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The Pathophysiology of Heart Failure With Normal Ejection Fraction

Exercise Echocardiography Reveals Complex Abnormalities of Both Systolic and Diastolic Ventricular Function Involving Torsion, Untwist, and Longitudinal Motion

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Objectives The purpose of this study was to test the hypothesis that in heart failure with normal ejection fraction (HFNEF) exercise limitation is due to combined systolic and diastolic abnormalities, particularly involving ventricular twist and deformation (strain) leading to reduced ventricular suction, delayed untwisting, and impaired early diastolic filling.

Background A substantial proportion of patients with heart failure have a normal left ventricular ejection fraction. Currently the pathophysiology is considered to be due to abnormal myocardial stiffness and relaxation.

Methods Patients with a diagnosis of HFNEF and proven cardiac limitation by cardiopulmonary exercise testing were studied by standard, tissue Doppler, and speckle tracking echocardiography at rest and on submaximal exercise.

Results Fifty-six patients (39 women; mean age 72 ± 7 years) with a clinical diagnosis of HFNEF and 27 age-matched healthy control subjects (19 women; mean age 70 ± 7 years) had rest and exercise images of sufficient quality for analysis. At rest, systolic longitudinal and radial strain, systolic mitral annular velocities, and apical rotation were lower in patients, and all failed to rise normally on exercise. Systolic longitudinal functional reserve was also significantly lower in patients ($p < 0.001$). In diastole, patients had reduced and delayed untwisting, reduced left ventricular suction at rest and on exercise, and higher end-diastolic pressures. Mitral annular systolic and diastolic velocities, systolic left ventricular rotation, and early diastolic untwist on exercise correlated with peak VO_2max.

Conclusions In HFNEF there are widespread abnormalities of both systolic and diastolic function that become more apparent on exercise. HFNEF is not an isolated disorder of diastole. (J Am Coll Cardiol 2009;54:36–46) © 2009 by the American College of Cardiology Foundation

It is now well-established that at least one-half of the patients presenting with symptoms and signs of heart failure will have a normal left ventricular ejection fraction (LVEF) (1,2). This form of heart failure has been variously labeled as diastolic heart failure, heart failure with preserved systolic function, or more simply heart failure with a normal ejection fraction (HFNEF). The pathophysiology of HFNEF and the generation of symptoms remain controversial (3). Zile et al. (4) suggested on the basis of invasive hemodynamic studies that patients with HFNEF have significant abnormalities in active relaxation and passive stiffness, and concluded that the pathophysiological cause of elevated diastolic pressures and symptoms is abnormal diastolic function alone, because systolic function was considered normal. Similarly, Westermann et al. (5) demonstrated recently increased LV stiffness at rest in HFNEF, although this did not increase with hand-grip or atrial pacing. Both of these

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studies used invasive techniques with the subjects at rest, but the primary symptom of HFNEF patients is breathlessness on exercise. Furthermore, the orthodox view that systolic function is entirely normal has been challenged in studies using newer echocardiographic techniques, which have shown that systolic function does not seem to be entirely normal in all subjects with HFNEF (6–8) or those with LV hypertrophy (9) and diabetes (10), both etiologic factors for HFNEF (11). New developments in echocardiography enable a much fuller assessment of LV systolic and diastolic function, including measurement of myocardial deformation or strain in 3 planes, ventricular twist and untwist, annular motion (longitudinal function), and LV suction, which is a vital mechanism in early diastolic ventricular filling (12–14). We hypothesized that in HFNEF there are combined systolic and diastolic abnormalities particularly involving ventricular twist and deformation (strain) leading to reduced ventricular suction, delayed untwisting, and impaired early diastolic filling and that these mechanisms are more important in the generation of symptoms, especially on exercise when diastole shortens, than increased ventricular stiffness alone.

Methods

We assessed LV systolic and diastolic function noninvasively at rest and on exercise with echocardiography in patients with HFNEF and in healthy control subjects.

Patients with signs or symptoms of heart failure (New York Heart Association [NYHA] functional class II or more) with an LVEF >50% by transthoracic echocardiography who met the criteria of Vasan and Levy (15) for probable diastolic heart failure and healthy control subjects with a comparable mean age chosen randomly from local primary care surgeries were recruited in this study. Patients were studied on treatment (Table 1). Exclusion criteria included moderate-to-severe pulmonary disease, significant congenital or valvular heart disease, electrical pacemakers or implantable cardiac defibrillators, and established history of ischemic heart disease. All subjects gave written informed consent before their participation, and the study was approved by the institutions' research ethical committees.

Cardiopulmonary exercise test. Subjects had standard spirometry before they underwent incremental treadmill exercise testing with metabolic gas exchange and simultaneous heart rate, blood pressure (BP), and oxygen saturation monitoring with a modified Bruce protocol (16,17). A respiratory exchange ratio >1 was taken to indicate maximal effort (18). Breathing reserve <15 l/min was taken as respiratory limitation. A blood sample was taken before exercise for N-terminal pro-brain natriuretic peptide (NT-proBNP) analysis (19).

