Impacts of Mitral E/e′ on Myocardial Contractile Motion and Synchronicity in Heart Failure Patients With Reduced Ejection Fraction: An Exercise–Echocardiography Study

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ABSTRACT

Background: The association between diastolic abnormality and postexercise contractile decompensation is uncertain in heart failure (HF) patients with reduced left ventricular ejection fraction (LVEF).

Hypothesis: The higher mitral E/annular early diastolic velocity (E/e′) is relevant to postexercise regional myocardial contractile maladaptation.

Methods: Seventy HF patients with LVEF <50 % (56 males, 58 ± 15 years) were studied pre- and postexercise using tissue Doppler echocardiography. We evaluated the mean and standard deviation of systolic myocardial velocity (Sm) and electromechanical delay (Ts) of 12 left ventricular segments, and further analyzed the corresponding changes of septal and posterolateral segments.

Results: The higher mitral E/e′ was associated with more blunted heterogeneity of Sm and greater ventricular dyssynchrony after exercise. This is due to the posterolateral wall not being able to increase Sm with exercise to the same degree as the septum (decreased posterolateral/septal Sm ratio). Furthermore, the postexercise aggravated difference of Ts between septum and posterolateral segments leads to more dyssynchronous contraction in the higher E/e′ groups. An E/e′ ≥10 predicted a postexercise posterolateral/septal Sm ≤ 1 (odds ratio [OR]: 5.8, 95% confidence interval [CI]: 1.5-22.6, $P = 0.011$), and a difference of Ts between septum and posterolateral segments >65 ms (OR: 64, 95% CI: = 6–651, $P < 0.001$) in HF patients with reduced LVEF in multivariate analysis.

Conclusions: The higher mitral E/e′-related postexercise maladaptation of myocardial contractile motion and synchronicity suggests the involvement of systolic abnormality in exercise pathophysiology in HF patients with reduced LVEF.

Introduction

Diastolic abnormality has been considered as a key contributor to symptoms of heart failure (HF),[1,2] and several echocardiography or device-derived indicators of left ventricular (LV) diastolic function have been shown to correlate well with HF functional class or acute decompensated events in HF patients with reduced left ventricular ejection fraction (LVEF).[3–6] Among these diastolic parameters, the ratio of mitral E-flow velocity to annular early diastolic velocity (E/e′) could provide reliable information about LV filling pressures or pulmonary capillary wedge pressure, and accurately predict exercise tolerability,[7–11] HF hospitalization, and long-term prognosis.[12]

Because diastolic filling is coupled with systolic emptying, abnormal diastolic filling-related greater wall stress could compromise myocardial contraction. In the past, however, whether systolic dysfunction is related to diastolic abnormality or the genesis of HF symptoms remains controversial, probably owing to the reference of a less-sensitive parameter of systolic function (eg, LVEF).[13,14] With the current application of tissue Doppler imaging (TDI) to HF studies, segmental analysis of systolic myocardial motion makes the detailed quantification of myocardial contractile characteristics feasible. Patients with HF and LVEF below 45% were reported to have poorer outcome if they had a lower average of peak systolic myocardial velocity (Sm).[15] In addition, the contractile synchronicity defined as the absolute difference or standard deviation of the electromechanical

The study is partly supported by grants from National Science Council Taiwan: NSC 99-2314-B-002-116-MY3.
The authors have no other funding, financial relationships, or conflicts of interest to disclose.

Clin. Cardiol. 36, 8, 462–467 (2013)
Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22141

Received: February 20, 2013
Accepted: April 15, 2013

time delay from QRS onset to peak Sm among LV segments has emerged as a more specific predictor of worsening HF, event-free survival, and LV reverse remodeling after resynchronization therapy in patients with HF and reduced LVEF.[16–18]

Theoretically, poorer contractile adaptation for the myocardium to increased demands of exercise could lead to a reduction in cardiac efficiency and more impairment of exercise capacity in HF patients with reduced LVEF.[19] In the present study, we investigated the association between mitral E/e′ and TDI-derived myocardial contractile parameters, and explored the role of higher E/e′ in the postexercise dynamic change of myocardial contractile motion and synchronicity in HF patients with reduced LVEF.

