LV not suitable for analysis by 2-dimensional speckle-tracking echocardiography. In addition, 40 patients were excluded because of severe kidney disease (n=2), cardiac pacing (n=1), severe chronic liver disease (n=1), non-ST-segment elevation myocardial infarction within the last 72 hours (n=2), ST-segment elevation acute myocardial infarction within the last 30 days (n=2), coronary artery bypass graft within the last 90 days (n=1), evidence of myocardial ischemia assessed by stress echocardiography (n=2), mild aortic stenosis (n=1), and atrial or ventricular arrhythmias at the time of inclusion in the study (n=28). Thus, 322 patients were finally studied and analyzed (92 with HFNEF and 230 with asymptomatic LVDD). Clinical characteristics and conventional echocardiographic measurements of these patients are shown in Table 1. Patients with HFNEF presented the following signs or symptoms of HF: dyspnea 100% (NYHA functional class II 69.6% [n=64], class III 17.4% [n=16], class IV 13% [n=12]), cardiogenic pulmonary edema 30.4% (n=28), bilateral lower extremity edema 44.5% (n=41), chronic stable HF 69.6% (n=64), and acute HF (first presentation or as decompensation of chronic HF) 30.4% (n=28).

Myocardial Systolic and Diastolic Global Function or Performance of the LV in HFNEF

Patients with HFNEF had significantly more impaired LV myocardial systolic and diastolic performance than asymptomatic patients with LVDD (Table 2; Figure 1A and 1B). In relation to these findings, the rates of low systolic and diastolic LV myocardial performance were considerably elevated in patients with HFNEF (44.6% and 63%, respectively), whereas in asymptomatic subjects the rates of low systolic and diastolic LV myocardial performance were only 13.9% and 32.2%, respectively (Table 3). In addition, concerning the myocardial mechanisms that could contribute to these LV alterations in HFNEF, we found that patients with HFNEF with low systolic and diastolic LV myocardial performance were characterized by having a significant impairment of the longitudinal systolic and diastolic function of the LV, in contrast to circumferential, radial, and rotational systolic and diastolic LV functions which were mildly altered in these patients (Tables 2 and 3; Figure 2A and 2B).

Clinical and Echocardiographic Variables Linked to Low Systolic and Diastolic LV Myocardial Performance

In the analysis of the clinical and echocardiographic variables that could be associated with a low LV myocardial performance in patients with HFNEF, we found that comorbidities, such as diabetes mellitus, hypertension, obesity, history
of coronary artery disease, and severe LV hypertrophy, were significant predictors of a low systolic and diastolic LV myocardial performance in those patients (Table 4). Furthermore, in relation to the aforementioned effects of an impaired LV longitudinal function on the global function or performance of the LV, we found that LV longitudinal dysfunction was an important factor linked to low LV myocardial performance in HFNEF (Table 4). Nonetheless, the presence of radial or circumferential LV dysfunction, while it occurred in few subjects with HFNEF, also was significantly related to low systolic and diastolic LV myocardial performance. In addition, interestingly, we found that systolic and diastolic LV myocardial performance were significantly related to each other (ie, myocardial contraction-relaxation coupling) \((r=0.50; P<0.0001)\).

### Clinical Consequences of Low Systolic and Diastolic LV Myocardial Performance in Patients With HFNEF

In the analyses that we have performed to assess the possible consequences of an impaired systolic and diastolic LV myocardial performance in subjects with HFNEF, we found that patients with HFNEF with low systolic and diastolic LV myocardial performance had significantly higher LV filling pressures, as well as lower SV and CO, than patients with preserved LV myocardial performance (Table 5 and Figure 3). In relation to these findings, the NYHA functional class was significantly more altered in patients with HFNEF with low systolic and diastolic LV myocardial performance than in patients with normal LV myocardial performance (Table 5). In line with this, the alteration of NYHA functional class was significantly linked to the grade of impairment of the systolic and diastolic LV myocardial performance (Table 6). In addition, we found that low systolic and diastolic LV myocardial performance were strongly linked to elevated LV filling pressures and worse symptomatic status (ie, NYHA functional class \(\geq 3\)) in patients with HFNEF (Table 4).