2-dimensional and tissue Doppler echocardiography. All subjects underwent full echocardiography examination with a GE Vingmed Vivid Seven scanner (Horton, Norway) at rest and during exercise. Symptom-limited (fatigue or dyspnea) exercise testing was done on a semi-recumbent and tilting bicycle ergometer (Lode BV, Groningen, the Netherlands) to a maximum heart rate of 100 beats/min (i.e., submaximal exercise to maximize frame rates). At least 3 sets of images with loops consisting of at least 3 consecutive cardiac cycles each were stored for offline analysis with a customized software package (EchoPac, GE Vingmed). The LV volume and ejection fraction (EF) were measured with the modified biplane Simpson's method from the apical 4- and 2-chamber views (20). LV mass was calculated according to Devereux formula (21). Left atrial volume was calculated with the biplane area-length method from the apical 4- and 2-chamber views and indexed to body surface area to derive left atrial volume index (22). The early filling (E) and atrial (A) filling peak velocities, E/A ratio, and deceleration time (DT) of early filling and isovolumic relaxation time were measured from transmitral flow.

Color M-mode Doppler was obtained by positioning the scan line through the mitral valve with the Nyquist limit and the color baseline adjusted to obtain the best spatial resolution. The mitral flow propagation velocity (Vp) was measured by the slope along the aliasing isovelocity line as previously described (23,24).

Peak mitral annular myocardial velocity of all 4 walls of the LV (septal, lateral, inferior, and anterior) was recorded with real time pulsed wave tissue Doppler method as previously described (25). The sample volume and gain were optimized, and the Nyquist limit was set to 15 to 20 cm/s. The peak systolic (S′), early diastolic (E′), and late diastolic (A′) mitral annular velocities were measured, and the ratio of early mitral diastolic inflow velocity to early diastolic mitral annular velocity (E/E′), which is an index of LV filling pressure, was calculated (26). Color-coded tissue Doppler images were also acquired over 3 consecutive cardiac cycles for each of the 4 myocardial walls and analyzed offline as previously described (27,28). Systolic (Sm) and diastolic (Em) velocities were measured by placing a 4 × 4 mm region of interest in the midmyocardial area of each wall.

Speckle tracking. The LV longitudinal strain, radial strain, and rotation were assessed with the speckle tracking method (12–14). Offline analysis of apical 4- and 2-chamber images and short-axis images at 3 levels (basal, midventricular, and

Abbreviations and Acronyms

A′ = peak late diastolic myocardial mitral annular velocity by pulse wave Doppler imaging

Am = peak late diastolic myocardial mitral annular velocity by color tissue Doppler imaging

DT = deceleration time

E′ = peak early diastolic myocardial mitral annular velocity by pulse wave Doppler imaging

Em = peak early diastolic myocardial mitral annular velocity by color tissue Doppler imaging

LV = left ventricle/ventricular

NT-proBNP = N-terminal pro-brain natriuretic peptide

S′ = peak systolic myocardial mitral annular velocity by pulse wave Doppler imaging

Sm = peak systolic myocardial mitral annular velocity by color tissue Doppler imaging

VO_2max = maximum oxygen consumption

Vp = mitral flow propagation velocity

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Table 1 Clinical Characteristics and Standard Echocardiographic Parameters

	Patients (n = 56)	Control Subjects (n = 27)	p Value
Age, yrs	72 ± 7	70 ± 7	0.195
Sex, F/M	39/17	19/8	0.579*
BMI, kg/m^2	30 ± 5	24 ± 4	<0.001
NYHA functional class			
II	41	—	
III	15	—	
VO_2max, ml/min/kg (% of predicted)	17.9 ± 4.0 (78 ± 16)	30.9 ± 4.3 (135 ± 18)	<0.001
Hypertension	45/56 (80%)	0/27 (0%)	<0.001*
Years of hypertension	8.3 ± 10.0	0	<0.001†
Diabetes mellitus	12/56 (21%)	0/27 (0%)	0.006*
Atrial fibrillation	3/56 (5%)	0/19 (0%)	0.302*
Coronary artery disease	6/56 (11%)	0/19 (0%)	0.086*
ACE inhibitor	18 (32%)	0	<0.001*
AT1-blocker	16 (29%)	0	<0.001*
Beta-blocker	20 (36%)	0	<0.001*
Calcium-channel blocker	13 (23%)	0	0.003*
Diuretic	28 (50%)	0	<0.001*
Alpha-blocker	11 (20%)	0	0.009*
Statin	19 (34%)	0	<0.001*
LVEDD, cm	4.7 ± 0.7	4.6 ± 0.5	0.275
Biplane LVEF, %	61 ± 6	62 ± 8	0.306
FS, %	40 ± 10	39 ± 7	0.558
IVSd, cm	1.1 ± 0.3	1.0 ± 0.2	0.092
LVMI, g/m^2	96 ± 34	82 ± 22	0.081
LAVI, ml/m^2	32 ± 11	24 ± 9	0.002
E-wave, cm/s	0.69 ± 0.19	0.57 ± 0.11	0.003
A-wave, cm/s	0.85 ± 0.19	0.70 ± 0.14	0.001
E/A	0.83 ± 0.26	0.84 ± 0.19	0.877
DT, ms	250 ± 58	258 ± 46	0.515
IVRT, ms	96 ± 27	100 ± 22	0.569
E/E′	11.4 ± 4.3	8.2 ± 2.0	0.001

*Fisher exact test between patients and control subjects. †Mann-Whitney *U* test between patients and control subjects.

