Exercise Hemodynamics in Patients With and Without Diastolic Dysfunction and Preserved Ejection Fraction After Myocardial Infarction

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Background—Left ventricular diastolic dysfunction (DD) is common after myocardial infarction (MI) despite preservation of left ventricular ejection fraction, yet it remains unclear how or whether DD affects cardiac hemodynamics with stress.

Methods and Results—Invasive hemodynamic exercise testing was performed in 46 patients with a recent MI and left ventricular ejection fraction >45% and in 10 healthy volunteers. MI patients were enrolled prospectively and divided into those with DD (MI+DD; left atrial volume index >34 mL/m² and diastolic E/e' ratio>8; n=35) and those without DD (MI–DD; left atrial volume index <34 mL/m² and E/e' ratio<8; n=11). All underwent a supine cycle ergometer test with simultaneous right heart catheterization and echocardiography. At rest, 10 patients in MI+DD (29%) had pulmonary capillary wedge pressure >15 (14±4 mm Hg), whereas none of the MI–DD (10±2 mm Hg) or controls (9±2 mm Hg) displayed pulmonary capillary wedge pressure elevation (P=0.03). During exercise, an abnormal rise in pulmonary capillary wedge pressure (>25 mm Hg) was observed in 94% of MI+DD (36±6 mm Hg) compared with 36% of MI–DD (24±6 mm Hg) and none of the controls (16±6 mm Hg; P<0.0001). Exercise right atrial pressure was the highest in MI+DD followed by MI–DD and control (15±5 versus 9±4 versus 7±5 mm Hg; P<0.001), whereas no difference in cardiac index was found between groups.

Conclusions—In post-MI patients with preserved ejection fraction and left ventricular DD, cardiac output with exercise is maintained at the expense of substantially increased filling pressure. DD and loss of diastolic reserve may promote progression from stage B to stage C heart failure after MI. (Circ Heart Fail. 2012;5:444-451.)

Key Words: diastolic dysfunction ■ exercise ■ myocardial infarction ■ heart failure

Myocardial infarction (MI) is associated with neuro-hormonal activation, microvascular dysfunction, and regional wall motion abnormalities that will influence left ventricular (LV) contractility as well as active and passive diastolic relaxation. Doppler echocardiographic studies have demonstrated that a normal filling pattern is seen in only one third of patients in the acute phase of MI. When filling is severely abnormal, several studies have demonstrated that survival is poor and the risk for development of heart failure (HF) is high.2-4 However, most patients do not present with severely abnormal LV filling pattern, and patients with less severe diastolic dysfunction (DD) often display only minor evidence of myocardial damage, with preserved LV systolic function and no symptoms of HF. In these patients, LV filling pressures are normal or only mildly elevated when estimated by echocardiography at rest. Nonetheless, this group displays increased mortality compared with patients with no echocardiographic signs of elevated LV filling pressure.5,6 The cause and hemodynamic consequences of abnormal LV filling in these patients are poorly understood, and abnormalities may only be apparent during increased circulatory demands, such as exercise, although loss of diastolic function could accelerate the transition to symptomatic HF in patients with MI.

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We hypothesized that patients after MI with preserved systolic function and resting Doppler echocardiographic signs of moderate DD would have an abnormal increase in cardiac filling pressures during exercise compared with MI patients without DD and healthy controls.

Methods

Patients and Controls

Forty-six patients aged >50 years were prospectively enrolled 32±16 days after documented MI. Patients in sinus rhythm were eligible if LV ejection fraction (LVEF) exceeded 45% on echocardiography...
performed within 72 hours of revascularization, and resting Doppler echocardiography suggested abnormal diastolic function defined by a ratio of peak E-wave velocity to early mitral annular diastolic velocity (E/E’) >8 and left atrial (LA) volume index >34 mL/m² (MI+DD; n=35) or suggested normal diastolic function (E/E’<8 and LA volume index <34 mL/m²; MI−DD; n=11).1–3 Patients with obstructive pulmonary disease, moderate or severe left-sided valve disease, or those requiring additional revascularization were excluded. Ten healthy volunteers aged >40 years with no apparent cardiovascular disease, normal spirometry, no exertional dyspnea, and with normal Doppler echocardiography served as controls. In patients presenting with ST-segment elevation MI (STEMI), coronary angiography and revascularization were performed immediately at presentation. Patients presenting with non-STEMI were medically stabilized, and coronary angiography was performed subsequently.