### Reproducibility

The variability of the measurements of the systolic and diastolic LV myocardial performance was not of clinical significance (Figure 4).

### Discussion

In the present study, we have performed a comprehensive assessment of the systolic and diastolic global function or myocardial performance of the LV in patients with HFNEF.

---

**Table 1. Clinical Characteristics and Conventional Echocardiographic Measurements**

<table>
<thead>
<tr>
<th></th>
<th>HFNEF (n=92)</th>
<th>Asymptomatic LVDD (n=230)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>71.2±10.2</td>
<td>68.1±9.4</td>
<td>0.0087</td>
</tr>
<tr>
<td>Women</td>
<td>46.7%</td>
<td>39.1%</td>
<td>0.2115</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td>29.3±5.1</td>
<td>27.4±4.4</td>
<td>0.0105</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.3±1.6</td>
<td>13.5±1.6</td>
<td>0.3302</td>
</tr>
<tr>
<td>GFR, mL/min per 1.73m(^2)</td>
<td>68.3±21.6</td>
<td>76.0±21.6</td>
<td>0.0049</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>140.5±22.6</td>
<td>135.2±21.2</td>
<td>0.1074</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>80.7±12.5</td>
<td>79.5±12.2</td>
<td>0.4929</td>
</tr>
</tbody>
</table>

**Comorbidities**

- Hypertension: 100% vs. 79.6%, \(<0.0001\)
- Type II diabetes mellitus: 32.6% vs. 20.4%, \(0.0207\)
- Obesity: 33.3% vs. 11.6%, \(<0.0001\)
- History of CAD: 64.1% vs. 33.9%, \(<0.0001\)

**Conventional echocardiographic measurements**

- LV ejection fraction, %: 59.9±6.8 vs. 62.0±6.7, \(0.0144\)
- LVEDV, mL/m\(^2\): 44.3±14.0 vs. 43.1±11.2, \(0.5320\)
- LV mass, g/m\(^2\): 123.8±28.9 vs. 104.1±24.6, \(<0.0001\)
- Severe LV hypertrophy: 33.8% vs. 6.6%, \(<0.0001\)
- Concentric LV hypertrophy: 66.2% vs. 34.1%, \(<0.0001\)
- Septal e' mitral annular peak velocity, cm/s: 4.3±1.4 vs. 6.0±1.5, \(<0.0001\)
- Lateral e' mitral annular peak velocity, cm/s: 6.4±1.4 vs. 8.1±1.5, \(<0.0001\)
- LV filling pressures (E/e' mitral ratio): 17.2±6.1 vs. 10.6±3.9, \(<0.0001\)

**HFNEF indicates heart failure with normal left ventricular (LV) ejection fraction; LVDD, LV diastolic dysfunction; SRe, peak early diastolic strain rate.**

**Table 2. LV Measurements With 2-Dimensional Speckle-Tracking Echocardiography**

<table>
<thead>
<tr>
<th></th>
<th>HFNEF (n=92)</th>
<th>Asymptomatic LVDD (n=230)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV global longitudinal function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic strain, %</td>
<td>−14.17±3.21</td>
<td>−18.92±2.71</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Early-diastolic SRe, s(^{-1})</td>
<td>0.83±0.26</td>
<td>1.02±0.31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV global circumferential function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic strain, %</td>
<td>−15.10±3.92</td>
<td>−18.89±3.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Early-diastolic SRe, s(^{-1})</td>
<td>0.94±0.31</td>
<td>1.20±0.41</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV global radial function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic strain, %</td>
<td>31.11±14.95</td>
<td>38.17±15.80</td>
<td>0.0003</td>
</tr>
<tr>
<td>Early-diastolic SRe, s(^{-1})</td>
<td>−1.67±0.63</td>
<td>−1.88±0.60</td>
<td>0.0063</td>
</tr>
<tr>
<td>LV rotational systolic function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twist, °</td>
<td>11.72±4.02</td>
<td>13.50±5.16</td>
<td>0.0126</td>
</tr>
<tr>
<td>LV rotational diastolic function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untwist Rate, °/s</td>
<td>−114.6±31.8</td>
<td>−142.1±40.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV myocardial systolic performance, strain %</td>
<td>20.13±6.02</td>
<td>25.3±6.06</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV myocardial diastolic performance, SRe, s(^{-1})</td>
<td>1.14±0.27</td>
<td>1.37±0.33</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