ACE = angiotensin-converting enzyme; AT1 = angiotensin 1; A-wave = late mitral diastolic inflow velocity; BMI = body mass index; DT = deceleration time of peak early Doppler mitral filling velocity; E/A = ratio of early to late mitral inflow velocities; E/E′ = ratio of early mitral diastolic inflow velocity to early diastolic mitral annular velocity; E-wave = early mitral diastolic inflow velocity; FS = fractional shortening; IVRT = isovolumic relaxation time; IVSd = diastolic interventricular septal thickness; LAVI = left atrial volume index; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; NYHA = New York Heart Association; VO_2max = maximum oxygen consumption.

apical) were completed by tracing the endocardium in end-diastole and the thickness of the region of interest adjusted to include the entire myocardium. The software automatically tracks the myocardial motion on the subsequent frame, and results were displayed graphically. Rotation and strain in the radial, longitudinal, and circumferential planes were measured as previously described (12–14,29). All echocardiographic measurements were done in duplicate by 2 independent observers (Y.T.T. and F.W.) blinded to each other's results.

Derived parameters for assessing systolic and diastolic function. Stroke volume was calculated by using the aortic valve pulsed wave Doppler method whereby the velocity time integral of aortic annular flow was obtained by tracing the pulsed Doppler profile and multiplied by the area of the aortic annulus as previously described (30). Pre-load recruitable stroke work index, peak power index, single beat estimated end-systolic elastance, arterial elastance (31–33), chamber stiffness (34), pressure volume ratio (35), and longitudinal reserve indexes (36) were calculated:

$$\text{Arterial elastance} = 0.9 \times \text{BP systole/stroke volume}$$

$$\text{End-systolic elastance} = 0.9 \times \text{BP systole/end-systolic volume}$$

$$\text{Peak power index} = \text{peak ejection rate (LV outflow tract peak velocity)} \times \text{BP systole/end-diastolic volume}$$

$$\text{Pressure/volume ratio} = (E/E')/\text{end-diastolic volume}$$

$$\text{Chamber stiffness} = 70/(DT\text{-}20)^2$$

$$\text{Systolic longitudinal function reserve index} = \Delta Sm \times [1 - (1/Sm_{rest})]$$

$$\text{Diastolic longitudinal function reserve index} = \Delta Em \times [1 - (1/Em_{rest})]$$

Statistical analysis. Sample size was estimated with pilot data. For systolic longitudinal function with anticipated difference in mean of 1.5 and SD 2, a sample size of 30 would provide 99% power for a paired *t* test and 89% for an unpaired *t* test with $\alpha = 0.05$ (1 tail). For rotation with anticipated difference in mean of 3 degrees and SD 4, a sample size of 30 would provide 99% power for a paired *t* test and 89% for an unpaired *t* test with $\alpha = 0.05$ (1 tail). Statistical analysis was performed with SPSS version 15.0 (Chicago, Illinois). Continuous variables were expressed as mean ± SD. Comparisons between HFNEF patients and control subjects were performed with unpaired *t* test for normally distributed data and the Mann-Whitney *U* test for non-normally distributed data. Comparisons within HFNEF patients and control subjects were performed with paired *t* test only, because all data were normally distributed. Linear regression (Pearson's coefficient) was performed to test correlations.

Interobserver and intraobserver agreements were performed with readings of 10 randomly selected subjects and were calculated with α model reliability analysis and reported as interclass correlation coefficient (ICC) with a 95% confidence interval. A value of $p < 0.05$ was considered significant.

Results

A total of 121 subjects (74 patients and 47 control subjects) were recruited in this study. Eighteen patients were excluded: 7 were found to have respiratory limitation on cardiopulmonary exercise test, 6 were unable to exercise and had poor picture quality for analysis, 2 had no increase in heart rate on exercise, 1 was found to have evidence of ischemia on cardiopulmonary exercise test, 1 had normal maximum oxygen consumption (VO_2max) on exercise, and 1 had entirely normal echocardiography and symptoms were thought to be related to atrial fibrillation. Of 47 recruited, only 27 completely healthy control subjects without past medical history and receiving no medications could be included in this study. Twenty subjects were excluded due to evidence of hypertension (previously undiagnosed) at rest (n = 17), reduced VO_2max on cardiopulmonary exercise test (n = 1), fulfilled echocardiographic criteria for HFNEF (n = 1), and sinus tachycardia at rest due to anxiety (n = 1).

The mean age of the patients was 72 ± 7 years, and 70% were women. Control subjects were of comparable age (70 ± 7 years, p = NS) and 70% were women. The past medical history and drug history of the patients are summarized in Table 1. All patients were receiving treatment and had had symptoms of heart failure with NYHA functional class II or III. Patients had a significantly higher body mass index compared with control subjects, but VO_2max, which accounted for body mass index and age, was significantly lower in patients compared with control subjects (Table 1). Thirty-six patients were able to perform a satisfactory full cardiopulmonary exercise test, 11 were unable to perform the test, and 9 did not achieve a respiratory exchange ratio >1. The median NT-proBNP of patients was 85.8 pg/ml (interquartile range 37.3 to 179.1 pg/ml). The LVEF and LV dimensions were comparable between patients and control subjects. Left atrial volume index, mitral inflow E and A waves, and E/E′ were significantly higher in the patients (Table 1).

Hemodynamic changes. The resting and exercise heart rate and BP were comparable between patients and control subjects (Table 2). The increase in aortic outflow velocity time integral, peak left ventricular outflow tract velocity, stroke volume, and cardiac output on exercise was significantly higher in control subjects. Even though control subjects had a slightly lower initial aortic outflow velocity time integral, stroke volume, and cardiac output, they were able to achieve a significant increase on exercise compared with the patients (Table 2).