On the day of the hemodynamic exercise testing, patients and controls underwent spirometry and a resting comprehensive Doppler echocardiographic examination according to current recommendations.6–9 Subsequently, a symptom-limited supine cycle ergometer exercise test was performed during right heart catheterization and simultaneous echocardiography. Medications were not withheld on the day of the study. The study was approved by the Ethics Committee for Copenhagen protocol No. H-A-2009-023, and all patients provided written informed consent.

Echocardiography

All examinations were performed by an experienced echocardiographer using a Philips iE33 (Philips HealthCare, Best, the Netherlands) cardiac ultrasound system. Images were stored digitally for off-line analysis using Philips Xcelera analysis software version 3.1 (Philips Healthcare). LV volumes and LVEF were assessed using Simpson modified rule from the apical 4- and 2-chamber views. LA maximal volume was estimated from the apical 4- and 2-chamber views using area length method. Mitral inflow was assessed in the apical 4-chamber view with the pulsed wave Doppler sample volume placed at the tips of mitral leaflets during diastole. From the inflow, peak E-wave velocity was measured. Mitral annular motion was assessed using pulsed wave tissue Doppler with the sample volume placed in the septal and lateral mitral annulus. The mean of the septal and lateral e’ velocity was used for calculation of E/e’. Wall motion scores were semiquantitatively assessed using a standard 16 segmental model in accordance with current guidelines.2 For Doppler recordings, horizontal sweep was 75 to 100 cm/s, and a mean of 3 to 5 consecutive beats were measured and averaged. The analyses were performed blinded to clinical status and to invasive measurements.

Invasive Hemodynamic Measurements

Right heart catheterization was performed using a standard 7.5 French triple lumen Swan-Ganz thermistor and balloon-tipped catheter (Edwards Lifesciences, Irvine, CA). The catheter was introduced, guided by ultrasound under local anesthesia, using the Seldinger technique into the right internal jugular vein and advanced to the pulmonary artery. Pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP), systolic pulmonary artery pressure (PAP), diastolic PAP, mean PAP, and cardiac output (CO) using thermodilution were measured at rest and adjusted for body surface area (cardiac index [CI]), at each level of exercise until exhaustion and after 5 minutes of rest. PCWP at rest and postexercise was measured at end-expiration. During exercise, a mean PCWP was used. An average of 3 measurements of CO that did not differ >10% was used to calculate CO. Transmural filling pressure (pressure difference between LV diastolic pressure and pericardial pressure) was estimated to be the difference between PCWP and RAP.10–12 Pulmonary vascular resistance index was calculated as 80x(mean PAP-PCWP)/CI. Systemic vascular resistance index was calculated as 80x(mean arterial pressure-RAP)/CI. Rate pressure product was calculated as heart rate x systolic blood pressure. Diastolic operating stiffness was calculated as PCWP/end-diastolic volume index. At rest and at maximal exercise, a central venous blood sample was drawn from the distal tip of the catheter and analyzed for lactate concentration, mixed venous oxygen saturation, and pH.

Exercise Protocol

All patients performed a multistage symptom-limited supine cycle ergometer exercise test using an Echo Cardiac Stress Table (Lode B.V., Groningen, the Netherlands). Workload started at 0 W and increased by 25 W every 2 minutes. Patients were encouraged to exercise until exhaustion (Borg>18).13 Brachial blood pressure was measured by sphygmomanometry at baseline and at every 2 minutes until maximum workload was reached and repeated after 5 minutes of rest. First measurement of CO was started after 20 s of exercise, and PCWP was measured after 90 s of exercise on each level. Based on previous studies of healthy controls, we considered a PCWP at rest exceeding 15 mm Hg and 25 mm Hg during supine exercise to be abnormally increased.14–16