HFNEF indicates heart failure with normal left ventricular (LV) ejection fraction; LVDD, LV diastolic dysfunction; SRe, peak early diastolic strain rate. Data are expressed as mean±SD.
In this regard, using 2-dimensional speckle-tracking echocardiography at rest, we have determined the clinical use of 2 novel LV myocardial indices, which identify patients with HFNEF with important systolic and diastolic alterations in the whole myocardium of the LV. Other interesting findings of this study were that patients with HFNEF with low systolic and diastolic LV myocardial performance had significantly higher LV filling pressures, lower CO, and worse NYHA functional class than those with preserved LV myocardial performance.

**Link Between LV Longitudinal Dysfunction and the Global Dysfunction or Low Performance of the LV in HFNEF**

Unlike systolic HF, HFNEF is characterized by a normal LV systolic function often evaluated by the biplane Simpson method. However, recent studies have shown that despite a normal LVEF, patients with HFNEF have a significant impairment of the longitudinal systolic function of the LV, suggesting that in these patients the myocardial systolic function of the LV is not preserved. Furthermore, several investigations have highlighted the key role of the longitudinal diastolic dysfunction of the LV in the pathophysiology of HFNEF. Nonetheless, despite these studies, whether a longitudinal systolic and diastolic LV dysfunction is associated with an impairment of the global function or myocardial performance of the LV in patients with HFNEF remains poorly understood. In addition, echocardiographic indices that evaluate the systolic and diastolic myocardial performance of the LV have not been investigated in these patients.

In the present study using 2-dimensional speckle-tracking indices, which identify patients with HFNEF with low systolic and diastolic LV myocardial performance had significantly higher LV filling pressures, lower CO, and worse NYHA functional class than those with preserved LV myocardial performance.

### Table 3. Rates of LV Myocardial Systolic and Diastolic Dysfunctions in Patients With HFNEF

<table>
<thead>
<tr>
<th></th>
<th>HFNEF (n=92)</th>
<th>Asymptomatic LVDD (n=230)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV global longitudinal systolic dysfunction</td>
<td>79.3</td>
<td>20.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV global longitudinal diastolic dysfunction</td>
<td>67.4</td>
<td>45.7</td>
<td>0.0004</td>
</tr>
<tr>
<td>LV global circumferential systolic dysfunction</td>
<td>26.1</td>
<td>1.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV global circumferential diastolic dysfunction</td>
<td>12.1</td>
<td>2.2</td>
<td>0.0002</td>
</tr>
<tr>
<td>LV global radial systolic dysfunction</td>
<td>19.6</td>
<td>7.4</td>
<td>0.0015</td>
</tr>
<tr>
<td>LV global radial diastolic dysfunction</td>
<td>6.5</td>
<td>3.5</td>
<td>0.2276</td>
</tr>
<tr>
<td>LV rotational systolic dysfunction</td>
<td>0.0</td>
<td>0.9</td>
<td>0.9107</td>
</tr>
<tr>
<td>LV rotational diastolic dysfunction</td>
<td>5.4</td>
<td>0.9</td>
<td>0.0220</td>
</tr>
<tr>
<td>LV untwist rate &gt;−73°/s *</td>
<td>44.6</td>
<td>13.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Low LV myocardial systolic performance</td>
<td>63</td>
<td>32.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Low LV myocardial diastolic performance</td>
<td>1.78 ± 0.29</td>
<td>1.78 ± 0.29</td>
<td></td>
</tr>
</tbody>
</table>

HFNEF indicates heart failure with normal left ventricular (LV) ejection fraction; LVDD, LV diastolic dysfunction; SRe, peak early diastolic strain rate. Data are expressed as percentages.