Longitudinal function: tissue Doppler and speckle tracking. Mitral annular velocities in systole (Sm), early diastole (Em), and late diastole (Am) at rest were significantly lower in patients compared with control subjects. On exercise, the differences in Sm and Em between patients and control subjects became highly significant (Table 2). The Sm and Em were used to calculate the systolic and diastolic longitudinal reserve indexes. The HFNEF patients had a significantly lower systolic (0.64 ± 0.51 vs. 1.54 ± 0.51, $p < 0.001$) and diastolic (1.49 ± 0.77 vs. 2.32 ± 1.24, $p < 0.011$) longitudinal reserve compared with control subjects (Table 2).

With 2-dimensional speckle tracking patients had significantly lower longitudinal strain during systole at rest, regardless of the wall used to assess. Calculation of the average longitudinal strain with 6 segments of the septal and lateral walls or the average from the 6 segments of the inferior and the anterior walls or the average of all 12 segments of all 4 walls yielded similar results. This indicated a reduction in global longitudinal systolic function in patients (Table 3). Even though patients had a significant increase in longitudinal strain on exercise, the magnitude of longitudinal strain on exercise only approximated to the magnitude of longitudinal strain in control subjects at rest. The longitudinal strain on exercise was significantly lower in patients compared with control subjects (Table 3).

Radial function: 2-dimensional strain. Radial strain during systole was also significantly reduced in patients at rest, more so on exercise compared with healthy control subjects (Table 3). Interestingly, radial strain increased significantly on exercise in patients, but the mean radial strain on exercise in patients only equated to the resting radial strain in control subjects.

LV rotation and untwist. The ability of the LV to rotate in systole and untwist in diastole was significantly reduced in patients compared with control subjects both at rest and on exercise. The percentage of LV untwist in early (25% of untwist duration) and late diastole (75% of untwist dura-

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Table 2 Hemodynamic Status and Doppler Echocardiography

	Patients at Rest	Patients on Exercise	p Value (Paired *t* Test)	Control Subjects at Rest	Control Subjects on Exercise	p Value (Paired *t* Test)	p Value (Unpaired *t* Test)
BP systolic (mm Hg)	146 ± 16	168 ± 18	<0.001	140 ± 15	163 ± 15	<0.001	0.114* 0.298†
BP diastolic (mm Hg)	75 ± 10	86 ± 13	<0.001	78 ± 8	87 ± 9	<0.001	0.166* 0.687†
Heart rate (beats/min)	69 ± 11	89 ± 10	<0.001	67 ± 9	92 ± 5	<0.001	0.484* 0.157†
VTI (cm)	21.5 ± 4.8	22.8 ± 5.3	0.066	19.3 ± 3.9	23.3 ± 3.4	<0.001	0.045* 0.743†
ΔVTI (cm)		1.3 ± 4.2			4.3 ± 1.9		0.003
Stroke volume (ml)	73 ± 20	74 ± 23	0.239	62 ± 13	79 ± 20	0.004	0.015* 0.364†
Δ stroke volume (ml)		4 ± 24			18 ± 24		0.039
Cardiac output (l/min)	4.8 ± 1.5	6.4 ± 2.0	<0.001	4.2 ± 0.9	7.4 ± 2.0	<0.001	0.059* 0.097†
Δ cardiac output (l/min)		1.6 ± 2.2			3.1 ± 2.4		0.027
Peak LVOT velocity (m/s)	1.1 ± 0.2	1.2 ± 0.3	0.004	1.0 ± 0.2	1.2 ± 0.1	<0.001	0.044 0.682
Δ peak LVOT velocity (m/s)		0.1 ± .2			0.2 ± 0.1		0.007
Sm (cm/s)	5.1 ± 1.0	6.0 ± 1.0	<0.001	5.7 ± 0.9	7.7 ± 1.0	<0.001	0.025* <0.001†
Em (cm/s)	4.4 ± 1.2	6.4 ± 1.5	<0.001	5.4 ± 1.1	8.3 ± 1.2	<0.001	0.004* <0.001†
Δ Em (cm/s)		2.0 ± 1.0			2.9 ± 1.6		0.023
E-wave (cm/s)	0.70 ± 0.17	0.95 ± 0.17		0.57 ± 0.11	0.95 ± 0.12		<0.001 0.853
Δ E-wave		0.27 ± 0.19			0.38 ± 0.13		0.015
Am (cm/s)	6.8 ± 1.5	8.7 ± 1.6	<0.001	7.8 ± 1.4	9.7 ± 1.7	<0.001	0.012* 0.063†
E/E′	11.4 ± 4.3	11.4 ± 4.5	0.298	8.2 ± 2.0	8.8 ± 1.8	0.384	<0.001* 0.009†
Systolic reserve index		0.6 ± 0.5			1.5 ± 0.7		<0.001
Diastolic reserve index		1.5 ± 0.8			2.3 ± 1.2		0.011

Data are mean ± SD. **t* test between patients and control subjects at rest. †*t* test between patients and control subjects on exercise.
Am = late diastolic annular velocity; BP = blood pressure; E/E′ = ratio of early mitral diastolic inflow to early diastolic annular velocity; Em = early diastolic annular velocity; LVOT = left ventricular outflow tract; Sm = systolic mitral annular velocity; VTI = aortic outflow velocity time integral.

tion) at rest were significantly lower in patients compared with control subjects. However, on exercise, the percentage of untwist in early and mid-diastole (50% untwist duration) were significantly lower in patients, and the percentage of untwist in late diastole showed a trend toward significance. The untwist rate was not significantly different at rest but became significantly different on exercise with control subjects having a significantly higher untwist rate compared with patients (Table 3, Fig. 1).