Methods

Study Population

We consecutively enrolled 70 HF patients (58 ± 15 years; 56 male) with reduced LVEF defined as the presence of LVEF <50% (mean, 37 ± 8%) and HF signs/symptoms by Framingham criteria with New York Heart Association (NYHA) functional class II to III. All patients had to be maintained in stabilized HF condition for at least 3 months. The underlying etiology of HF was considered ischemic if patients had either a history of prior (>6 months) myocardial infarction or angiographic evidence of significant coronary artery disease sufficient to explain the compromised LV systolic function by the cardiologist's discretion. All treatable coronary lesions had to be revascularized by surgery or percutaneous angioplasty to minimize ischemic burden and stabilize HF before enrolling. Exclusion criteria included recent myocardial infarction (<6 months), chronic atrial fibrillation, chronic pulmonary disease, chronic renal failure (serum creatinine concentration >2.0 mg/dL), and situations that could make the measurement of E/e′ unreliable, including severe mitral regurgitation, severe mitral annular calcification, and the presence of abnormal septal motion such as intrinsic or pacemaker related left bundle branch block. This study complied with the Declaration of Helsinki, the protocol was approved by the institutional research ethics committee, and all patients gave written informed consent.

Echocardiography

Standard echocardiography was performed (Sonos 7500; Philips, Andover, MA) with a 1- to 3-MHz transducer with the sweep speed at 100 cm/s to measure left atrial (LA) dimension, LV chamber sizes, and LVEF (area-length method in apical 4-chamber view). Isovolumic relaxation time was measured as the time interval between the end of LV outflow and the start of LV inflow signals using a continuous-wave beam directed from the apical 5-chamber view across the region between the aortic outflow tract and the mitral inflow tract. Interventricular contraction delay was defined as the time difference between the QRS onset to the onset of the pulmonary and aortic flow by pulsed-wave Doppler imaging. The mitral E/e′ was measured as the ratio of the peak early mitral inflow velocity over the peak e′ (mean of septal and lateral mitral annular early diastolic velocity by TDI). Meanwhile, the 6-basal and 6-mid LV segments including septal, anteroseptal, anterior, lateral, posterior, and inferior aspects were then studied using apical views for the long-axis motion of the LV with a frame rate of 100 Hz using pulsed Doppler scanning. In this way, the peak velocity of Sm of the 12 LV segments and the electromechanical time delay from the QRS onset to segmental Sm (Ts) were measured as in our prior studies.[20,21] The mean and heterogeneity (standard deviation [SD]) of the Sm and Ts of the 12 LV segments were calculated before and after exercise, and the corresponding segmental changes of Sm and Ts over the septum and posterolateral wall were further analyzed. The intraobserver variability was 1.67% for mitral Ea, 1.09% for mean Sm, and 1.91% for SD-Ts. The corresponding values for interobserver variability were 2.38%, 1.31%, and 3.84%, respectively, in the present study.

Grouping

To gain insight into the relationship of mitral E/e′ with TDI-derived myocardial contractile parameters, the study cohort was arbitrarily grouped by E/e′ into below 10 (26 patients), between 10 and 15 (25 patients), and above 15 (19 patients).

Exercise Protocol

After baseline echocardiography study, all patients completed a treadmill exercise test (Exercise System CH 2000; Cambridge Heart, Inc., Bedford, MA) for up to 6 minutes (stage 2) using the modified Bruce protocol (1.7 MPH, slope = 5 %, 3.47 metabolic equivalents). TDI for the measurement of Sm and Ts of the 12 LV segments was collected immediately after exercise by the same position as pre-exercise.

Statistical Analysis

All values are expressed as the mean ± SD or as percentages. Comparisons among subgroups were performed by analysis of variance (ANOVA). If there was a P value <0.05 by ANOVA test, between-group differences were further compared by the unpaired Student t test or the χ^2 test. To evaluate the effect of exercise, parameters at rest and after exercise were compared by paired t test. Correlation between variables was derived by the Pearson or Spearman test. In multivariate logistic regression analysis, a forward stepwise model was used to include factors with a P value <0.10. For all tests, a P value <0.05 was considered statistically significant. All analyses were performed using the SPSS 17.0 software package (SPSS Inc., Chicago, IL).