*Values below 2.5th percentile from healthy subjects.

In these figures, it can be seen that patients with HFNEF have significantly more impaired LV myocardial systolic and diastolic performance than asymptomatic patients with LV diastolic dysfunction (LVDD) and healthy subjects (mean±SD values of each group are shown inside boxes). In the box plots, the central line represents the median, the length of the box represents the interquartile range (25th to 75th percentile), and the bars indicate the 10th and 90th percentile.

![Figure 1. A and B. Low left ventricular (LV) myocardial systolic and diastolic performance in patients with heart failure with normal LV ejection fraction (HFNEF). In these figures, it can be seen that patients with HFNEF have significantly more impaired LV myocardial systolic and diastolic performance than asymptomatic patients with LV diastolic dysfunction (LVDD) and healthy subjects (mean±SD values of each group are shown inside boxes). In the box plots, the central line represents the median, the length of the box represents the interquartile range (25th to 75th percentile), and the bars indicate the 10th and 90th percentile.](http://circheartfailure.ahajournals.org/attachment/3987211097/322d2e03c1c6.jpg)
subjects and in patients with HF that the longitudinal LV function has a key role in the myocardial performance or global function of the LV. Furthermore, we found that a low systolic and diastolic LV myocardial performance is linked to an increase in LV filling pressures, a decrease in CO, and a worsening of the symptomatic status in these patients.

Accordingly, we consider that a low systolic and diastolic LV myocardial performance could play an important role in the physiopathology of HFNEF.

Low MSP and Compensatory Mechanisms in HFNEF

Although patients with HFNEF have principally impaired longitudinal contractile function of the LV with consequent low MSP (as we have demonstrated), these patients are characterized by having normal LVEF; therefore, compensatory mechanisms to counteract this myocardial systolic dysfunction of the LV could exist. In this respect, Phan et al. and Wang et al. recently demonstrated that LV twist is preserved in patients with HFNEF. Thereby, LV twist could serve as a compensatory mechanism that allows counteracting the systolic dysfunction of the LV in patients with HFNEF and thus to maintain a normal LVEF. According to these findings, in our study, 100% of subjects with HFNEF had a normal LV rotational systolic function, which could act as a regulatory mechanism to balance the low MSP of the LV in these patients.

Notwithstanding, based on previous reports and our results, we consider that in patients with HFNEF the aforementioned compensatory mechanism would not be enough to maintain a normal SV or CO. In this regard, recent studies demonstrated that patients with HFNEF have a significant decrease of SV or CO at rest as well as a reduced CO reserve during exercise compared with healthy subjects, as a result of concentric LV remodeling, chronotropic incompetence, and impaired arterial vasodilation. In addition, on the basis of our findings, we consider that in patients with HFNEF the diminution at rest or the inefficient increase during exercise of SV or CO could further be related to a low MSP of the LV. In this respect, we found that an impairment of MSP of the LV was significantly linked to a considerable diminution of SV and CO in patients with HFNEF. Hence, we believe that one of the mechanisms by which patients with HFNEF have a decrease at rest or inefficient rise at exercise of SV and CO could be, in part, because of a low MSP of the LV.

Association of a Low Systolic and Diastolic LV Myocardial Performance With Symptoms of HFNEF

Several investigations have highlighted the central role of LV diastolic dysfunction in the pathophysiology of HFNEF. The present study confirms and extends these data by showing that the symptomatology of patients with HFNEF is associated not only with LV myocardial diastolic dysfunction but also with a myocardial systolic dysfunction of the LV. In this regard, we showed that patients with HFNEF with impaired systolic and diastolic LV myocardial performance had significantly higher LV filling pressures and worse NYHA functional class than those with normal LV myocardial performance. These findings are consistent with recent reports in hypertensive patients, which also showed, using measurements at rest with speckle-tracking echocardiography, that both...
Table 5. Consequences and Characteristics of Patients with HFNEF With Low Systolic and Diastolic LV Myocardial Performance