Statistical Analysis

Data are presented as means±SD or median (interquartile range) unless otherwise indicated. Between-group differences were tested using ANOVA, χ², or nonparametric rank sum test for non-Gaussian distributed variables. Random coefficient mixed-model analysis was performed to compare regression coefficients in repeated measurements in exercise-induced variables. Because of sample size, multivariate linear regression was restricted to age and group as covariates to adjust for group differences in CI, RAP, PCWP, and transmural filling pressure. Bivariate correlations between variables were assessed with Pearson correlation coefficient. All post hoc analyses of within- and between-group differences were adjusted with Bonferroni correction to adjust for multiple comparisons. P<0.05 was considered significant. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

All patients were free of angina on the day of the exercise test. MI patients with or without DD were older than controls (Table 1). In the group with MI+DD, 28 patients (80%) presented with STEMI, and 7 patients (20%) with non-STEMI. All patients with MI−DD presented with STEMI. Between MI+DD and MI−DD patients presenting with STEMI, there were neither significant differences in the TIMI flow before (1.1±1.4 versus 1.5±1.4; P=0.36) or after (2.8±0.6 versus 3.0±0.1; P=0.11) intervention, nor significant differences in time from diagnostic ECG to first balloon inflation (103 [range, 78–129] minutes versus 94 [range, 66–148] minutes; P=1).

In the MI+DD group presenting with non-STEMI, revascularization was performed within 72 hours (1±1 day; range, 0–3 days) after initial presentation. In the MI+DD group, there was 1 patient with no reflow and 2 patients with slow reflow, and no patients in the MI−DD experienced no flow or slow flow (P=0.57). None of the 3 patients with slow flow or no flow had evidence of reversible ischemia during the exercise test. MI+DD had a higher frequency of hypertension (P=0.04) and higher wall motion scores (P=0.05) compared with MI−DD, higher N-terminal pro-brain natriuretic peptide, LV mass, LA volume, and E/e’ compared with MI−DD and controls. There were no differences in localization of the culprit lesion, functional status, pulmonary function, enzymatic infarct size, or age between MI+DD and MI−DD. There was a nonsignificant trend toward higher use of blood pressure–lowering medication, especially angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, in MI+DD compared with MI−DD and controls.
At rest, MI+DD had significant higher mean PAP (20 ± 5 vs 17 ± 2 vs 15 ± 3 mm Hg; P = 0.004) and PCWP (14 ± 4 vs 10 ± 2 vs 9 ± 2 mm Hg; P = 0.002) compared with MI−DD and controls (Table 2). There were no differences in PCWP and mean PAP between patients with MI−DD and controls. At rest there were no differences in CI, RAP, mean arterial blood pressure, rate pressure product, systemic vascular resistance index, or pulmonary vascular resistance index between groups (Table 2). In MI+DD, 10 patients (29%) had a resting PCWP>15 mm Hg. No MI−DD patients or controls had a resting PCWP>15 mm Hg.

**Exercise Hemodynamics**

In all cases, the exercise test was terminated because of exhaustion, which was accompanied by an increase of central venous blood lactate and reductions in pH and O₂ content, indicating that the anaerobic threshold was met in all subjects (Table 2). Patients with MI+DD tended to achieve lower workload compared with patients with MI−DD and controls (P=0.07). Exercise was associated with a rapid and substantial increase in PCWP, RAP, and mean PAP in MI+DD patients that exceeded both MI−DD patients and controls (Figure 1; Table 2). This increase was noted even at passive exercise (free-cycling with no resistance). During exercise, mean PCWP increased to >25 mm Hg in all but 2 patients in MI+DD (94%). In contrast, only 4 patients in MI−DD and none of the controls displayed this pathological elevation in filling pressures (P<0.0001); this was unchanged when adjusting for age. Controls showed no significant increase in RAP and an intermediate increase in PCWP during exercise, whereas MI−DD showed an intermediate elevation in RAP and filling pressures (Figure 1).
Table 2. Exercise-Induced Changes in Invasive Hemodynamics and LV Volumes From Rest to Peak Exercise