Results

Baseline Characteristics

The clinical characteristics and baseline echo parameters of these patients are listed in Table 1 and Table 2. Among the 3 groups, as shown in Table 2, patients with mitral E/e′ <10 had the smallest LA and the greatest mitral e′. They also had smaller LV chamber dimensions than patients with E/e′ >15. The table also suggests a correlation between higher E/e′ and clinical manifestations of HF, as represented by

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DOI:10.1002/clc.22141

Table 1. Baseline Characteristics

	All Patients, N = 70
Age, y	58 ± 15
Gender, male/female	56/14
Hypertension (%)	30 (43)
Diabetes mellitus (%)	13 (19)
Smoking (%)	28 (40)
Prior stroke (%)	2 (3)
History of atrial fibrillation (%)	12 (17)
Ischemic origin (%)	32 (46)
NYHA functional class, II/III	54/16
Aspirin (%)	34 (49)
Nitrates (%)	15 (21)
Calcium channel blockers (%)	11 (16)
β-Blockers (%)	35 (50)
ACEI/ARB (%)	53 (76)
Diuretics (%)	48 (69)
Digitalis (%)	27 (39)
Antiarrythmic agents (%)	16 (23)

Abbreviations: ACEI/ARB, angiotension-converting enzyme inhibitor/angiotension II receptor blocker; NYHA, New York Heart Association.

Table 2. Comparisons of Baseline NYHA Functional Class, QRS Width, and Echocardiographic Characteristics

	E/e′ > 15, n = 19	E/e′ 10–15, n = 25	E/e′ <10, n = 26	P by ANOVA
NYHA class II/III, n	8/11	23/2[a]	23/3[a]	<0.001
QRS width, ms	116 ± 37	108 ± 22	102 ± 25	0.326
Echo parameters				
LA diameter, mm	41 ± 9	40 ± 8	35 ± 6[a b]	0.021
LVEDD, mm	64 ± 9	59 ± 10	55 ± 9[a]	0.010
LVESD, mm	54 ± 10	47 ± 10[a]	44 ± 9[a]	0.005
LVEF, %	34 ± 8	37 ± 8	39 ± 7	0.114
Mitral E-flow, cm/s	87 ± 33	73 ± 27	58 ± 19[a b]	0.002
Mitral A-flow, cm/s	74 ± 29	75 ± 19	70 ± 12	0.620
Mitral E/A	1.4 ± 0.8	1.0 ± 0.4	0.9 ± 0.4[a]	0.014
E-flow DT, ms	183 ± 99	231 ± 66	244 ± 91	0.063
IVRT, ms	108 ± 40	113 ± 25	118 ± 49	0.723
Mitral e′, cm/s	4.1 ± 1.6	6.0 ± 2.2[a]	8.6 ± 3.3[a b]	<0.001
Mitral E/e′	23 ± 12	12 ± 2[a]	7 ± 2[a b]	<0.001

Abbreviations: ANOVA, analysis of variance; DT, deceleration time; e′, annular early diastolic velocity; IVRT, isovolumic relaxation time; LA diameter, left atrial diameter; LVEDD, left ventricular end-diastole dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systole dimension; NYHA, New York Heart Association.
[a] $P < 0.05$, E/e′ <10 or 10–15 group vs ≥15 group. [b] $P < 0.05$, E/e′ <10 group vs 10–15 group.

worsening NYHA functional class ($r = 0.411, P < 0.001$). Not surprisingly, a higher E/e′ was also associated with a trend toward pseudonormalized mitral inflow pattern (increased mitral E/A and shortened mitral deceleration time).

Impact of E/e′ on Myocardial Contractile Motion and Electromechanical Time Delay Before and After Exercise

As shown in Table 3, the baseline and postexercise interventricular delay was not associated with E/e′. The mitral E/e′, although without correlation with LVEF ($P > 0.05$ in the current study), significantly correlated negatively with baseline and postexercise mean Sm ($r = -0.361$, $P = 0.002$ at baseline, $r = -0.413$, $P = 0.001$ postexercise). Regarding contractile heterogeneity, more blunted heterogeneity of Sm but increased ventricular dyssynchrony developed after exercise in patients with higher E/e′.