<table>
<thead>
<tr>
<th>Variables</th>
<th>Low Systolic Performance</th>
<th>Low Diastolic Performance</th>
<th>Elevated LV Filling Pressures</th>
<th>NYHA Functional Class ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (n=41)</td>
<td>OR (n=249)</td>
<td>OR (n=58)</td>
<td>OR (n=190)</td>
</tr>
<tr>
<td>Low LV myocardial systolic performance</td>
<td>31.7*</td>
<td>17.1±6.6*</td>
<td>73.2±2.4*</td>
<td>6.7 ± 0.036</td>
</tr>
<tr>
<td></td>
<td>3.10†</td>
<td>12.0±5.1</td>
<td>28.9</td>
<td>10.3 ± 0.003</td>
</tr>
<tr>
<td></td>
<td>12.6±2.47</td>
<td>18.43±3.15</td>
<td>13.5±3.10</td>
<td>18.8±3.03</td>
</tr>
<tr>
<td></td>
<td>97.6*</td>
<td>26.5±26.5</td>
<td>82.8±26.5</td>
<td>26.5±26.5</td>
</tr>
<tr>
<td></td>
<td>0.79±0.25</td>
<td>1.0±0.31</td>
<td>0.74±0.22</td>
<td>1.0±0.31</td>
</tr>
<tr>
<td></td>
<td>70.7*</td>
<td>46.6±46.6</td>
<td>84.5±84.5</td>
<td>3.6±3.6</td>
</tr>
<tr>
<td></td>
<td>4.8±1.0</td>
<td>5.7±5.7</td>
<td>4.9±4.9</td>
<td>5.8±5.8</td>
</tr>
<tr>
<td></td>
<td>68.2*</td>
<td>22.5±22.5</td>
<td>63.8±63.8</td>
<td>19.5±19.5</td>
</tr>
<tr>
<td></td>
<td>70.0±13.3*</td>
<td>81.1±14.2</td>
<td>72.5±14.7</td>
<td>80.7±13.9</td>
</tr>
<tr>
<td></td>
<td>48.8*</td>
<td>14.8±14.8</td>
<td>43.1±43.1</td>
<td>13.2±13.2</td>
</tr>
</tbody>
</table>

HFNEF indicates heart failure with normal left ventricular (LV) ejection fraction; NYHA, New York Heart Association; OR, odds ratio; CAD, coronary artery disease; low LV myocardial systolic performance (MSP), MSP <18.7%; low LV myocardial diastolic performance (MDP), MDP <1.20 s⁻¹; LV global longitudinal systolic dysfunction, LV global longitudinal systolic strain <−16.6%; LV global longitudinal diastolic dysfunction, LV global longitudinal early-diastolic strain rate <−0.95 s⁻¹; LV global circumferential systolic dysfunction, LV global circumferential systolic strain <−12.5%; LV global circumferential diastolic dysfunction, LV global circumferential early-diastolic strain rate <−0.60 s⁻¹; LV global radial systolic dysfunction, LV global radial systolic strain <−20%; LV global radial diastolic dysfunction, LV global radial early-diastolic strain rate >−1.00 s⁻¹; elevated LV filling pressures, mitral E/e' average septal-lateral ratio ≥13.

The odds ratio in these analyses represents the ratio of the odds of an event (namely, the first row of the table, eg, elevated LV filling pressures) occurring in one group to the odds of it occurring in another group (ie, the opposite variable, eg, diabetes mellitus vs nondiabetes or low vs normal LV myocardial systolic performance). Data correspond to analysis of patients with HFNEF with low LV systolic and diastolic performance and patients with normal LV systolic and diastolic performance.

Data are expressed as mean±SD or percentage.