<table>
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<tr>
<th></th>
<th>MI and DD (n=35)</th>
<th>MI and no DD (n=11)</th>
<th>Controls (n=10)</th>
<th>P Overall Group ANOVA</th>
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<tr>
<td></td>
<td>Rest Maximal</td>
<td>Rest Maximal</td>
<td>Rest Maximal</td>
<td>Maximal</td>
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<td>HR</td>
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<td>Diastolic BP, mm Hg</td>
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<td>RPP, mm Hg/min</td>
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<td>MAP, mm Hg</td>
<td>89±13</td>
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<td>Cl, L/min/m²</td>
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<td>sPAP, mm Hg</td>
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<td>23±2</td>
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<td>dPAP, mm Hg</td>
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<td>13±2</td>
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<td>mPAP, mm Hg</td>
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<td>15±4</td>
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<td>PCWP, mm Hg</td>
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<td>10±2</td>
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<td>TMP, mm Hg</td>
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<td>3±2</td>
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<td>7.39±0.01</td>
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<td>SVO₂, %</td>
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<td>72.6±2.2</td>
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<td>Lactate, mmol/L</td>
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<td>SVRI, dynes/m²/cm⁻5</td>
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<td>2580±660</td>
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<td>PVRI, dynes/m²/cm⁻5</td>
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<td>LVEDV indexed, mL/m²</td>
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<td>0.20±0.06</td>
<td>0.15±0.04</td>
<td>0.06</td>
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</table>

LV indicates left ventricular; MI, myocardial infarction; DD, diastolic dysfunction; HR, heart rate; BP, blood pressure; RPP, rate pressure product (HR×systolic BP); MAP, mean arterial pressure; CI, cardiac index; RAP, right atrial pressure; sPAP, systolic pulmonary artery pressure; dPAP, diastolic PAP; mPAP, mean PAP; PCWP, pulmonary capillary wedge pressure; METS, metabolic equivalent; SVO₂, mixed venous oxygen saturation; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; OS, diastolic operating stiffness.

Data are presented as mean±SD.

All variables changed significantly (P<0.001) within group with exercise from rest to maximal exercise except for RAP in the control group (P=0.85) and LVEDV index in the MI+DD group (P=0.5). For between-group comparisons: *P<0.05 vs controls; †P<0.05 vs MI−DD.

Transmural LV filling pressure (PCWP-RAP) was also significantly increased in MI+DD with peak exercise (20±5 versus 15±4 versus 9±±2 mm Hg; P<0.0001; Figure 2); this difference was unchanged when adjusting for age.

At peak exercise, CI was lower in MI+DD compared with controls (P=0.03; Figure 2), but when adjusting for age, this difference became insignificant (P=0.31). Although there were significant within-group changes in mean arterial pressure, heart rate, rate pressure product, pulmonary vascular resistance index, and systemic vascular resistance index, there were no between-group differences at peak exercise (Table 2). Exclusion of patients with non-STEMI from analyses did not change any of the results.

No difference in LVEF in the MI+DD and MI−DD groups was seen (53±6% versus 56±6%; P=0.56), but was lower compared with controls (Table 1). LVEF increased with exercise in all 3 groups (60±7% versus 63±6% versus 72±4%), and the increase in LVEF was similar in all groups, P=1. LV end-systolic volume index was higher in MI+DD compared with MI−DD and controls. LV end-systolic volume index dropped with exercise in all patients to a similar extent, but persistently remained higher in MI+DD compared with MI−DD and control. LV end-diastolic volume index was not different at rest and tended to fall more in MI−DD and controls compared with MI+DD. Estimated LV operant diastolic stiffness was 0.22±0.1 versus 0.20±0.06 versus 0.15±0.04 mm Hg m²/mL; P=0.06 in MI+DD patients, MI−DD, and controls, respectively, at baseline and increased to 0.59±0.15 versus 0.48±0.14 versus 0.28±0.11 mm Hg m²/mL; P<0.0001 with exercise. No patient showed ischemic wall motion changes or displayed reduction in EF or increase in LV end-systolic volume index with stress.

Discussion

The present study demonstrates that in apparent low-risk, MI patients with preserved LVEF and DD on Doppler echocardiography, filling pressure with exercise increases substantially and significantly more than what is seen in comparable MI patients without DD and in healthy controls. Despite severely increased filling pressure, CO response to exertion was maintained. Thus, in MI patients with DD and preserved systolic function, an increase in cardiac performance with exercise can only be achieved at the cost of increased filling pressure. This loss of diastolic reserve with exercise stress likely represents an early key step in the progression from a compensated, asymptomatic state (stage B HF) to symptomatic HF (stage C).
and, accordingly, DD in the post-MI patient may represent an important window for initiation of novel therapies to prevent HF progression.