Segmental Sm and Ts: Contribution to Postexercise Change of Heterogeneity

The baseline and postexercise septal and posterolateral (mean of posterior and lateral segments) Sm and Ts at the LV basal portion were grouped by mitral E/e′ and are shown in Table 4. At baseline, the higher mitral E/e′ was associated with both lower septal and posterolateral Sm, whereas the ratio of posterolateral to septal Sm did not differ among the 3 groups. After exercise, however, the recruitment of Sm over posterolateral wall was much less than that over the septum in subgroups with mitral E/e′ = 10 to 15 and >15, compared to patients with E/e′ <10. This reflected in the significantly reduced ratio of posterolateral Sm/septal Sm after exercise in patients with mitral E/e′ >15 and between 10 and 15 ($P < 0.05$ by paired t test).

Regarding the electromechanical synchronicity, the maximal time difference between the septum and posterolateral wall did not differ significantly among the 3 subgroups at baseline (Table 4). However, after exercise, the maximal time difference between septum and posterolateral wall increased significantly ($P < 0.05$ by paired t test) in patients with mitral E/e′ >15 and between 10 and 15, but not in patients with E/e′ <10. This postexercise increase in the time delay between the septum and posterolateral wall in patients with higher E/e′ contributes to more contractile dyssynchrony after exercise.

Multivariate Analyses: The Effects of Mitral E/e′ on Postexercise Myocardial Adaptation of LV Posterolateral Wall

After adjusting for age, gender, presence of diabetes, existence of coronary artery disease, QRS duration,

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DOI:10.1002/clc.22141

Table 3. Comparisons of Baseline and Postexercise Myocardial Contractile Parameters

	E/e′ >15, n = 19	E/e′ 10–15, n = 25	E/e′ <10, n = 26	P by ANOVA
Heart rate, 1/min				
Baseline	89 ± 22	77 ± 17	84 ± 16	0.120
Postexercise	118 ± 22	106 ± 20	111 ± 22	0.245
Inter-V delay, ms				
Baseline	37 ± 19	25 ± 22	22 ± 22	0.062
Postexercise	20 ± 17	23 ± 19	21 ± 18	0.860
Mean Sm, cm/s				
Baseline	4.3 ± 1.1	5.2 ± 1.2[a]	5.7 ± 1.1[a]	<0.001
Postexercise	4.5 ± 1.1	5.5 ± 1.5[a]	6.3 ± 1.5[a]	<0.001
SD Sm, cm/s				
Baseline	1.3 ± 0.5	1.1 ± 0.4	1.3 ± 0.6	0.453
Postexercise	1.0 ± 0.3	1.1 ± 0.4	1.3 ± 0.6[a]	0.045
Mean Ts, ms				
Baseline	206 ± 27	209 ± 25	189 ± 25[b]	0.019
Postexercise	202 ± 26	207 ± 33	193 ± 28	0.222
SD Ts, ms				
Baseline	30 ± 19	32 ± 18	22 ± 16	0.099
Postexercise	35 ± 12	39 ± 17	24 ± 18[a, b]	0.004

Abbreviations: ANOVA, analysis of variance; e′, annular early diastolic velocity; Inter-V, interventricular; LVEF, left ventricular ejection fraction; SD, standard deviation; Sm, systolic myocardial velocity; Ts, electromechanical time delay.
[a] $P < 0.05$, E/e′ <10 or 10–15 group vs >15 group. [b] $P < 0.05$, E/e′ <10 group vs 10–15 group.