LV filling pressures were assessed by the mitral E/e' average septal-lateral ratio, ie, ratio of early-diastolic mitral inflow peak velocity by pulsed-wave Doppler [E] to early-diastolic mitral annular (average septal-lateral) peak velocity using spectral TDI [e'] and elevated LV filling pressures corresponding to mitral E/e' average septal-lateral ratio ≥13.

Cardiac output was derived as the product of LV stroke volume (SV) and heart rate (namely, SV was calculated as the product of the velocity time integral and the cross-sectional area of the LV outflow tract using pulsed-wave Doppler and 2-dimensional echocardiography). Low cardiac output corresponds to CO ≥2.2 L/min per m² or ≤5 L/min and low stroke volume to SV ≤35 mL/m².

LV global longitudinal systolic and diastolic dysfunction were determined as LV global longitudinal systolic strain >−16.6% and LV global longitudinal early-diastolic SRe <−0.95 s⁻¹, respectively.

*Values with P<0.001 in patients with HFNEF with low MSP vs patients with normal MSP.
†Values with P<0.001 in patients with HFNEF with low MDP vs patients with normal MDP.
the diastolic and the systolic LV myocardial dysfunction, even with normal LVEF, are significantly linked to an increase in LV filling pressures.31,32

Although elevated LV filling pressures have been implicated as one of the major mechanisms of the symptoms of HFNEF,33,34 other researches have recently shown that additional physiopathological processes, such as impaired CO reserve, could be involved in the pathogenesis of the symptoms of patients with HFNEF.24,29 In this regard, Borlaug et al24 and more recently Haykowsky et al29 demonstrated that a diminished response of CO to exercise is strongly associated with reduced functional capacity during exercise in subjects with HFNEF.24,29 In addition, we found that a low MSP of the LV (which contributes to a diminution of CO) was linked to a worse symptomatic status in these patients. Accordingly, we consider that both the systolic and the diastolic global dysfunction or low LV myocardial performance contribute significantly to the symptoms of patients with HFNEF.

**Limitations**

Our study has diverse limitations. Our analyses were limited by the lack of invasive hemodynamic data regarding LV filling pressures, SV, and CO. Nonetheless, several studies have demonstrated the high sensitivity, specificity, and accuracy of the mitral E/e’ ratio to determine LV filling pressures in patients with HFNEF.1,9,33 In addition, this noninvasive measurement of LV filling pressures is currently recommended by the consensus of experts on LV diastolic function and on HFNEF of the ASE and EAE.1,9 In line with this, the echocardiographic Doppler assessment of SV and CO has also shown a high correlation with invasive hemodynamic measurements in patients with HF15,36 and likewise is supported by the guidelines for quantification of Doppler echocardiography of the ASE.14 Furthermore, it is important to point out that in this work we did not perform an analysis of the variables under study using exercise echocardiography, which recently has shown that it might have an interesting role in HFNEF.37 Another point to consider is that this research is a

Table 6. Worsening of the Symptomatic Status Linked to the Deterioration of the Systolic and Diastolic LV Myocardial Performance

<table>
<thead>
<tr>
<th>NYHA Functional Class</th>
<th>Class I (n=230)</th>
<th>Class II (n=64)</th>
<th>Class III (n=16)</th>
<th>Class IV (n=12)</th>
<th>P-ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV myocardial systolic performance (strain %)</td>
<td>25.3±6.0</td>
<td>20.2±6.2*</td>
<td>20.1±6.0†</td>
<td>19.7±5.4‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV myocardial diastolic performance (SRe s⁻¹)</td>
<td>1.37±0.33</td>
<td>1.16±0.29*</td>
<td>1.11±0.21†</td>
<td>1.08±0.25‡</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

LV indicates left ventricular; NYHA, New York Heart Association; SRe, peak early diastolic strain rate.

Data are expressed as mean±SD.

*P<0.01, NYHA class II vs class I.

†P<0.01, NYHA class III vs class I.

‡P<0.01, NYHA class IV vs class I.
cross-sectional study. Therefore, the relationship of the factors linked to both a worsening of the symptomatic status and an increase in LV filling pressures does not determine causality but merely states an association.