Similar to our findings for longitudinal and radial strain, the magnitude of apical rotation, untwist rate, and percentage of untwist in late diastole on exercise in patients increased only to a level comparable to control subjects at rest. However, the percentage of untwist in early and mid-diastole in control subjects at rest remained significantly higher than that of patients on exercise (Table 3). There was significant correlation between apical rotation and LV torsion at rest and on exercise (at rest $r = 0.704$, $p < 0.001$; on exercise $r = 0.53$, $p = 0.016$) in those with good basal images ($n = 45$ at rest, $n = 20$ on exercise).

Vp. Mitral flow propagation velocity was used as an approximation to the intraventricular pressure gradient, reflecting ventricular suction. The Vp was comparable between the 2 groups at rest (40 ± 10 m/s vs. 39 ± 7 m/s, $p = 0.52$) but became significantly different on exercise with the control subjects having a higher ability to increase their Vp on exercise compared with patients. Even though patients were able to increase Vp on exercise, the magnitude of the increase was significantly less than control subjects (Table 4). The Vp on exercise correlated with peak Sm on exercise ($r = 0.47$, $p = 0.005$), suggesting a mechanistic link between systole and diastolic suction.

Correlations between peak VO_2max on exercise and echocardiographic parameters. Peak VO_2max correlated with the following echocardiographic parameters on exercise: Sm ($r = 0.61$, $p = 0.003$), Em ($r = 0.417$, $p = 0.038$), apical rotation ($r = 0.44$, $p = 0.026$), E/E′ ($r = -0.34$,

Table 3 2-Dimensional Strain and Rotation

	Patients at Rest	Patients on Exercise	p Value (Paired *t* Test)	Control Subjects at Rest	Control Subjects on Exercise	p Value (Paired *t* Test)	p Value (Unpaired *t* Test)
Long strain SepLat (%)	−19.4 ± 3.8	−20.4 ± 4.2	0.082	−21.5 ± 3.0	−24.4 ± 2.6	<0.001	0.018* <0.001†
Δ long strain SepLat (%)		−1.2 ± 3.9			−3.1 ± 2.8		0.051
Long strain InfAnt (%)	−18.4 ± 3.8	−20.1 ± 4.5	0.012	−20.4 ± 3.7	−23.2 ± 3.2	0.004	0.042* 0.008†
Δ long strain InfAnt (%)		−2.1 ± 4.2			2.8 ± 3.9		0.592
Global long strain (%)	−18.9 ± 3.5	−20.1 ± 4.1	0.005	−20.9 ± 3.0	−23.8 ± 2.5	<0.001	0.018* <0.001†
Δ global long strain (%)		−1.9 ± 3.3			−2.8 ± 2.7		0.315
Radial strain (%)	41.8 ± 13.5	49.1 ± 15.4	0.02	49.2 ± 12.9	61.9 ± 12.8	0.001	0.03* 0.002†
Δ radial strain (%)		6.6 ± 15.6			12.4 ± 12.3		0.154
Apical rotation (°)	10.4 ± 4.0	13.5 ± 4.7	0.008	13.0 ± 2.8	17.7 ± 3.6	0.003	0.015* 0.005†
Δ apical rotation (°)		3.0 ± 4.9			4.9 ± 4.1		0.216
Untwist rate (°/s)	−80 ± 34	−105 ± 32	<0.001	−96 ± 30	−129 ± 32	0.007	0.069* 0.013†
Δ untwist rate (°/s)		−33 ± 35			−29 ± 39		0.722
Untwist 25%	23.7 ± 9.3	21.2 ± 8.5	0.465	30.9 ± 9.7	29.2 ± 7.7	0.477	0.006* 0.002†
Δ untwist 25%		−2.0 ± 13.1			−2.4 ± 14.1		0.922
Untwist 50%	53.9 ± 12.6	50.5 ± 12.3	0.371	58.8 ± 8.4	61.7 ± 8.2	0.384	0.101* 0.001†
Δ untwist 50%		−3.3 ± 17.7			3.0 ± 14.2		0.223
Untwist 75%	77.3 ± 6.4	80.3 ± 9.8	0.477	81.8 ± 7.1	85.0 ± 4.7	0.126 0.057†	0.016*
Δ untwist 75%		1.8 ± 12.1			3.3 ± 8.7		0.652

Data are mean ± SD. **t* test between patients and control subjects at rest. †*t* test between patients and control subjects on exercise.
InfAnt = inferior and anterior walls; long = longitudinal; SepLat = septal and lateral walls; Untwist 25% (50%, 75%) = percentage untwist at 25% (50%, 75%) untwist duration.

p = 0.04), Vp (r = 0.35, p = 0.03), and 25% untwisting (r = 0.53, p = 0.007).

Derived measurements. There was no significant difference in arterial elastance or end-systolic elastance (a measure of systolic function and end-systolic stiffness) at rest (Table 5). However, we observed an increase in arterial elastance in patients on exercise (not significant), whereas control subjects had a reduced arterial elastance on exercise, resulting in a significant difference in the change in arterial elastance on exercise (Table 5). Stroke work index was similar between patients and control subjects at rest and on exercise, rising in both groups to the same degree. Estimated "chamber stiffness" was similar to control subjects.

Interobserver and intraobserver variability. The interobserver variability at rest by ICC was between 0.88 and 0.96. On exercise, ICC varied from 0.67 to 0.99; Vp had the highest interobserver variability. The intraobserver variability by ICC at rest varied from 0.88 to 0.98 and on exercise from 0.66 to 0.98. Again, Vp had the highest variability compared with other measurements.