Table 4. Influence on Postexercise Heterogeneity by Posterolateral Wall Adaptation: Effects of Mitral E/e′

	E/e′ >15, n = 19	E/e′ 10–15, n = 25	E/e′ <10, n = 26	P by ANOVA
Basal-septal Sm, cm/s				
Baseline	4.5 ± 1.7	5.7 ± 1.6[a]	5.4 ± 1.0[a]	0.031
Postexercise	4.9 ± 1.7	6.2 ± 2.0[a, b]	6.1 ± 1.2[a, b]	0.044
Basal-posterolateral Sm, cm/s				
Baseline	4.7 ± 1.4	5.7 ± 1.5[a]	6.6 ± 1.6[a, c]	<0.001
Postexercise	4.8 ± 1.3	5.7 ± 1.6	7.2 ± 2.1[a,b,c]	<0.001
Posterolateral Sm/septal Sm				
Baseline	1.17 ± 0.48	1.06 ± 0.30	1.27 ± 0.32	0.116
Postexercise	1.03 ± 0.30[b]	0.98 ± 0.31[b]	1.20 ± 0.33[c]	0.040
Basal-septal Ts, ms				
Baseline	195 ± 40	193 ± 33	186 ± 27	0.646
Postexercise	189 ± 51	187 ± 50	187 ± 43	0.991
Basal-posterolateral Ts, ms				
Baseline	213 ± 42	226 ± 46	195 ± 37[c]	0.035
Postexercise	211 ± 30	231 ± 43	191 ± 38[c]	0.003
Max Diff-Ts, ms				
Baseline	55 ± 40	59 ± 48	38 ± 38	0.165
Postexercise	70 ± 31[b]	79 ± 39[b]	39 ± 34[a, c]	0.001

Abbreviations: ANOVA, analysis of variance; e′, annular early diastolic velocity; Max Diff, maximal difference between posterolateral wall and septum; Sm, systolic myocardial velocity; Ts, electromechanical time delay.
[a] $P < 0.05$, E/e′<10 or 10–15 group vs>15 group; [b] $P < 0.05$, postexercise vs baseline by paired t test. [c] $P < 0.05$, E/e′ <10 group vs 10–15 group.

cardiovascular medications, and LVEF in a multivariate logistic regression analysis, a baseline mitral E/e′ ≥10 was shown to be an independent predictor of more impaired adaptation of LV posterolateral wall to exercise, defined as the presence of postexercise ratio of posterolateral to septal Sm ≤1 (odds ratio [OR]: 5.8, 95% confidence interval [CI]: 1.5-22.6, $P = 0.011$), and postexercise ventricular dyssynchrony defined as a maximal difference of Ts between the septum and posterolateral wall >65 ms[18] (OR: 64, 95% CI: 6–651, $P < 0.001$) in patients with HF and reduced LVEF in the present study.

Discussion

The principle finding of the study was that there is a significant correlation between the mitral E/e′ and TDI-derived mean LV myocardial contractile velocity at baseline and after exercise in HF patients with reduced LVEF. The higher mitral E/e′ was found to be associated with postexercise maladaptation of myocardial contractile response over posterolateral segments leading to the blunted heterogeneity of LV myocardial motion and aggravated ventricular dyssynchrony. This more impairment of myocardial contractile adaptation to exercise in the higher mitral E/e′ state could suggest the involvement of systolic abnormality in the exercise pathophysiology in patients with HF and reduced LVEF.

In the resting state, we found that in the present study the HF patients with an elevated mitral E/e′, even without a statistically different LVEF from those with a lower E/e′, had a more reduced mean myocardial contractile velocity. Prior studies have shown that TDI-derived mean systolic myocardial velocity may serve as a more accurate measurement of systolic dysfunction than ejection fraction (EF),[22] and that the mitral E/e′ could add incremental

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DOI:10.1002/clc.22141

prognostic information to conventional echocardiographic measure of LVEF for HF patients.[23,24] These findings are potentially attributable to the higher mitral E/e′-related much more depressed myocardial contractile velocity, irrespective of the gross EF in the population with HF and reduced LVEF as shown in our study.

Consideration of exercise intolerance or exertional dyspnea as the key symptoms of HF has also led some studies[20,25–27] to evaluate exercise-related changes of segmental myocardial contractile function by TDI. In the present study, we demonstrated that higher mitral E/e′ was accompanied with more blunted heterogeneity of Sm and more dyssynchronous myocardial contraction after exercise provocation. Meanwhile, we also showed a significant correlation between the mitral E/e′ and NYHA functional classification. Prior studies have demonstrated that the mitral E/e′ correlated well with pulmonary capillary wedge pressure and exercise tolerance in patients with reduced systolic function.[4,28] Lafitte et al. also reported that exercise–rest changes in LV dyssynchrony parameters were negatively correlated with exercise–rest changes in echo-derived cardiac output.[26] The findings of our study supported that the higher mitral E/e′ could lead to the development of more ventricular dyssynchrony after exercise, which might compromise more of the cardiac output and result in more exercise intolerance in HF patients with reduced LVEF.