Conclusions

In the present study using 2-dimensional speckle-tracking indices that assess the multidirectional global function of the LV, we have demonstrated that both the systolic and the diastolic LV myocardial performance are impaired in patients with HFNEF. Furthermore, our findings suggest that an impairment of both diastolic and systolic LV myocardial performance is linked to an increase in LV filling pressures, a decrease in CO, and a worsening of NYHA functional class in these patients. Therefore, the measurement of these myocardial parameters could be of great importance in HFNEF because these echocardiographic indices analyze the multidirectional function of the whole myocardium of the LV, thereby allowing detection of an alteration of the global function of the LV which is associated with a worse symptomatic status in these patients.

Acknowledgments

We thank the patients and staff of the Department of Echocardiography, Charité University Hospital (Campus Virchow-Klinikum), for their participation in this project.

Disclosures

None.

References


6. Brucks S, Little WC, Chao T, Kitzman DW, Wesley-Farrington D, Gandhi S, Shihabi ZK. Contribution of left ventricular diastolic performance...


CLINICAL PERSPECTIVE

Heart failure with normal left ventricular (LV) ejection fraction is a disease with complex pathophysiological mechanisms, for which, so far, no effective therapies have shown promise in randomized clinical trials. In the present study, using measurements at rest with 2-dimensional speckle-tracking echocardiography, we have demonstrated that both the systolic and the diastolic global function or myocardial performance of the LV (measured as the average value of peak systolic strain and peak early-diastolic strain rate in longitudinal, radial, and circumferential direction, respectively) are impaired in heart failure with normal LV ejection fraction. Furthermore, our findings suggest that an impairment of both diastolic and systolic LV myocardial performance is linked to an increase in LV filling pressures, a decrease in cardiac output, and a worsening of New York Heart Association functional class in these patients. Therefore, the measurement of these myocardial parameters could be useful in heart failure with normal LV ejection fraction because these echocardiographic indices assess the multidirectional function of the entire myocardium of the LV. Prospective clinical trials are needed to establish whether these findings have therapeutic or prognostic implications and lead to a better understanding of the physiopathology and treatment of heart failure with normal LV ejection fraction.
Myocardial Systolic and Diastolic Performance Derived by 2-Dimensional Speckle Tracking Echocardiography in Heart Failure With Normal Left Ventricular Ejection Fraction

Daniel A. Morris, Leif-Hendrik Boldt, Hermann Eichstädt, Cemil Özcelik and Wilhelm Haverkamp

_Circ Heart Fail_. 2012;5:610-620; originally published online August 8, 2012;
doi: 10.1161/CIRCHEARTFAILURE.112.966564

_Circulation: Heart Failure_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/5/5/610

Data Supplement (unedited) at:
http://circheartfailure.ahajournals.org/content/suppl/2012/08/08/CIRCHEARTFAILURE.112.966564.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Heart Failure_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Heart Failure_ is online at:
http://circheartfailure.ahajournals.org//subscriptions/
Myocardial Systolic and Diastolic Performance

Derived by Two-Dimensional Speckle Tracking Echocardiography

in Heart Failure with Normal Left Ventricular Ejection Fraction

Authors: Daniel A. Morris, MD; Leif-Hendrik Boldt, MD; Hermann Eichstädt, MD; Cemil Özcelik, MD; and Wilhelm Haverkamp, MD.

Institution: From the Department of Cardiology (Campus Virchow-Klinikum) of the Charité University Hospital, Berlin, Germany (D.A.M.; L.-H.B.; H.E.; W.H.); the Cardio-Genetic Laboratory of the Experimental & Clinical Research Center at the Max-Delbrück-Center for Molecular Medicine, Berlin, Germany (C.Ö.); and the Department of Cardiology of the Albert-Schweitzer-Krankenhaus, Helios-Kliniken, Northeim, Germany (C.Ö.).