Discussion

In this study, we have performed a comprehensive assessment of systolic and diastolic ventricular function with new noninvasive techniques at rest and on exercise in HFNEF patients and have demonstrated a variety of abnormalities of both systolic and diastolic function. These include reduced radial and longitudinal myocardial systolic strain both at rest and on exercise, reduced systolic and diastolic longitudinal functional reserve (mitral annular velocities fail to rise normally), reduced ventricular systolic rotation at rest that fails to increase normally on exercise, delayed ventricular untwisting with further worsening on exercise associated with a reduced LV suction, and a consequent reduced stroke volume rise on exercise. Recent studies (12–14,37) using similar echocardiographic techniques to ours have elegantly demonstrated the close temporal, functional, and tightly coordinated relationships in normal patients between LV twist during systole, with accompanying mitral annular motion toward the apex, and in early diastole, the untwisting process and recoil that generate the negative intraventricular pressure gradient or suction. This is followed by the rapid motion of the mitral annulus back toward the base of the heart, which also aids filling by simply moving the annulus around the column of the incoming blood (38). Thus, LV torsion or twist is a mechanism for generating stored energy during systole, which is released during early diastole to produce ventricular recoil, upward annular mo-

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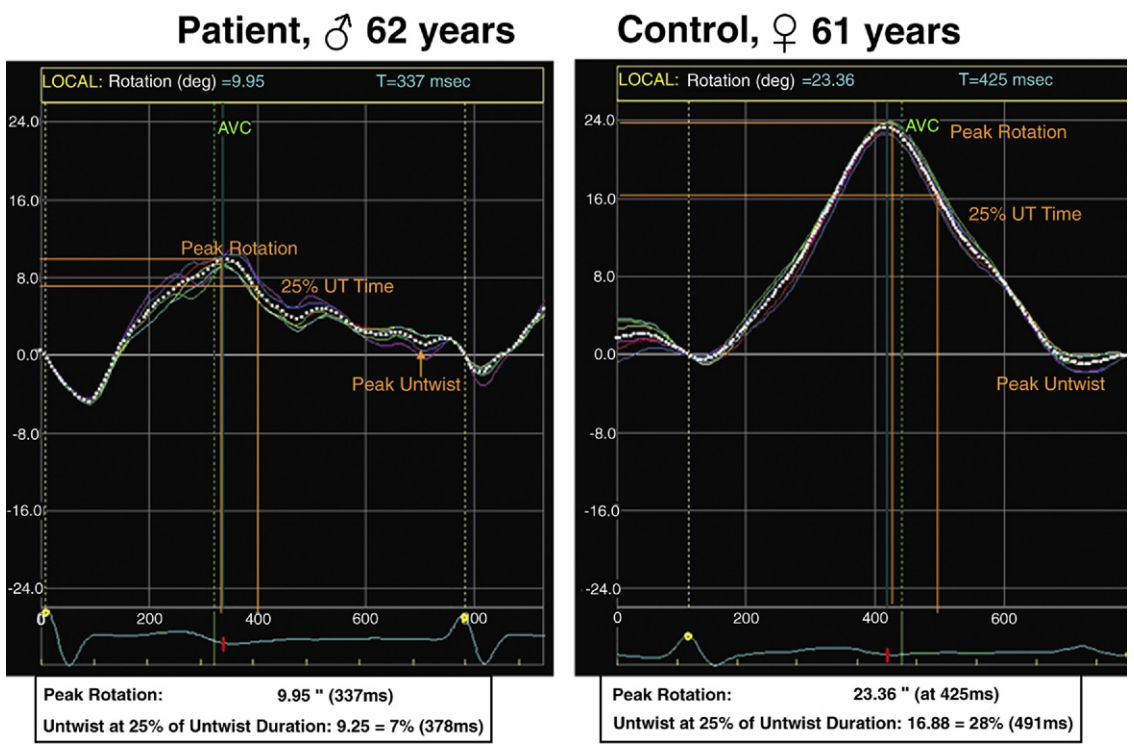

Figure 1 **Peak Apical Rotation and Untwist**

Rotation curve of patient **(left)** and control **(right)** showing magnitude of peak apical rotation and percentage of early untwist (25% of total untwist duration).

tion, and suction, confirming the close relation of systolic function to early diastole (39). In the normal heart, all of these aspects of ventricular function increase on exercise to aid fast ejection and, more important, enable rapid filling of the ventricle during a shortened diastole period while maintaining a low filling pressure. Notomi et al. (14) have shown how in hypertrophic cardiomyopathy these close relationships are disrupted on exercise with reduced LV torsion, annular motion, delayed untwisting, reduced LV suction, and ultimately impaired filling and thereby raised LV end-diastolic and left atrial pressures, which confirmed early studies that also linked diastolic dysfunction with regional inhomogeneity of contraction and relaxation in this condition (40). Our results are similar to Notomi et al. (14) in hypertrophic cardiomyopathy. It is likely that these fundamental abnormalities of ventricular function in both systole and diastole are more relevant to the genesis of the symptoms of breathlessness than the increased passive myocardial stiffness measured at end-diastole and at rest, as previously suggested (4,5).

In our study, we reported only apical rotation, because basal rotation on exercise was unreliable, possibly because of increased through-plane motion. In a subset, however, we found significant correlation between apical rotation and LV torsion at rest and on exercise, in keeping with other studies that showed that the apical rotation represents the dominant contribution to LV twist over a range of hemodynamic conditions (41,42). The LV twisting motion is a consequence of myocardial fiber orientation, which changes from an approximately longitudinal but slightly oblique orientation in the subendocardium to a circumferential orientation in the mid-wall and to an oblique orientation in the subepicardium (43,44). Thus, the subendocardial and subepicardial fibers represent 2 oppositely directed spirals.