Late-activated ventricular posterolateral segments were subjected to the greatest stress in patients with HF because of locally enhanced preload and afterload secondary to early systolic stretch and late systolic contraction against high LV cavity pressures.[29] Our study demonstrated that the higher mitral E/e′, which suggests a higher LV filling pressure, was associated with a relatively lower Sm and a longer electromechanical delay over the posterolateral segments, both at baseline and after exercise. The impairment of contractile adaptation of the LV posterolateral wall to exercise was also found in patients with a higher mitral E/e′, manifesting as flattening of postexercise posterolateral Sm response relative to the augmentation of septal Sm and the significantly increased maximal difference of electromechanical time delay between the posterolateral wall and the septum in the higher E/e′ groups. In an HF animal model study,[30] lower expression of key proteins involved in muscle mechanics and electrophysiology are shown to be located at the LV free wall, which bears greater hemodynamic load than the septum. This observation could help explain our echocardiographic findings of differences in resting state and postexercise maladaptation regarding contractile parameters under different grades of mitral E/e′ as well as the relevant variations of LV wall stress among distinct LV segments.

The presence of severely stenosed coronary arteries has been shown to be associated with exercise-induced global or regional ventricular dysfunction in human and animal studies since decades ago.[31,32] Several studies also showed that systolic shortening characteristics and diastolic dysfunction during exercise would improve with successful revascularization to major epicardial coronary arteries.[33,34] Because nearly half (46%) of the HF patients were due to ischemia (coronary artery disease) in the study, exercise-induced ischemia due to stenosed coronary arteries should have been corrected by revascularization, and its complex interaction with ventricular function during exercise could have been minimized. Revascularization before enrollment made it feasible to test the interplay between mitral E/e′ and postexercise contractile parameters in the study, and also provided the possible reason that mitral E/e′ served as an independent predictor of contractile adaptation to exercise irrespective of the presence of coronary artery disease in multivariate analysis.

Limitations

Our study has several limitations. First, the sample size of the study was relatively small. Because the study design was to investigate the exercise-related contractile parameters, it seemed risky and not feasible to include patients with functional class IV who have severe HF symptoms to undergo any exercise challenge. On the other hand, the study patients were diagnosed to have HF with reduced EF, basically due to the existence of HF signs or symptoms. This led to the difficulty in including a comparable number of asymptomatic patients with systolic dysfunction in the study. Whether the study results were applicable to the 2 groups of patients could not be answered. However, patients with a wide spectrum of mitral E/e′ in the study still could represent the majority of stable symptomatic HF patients in the daily practice. Second, the mitral E/e′ was measured at resting state only. Nevertheless, most contemporary HF studies investigating the clinical significance of E/e′ were based on the relevant values at rest. Third, although we had revascularized all treatable coronary lesions in patients with ischemic heart disease, the potential influence of microvascular ischemia on regional contractile function could not be excluded. However, multivariate analysis in the current study showed the mitral E/e′ to be an independent predictor of poorer postexercise myocardial adaptation irrespective of the presence of coronary artery disease. Fourth, patients with wider QRS duration other than left bundle branch block were not excluded in the study. The influence of wide QRS on the evaluation of mitral E/e′ remains uncertain from the literature. Fifth, whether a direct or independent link of the postexercise contractile decompensation to exercise intolerance or clinical outcomes exists could not be answered in the study and deserves further investigation.

Conclusion

The mitral E/e′ provides information about the dynamic variations in postexercise contractile adaptation of regional myocardium. The higher mitral E/e′ was associated with postexercise change of contractile heterogeneity, which suggested the potential involvement of contractile maladaptation in exercise pathophysiology in HF patients with reduced LVEF.

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DOI:10.1002/clc.22141