SUPPLEMENTAL MATERIAL
<table>
<thead>
<tr>
<th>Clinical Characteristics and Conventional Echocardiographic Measurements in Healthy Subjects</th>
<th>Healthy Subjects (n = 94)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>38.5 ± 12.0</td>
</tr>
<tr>
<td>Women</td>
<td>57.4%</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
<td>23.3 ± 1.5</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>13.8 ± 1.3</td>
</tr>
<tr>
<td>GFR, ml/min/1.73m$^2$</td>
<td>93.6 ± 20.8</td>
</tr>
<tr>
<td>Systolic Blood Pressure, mmHg</td>
<td>118.8 ± 9.9</td>
</tr>
<tr>
<td>Diastolic Blood Pressure, mmHg</td>
<td>80.8 ± 6.0</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.0%</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>0.0%</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.0%</td>
</tr>
<tr>
<td>History of CAD</td>
<td>0.0%</td>
</tr>
<tr>
<td><strong>Conventional Echocardiographic Measurements</strong></td>
<td></td>
</tr>
<tr>
<td>LV Ejection Fraction, %</td>
<td>62.0 ± 5.0</td>
</tr>
<tr>
<td>LVEDV, ml/m$^2$</td>
<td>44.5 ± 11.8</td>
</tr>
<tr>
<td>LV Mass, g/m$^2$</td>
<td>63.9 ± 16.3</td>
</tr>
<tr>
<td>LV Hypertrophy</td>
<td>0.0%</td>
</tr>
<tr>
<td>Septal e’ mitral annular peak velocity, cm/s</td>
<td>11.1 ± 2.1</td>
</tr>
<tr>
<td>Lateral e’ mitral annular peak velocity, cm/s</td>
<td>12.5 ± 2.3</td>
</tr>
<tr>
<td>LV Filling Pressures (E/e’ mitral ratio)</td>
<td>6.5 ± 1.4</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or percentages. GFR = estimated glomerular filtration rate (MDRD-formula); CAD = coronary artery disease; LV Hypertrophy = LV mass ≥ 96g/m$^2$ in women or ≥ 116g/m$^2$ in men; E/e’ mitral = ratio of E (early-diastolic) mitral inflow peak velocity by pulsed-wave Doppler / e’ mitral annular (average septal-lateral) peak velocity using spectral tissue Doppler imaging.
Supplemental Methods - LV Systolic and Diastolic Myocardial Performance – Exemplifications

Myocardial Systolic Performance  = \[\frac{([\text{global radial systolic strain}] - ([\text{global longitudinal systolic strain} + \text{global circumferential systolic strain}])}{3}\]

Myocardial Diastolic Performance  = \[\frac{([\text{global longitudinal early diastolic SRe} + \text{global circumferential early diastolic SRe}] - ([\text{global radial early diastolic SRe}])}{3}\]

( - indicates to subtract; / indicates to divide; + indicates to add; SRe indicates early diastolic strain rate)

Examples:

**Case 1:** Global Longitudinal Systolic Strain = -25%; Global Circumferential Systolic Strain = -20%; Global Radial Systolic Strain = 30%.

- Myocardial Systolic Performance (Strain, %) = \[\frac{([30] - ((-25) + (-20)))}{3}\]
- Myocardial Systolic Performance = \[75\] /3
- Myocardial Systolic Performance (Strain, %) = 25

- In Case 1 the value of LV Myocardial Systolic Performance is 25%.

**Case 2:** Global Longitudinal Diastolic SRe = 1.00 s\(^{-1}\); Global Circumferential Diastolic SRe = 1.50 s\(^{-1}\); Global Radial Diastolic SRe = -2.50 s\(^{-1}\)

- Myocardial Diastolic Performance (SRe, s\(^{-1}\)) = \[\frac{([1.00] - (1.5)) - (-2.5)]}{3}\]
- Myocardial Diastolic Performance = \[5\] /3
- Myocardial Diastolic Performance (SRe, s\(^{-1}\)) = 1.66

- In Case 2 the value of LV Myocardial Diastolic Performance is 1.66 s\(^{-1}\).