Table 4 **Vp**

	Patients at Rest	Patients on Exercise	p Value (Paired *t* Test)	Control Subjects at Rest	Control Subjects on Exercise	p Value (Paired *t* Test)	p Value (Unpaired *t* Test)
Vp (m/s)	40 ± 10	49 ± 11	0.001	39 ± 7	61 ± 14	0.001	0.516* <0.001†
Δ Vp (m/s)		11 ± 13			22 ± 14		0.001

Data are mean ± SD. **t* test between patients and control subjects at rest. †*t* test between patients and control subjects on exercise.
Vp = mitral flow propagation velocity.

Table 5 Derived Measurements

	Patients at Rest	Patients on Exercise	p Value (Paired *t* Test)	Control Subjects at Rest	Control Subjects on Exercise	p Value (Paired *t* Test)	p Value (Unpaired *t* Test)
P/V (1/ml)	0.17 ± 0.80	0.17 ± 0.70	0.135	0.13 ± 0.50	0.14 ± 0.44	0.543	0.035*
							0.039†
ΔP/V (1/ml)		0.01 ± 0.05			0.01 ± 0.06		0.744
Ea (mm Hg/ml)	2.0 ± 0.7	2.2 ± 0.9	0.083	2.1 ± 0.5	1.9 ± 0.4	0.227	0.403*
							0.145†
ΔEa (mm Hg/ml)		0.22 ± 0.71			−0.18 ± 0.65		0.044
K (mm Hg/ml)	1.6 ± 0.7	3.4 ± 1.6	<0.001	1.4 ± 0.6	3.8 ± 1.4	<0.001	0.200*
							0.380†
ΔK (mm Hg/ml)		1.9 ± 1.7			2.4 ± 1.7		0.249
PPI (mm Hg/s)	2.2 ± 0.7	3.1 ± 1.1	<0.001	2.2 ± 0.7	3.1 ± 0.8	<0.001	0.793*
							0.947†
ΔPPI (mm Hg/s)		1.0 ± 1.0			0.9 ± 0.8		0.702
Ees (mm Hg/ml)	4.9 ± 1.9	7.4 ± 2.7	<0.001	5.6 ± 2.2	6.9 ± 1.7	<0.001	0.206*
							0.461†
ΔEes (mm Hg/ml)		2.5 ± 2.6			1.4 ± 2.3		0.138
SWI (mm Hg)	94 ± 26	132 ± 49	0.001	101 ± 36	140 ± 46	0.02	0.405*
							0.579†
ΔSWI (mm Hg)		39.4 ± 52.9			36.6 ± 56.2		0.872

Data are mean ± SD. **t* test between patients and control subjects at rest. †*t* test between patients and control subjects on exercise.
Ea = arterial elastance; Ees = end-systolic elastance; K = chamber stiffness; PPI = peak power index; P/V = pressure/volume ratio; SWI = stroke work index.

Because of larger radii, the torque of subepicardial fibers dominates and accounts for the normal counterclockwise rotation of the LV apex. Previous studies have found that in LV hypertrophy, apical twist and untwisting might be augmented or reduced (45,46), and similarly, torsion is increased in patients with mild diastolic dysfunction but reduced in those with more severe degrees of diastolic dysfunction (47). This anatomical arrangement probably explains these variable results: in the early stage the subendocardial longitudinal fibers are primarily affected so that unopposed epicardial torque will increase apical twist, whereas later more widespread fibrosis or damage will affect global function and lead to reduced twist with delayed untwisting. This also explains why annular velocities that primarily reflect subendocardial fibers are such sensitive measures of ventricular function (48) and were reduced in our HFNEF patients, particularly on exercise. All previous studies of torsion and untwisting in HFNEF were done at rest, and this is the first study that has assessed both longitudinal function and apical rotation on exercise. Reduced and delayed untwisting on exercise will undoubtedly impede LV suction in early diastole and delay rapid filling so that more filling will occur in late diastole during atrial systole, and this will explain the common finding of the delayed relaxation pattern (reduced early but increased atrial velocity) on the mitral inflow velocities associated with aging and LV hypertrophy (49,50).

The net differences in global longitudinal strain, radial strain, and apical rotation from rest to exercise seemed comparable between patients and control subjects, most likely due to a relatively small sample size. However, the magnitude of increase in strain and rotation was consistently higher in control subjects. It is also noteworthy that strain and apical rotation were significantly lower at rest in patients and did not exceed that of control subjects even on exercise, indicating that patients have a significantly lower functional capacity even at rest and more so on exercise.

Derived measurements of stiffness, arterial stiffness, and ventricular systolic compliance did not show any major changes between patients and control subjects. In part this might be because these measurements are often derived from single beats and have many assumptions involved in their calculations. Chamber stiffness is derived from the E-wave DT but probably only is accurate in those with a short DT, whereas some of our patients had a delayed DT. Furthermore there are no data on the effects of exercise and DT has been shown to be a function of both chamber stiffness and chamber relaxation viscoelasticity (51). However, the derived pressure-volume index, an indirect measure of compliance, was higher in patients, as expected. Clearly other noncardiac factors are also involved. Decreased arterial compliance and ventricular interactions will impair ventricular function (both systolic and diastolic) on exercise. Interestingly, the other derived measurements of global systolic function (end-systolic elastance, stroke work index, and peak power index) were not significantly different from the control group. This might reflect the method or that abnormalities of systolic function are subtle and do not affect pump function to any great degree but have a profound influence on early diastolic filling.

Study limitations. Our initial power calculation was performed with a sample size of 30, which provided

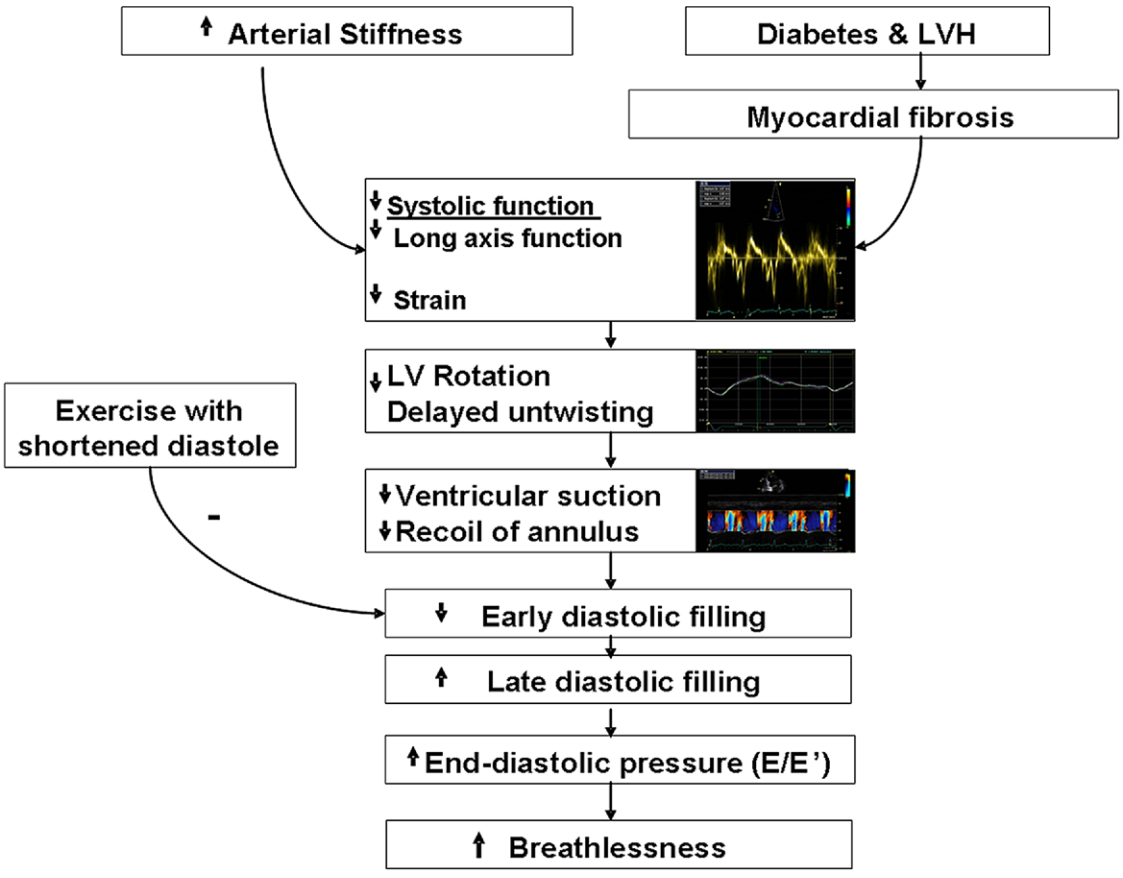

Figure 2 Schema Illustrating the Pathophysiology of Heart Failure With a Normal Ejection Fraction

E/E′ = ratio of early mitral diastolic inflow velocity to early diastolic mitral annular velocity; LV = left ventricular; LVH = left ventricular hypertrophy.

adequate power. However, we only included 27 healthy control subjects, but a repeat power calculation with a sample size of 27 yielded comparable power. All patients were taking medication, because it was considered unethical to stop treatment entirely. It is probable that the effect of treatment would be to improve deformation or strain and rotation, and therefore the differences might have been greater without treatment although it would be difficult to account for a resulting increase in arterial BP on exercise. Diuretic drugs do reduce symptoms, and there is a suggestion that angiotensin-converting enzyme inhibitors or receptor antagonists might improve longitudinal function (52). Exercise was submaximal, but the patients were breathless at this level. For a more elderly population, submaximal exercise is more relevant and comparable to usual activities than exercising to exhaustion, which is probably done very rarely in daily life. Diagnostic criteria for HFNEF patients receiving treatment are not available, and the BNP results were quite variable, but these were also taken on treatment. However, metabolic exercise testing was used to confirm that the symptoms of breathlessness were cardiac in origin.

Conclusions

We have demonstrated that HFNEF patients have a combination of systolic and diastolic abnormalities of ventricular function that is more obvious on exercise than at rest and that includes reduced myocardial systolic strain, rotation, LV suction, longitudinal (annular) function, and delayed untwisting. Figure 2 illustrates a unifying hypothesis. This is not a condition of isolated diastolic dysfunction or a problem of ventricular stiffness alone. A variety of etiologies including aging, hypertension, LV hypertrophy, fibrosis, and diabetes all could induce changes in the myocardial tissue that affect the architecture of the heart and its global function. But, treatments that just reverse myocardial tissue changes without restoring the architectural function of the heart are unlikely to improve symptoms.

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Key Words: diastolic ■ heart failure ■ rotation ■ strain ■ untwist.