All patients in the present study were characterized by a mildly depressed LVEF, complete revascularization, and no or mild dyspnea on exertion: patients who normally would be considered to have a favorable prognosis. However, per protocol, patients were selected and grouped on the basis of presence or absence of LV DD (dilated LA and an abnormal E/e' ratio), which was on the basis of current recommendations and previous studies demonstrating that LA dilation as well as an abnormally increased E/e' ratio after MI are independent predictors of outcome also when LVEF is preserved. It is believed that the LA will dilate in response to either volume or pressure overload. None of the patients in the present study had mitral valve regurgitation at rest or during exercise, or other conditions associated with high CO. Thus, it is unlikely that the difference in LA size was a consequence of differences in LA volume load. The present study suggests that LA dilatation and abnormal E/e' in fact was a consequence of increased filling pressure (increased LA afterload). At rest, this increase in LA afterload (higher PCWP) in MI+DD is modest, at a level that most physicians would not consider pathological. However, during even low-level exertion (as typical of daily life), we observed marked elevation in filling pressures. This supports the notion that LA volume provides an effective marker of chronic elevation in LV filling pressure (intermittent or sustained) in the post-MI setting similar to patients with HF with preserved EF (HFpEF).

We found, in MI patients with DD, that even a mild increase in venous return during physical exercise was associated with a rapid increase of RAP, PAP, and mean PCWP, a response not seen in MI patients with normal diastolic function and in healthy controls. This suggests...
an inability to accommodate mild elevations in venous return without concomitant elevation of PCWP. Thus, even though these patients may have normal or mildly increased filling pressure at rest, they are repeatedly faced with severely increased filling pressure during even mild exertion. Because LV volumes and stroke volume were unaffected, this is suggestive of an upward displacement of the pressure volume relationship suggestive of a primary diastolic impairment. Similar pressure volume relationship and diastolic impairment has been demonstrated in patients with HfPEF. This diastolic impairment is complex and not completely understood, but titin isoform switching and phosphorylation deficits, changes in ventricular collagen turnover, and impaired removal of intracellular calcium are believed to influence diastolic function and filling pressure. To what extent this was because of preexisting DD in the present population is however unclear. But the higher prevalence of hypertension in the MI+DD group does suggest that preexisting DD may have been present in some patients. PCWP is also influenced by right heart function and pericardial restraint. However, transmural filling pressure (PCWP-RAP, a marker of LV distending pressure) increased significantly more in MI+DD than in MI−DD and controls suggesting that pericardial restraint and right ventricular function were of less importance for the observed increase in PCWP. The inability to fully accommodate the venous return without increase in RAP further impairs LV filling because of pericardial constraint and thus impairs the ability to increase stroke volume and CO. This is very similar to what has been reported in patients with HfPEF where an increase in pulmonary pressures, RAP, and PCWP at the same magnitude as in the present study has been reported.

**Figure 2.** Changes in (A) cardiac index (CI) and (B) transmural filling pressure with exercise. Submax=4 METS. Error bars represent SD; *P<0.05 MI+DD vs controls; †P<0.05 MI+DD vs MI−DD; ‡P<0.05 MI−DD vs controls; ‡P<0.05 for within-group changes. METS indicates metabolic equivalent; MI, myocardial infarction; DD, diastolic dysfunction.
There are many important distinctions between the MI+DD subjects in the present study and HFP EF subjects enrolled in prior studies. HFP EF subjects by definition presented with symptoms of HF, in contrast to the current subjects who were selected on the basis of the echocardiography. Furthermore, more widespread findings of inadequate cardiovascular reserve were noted in HFP EF patients, including blunted increases in CO, contractility, arterial vasodilation, and heart rate with exercise.14,26-29 Thus, it may be that development of other components of cardiovascular reserve limitation is what causes the development of symptomatic HF after MI. As such, the present study may provide an important hemodynamic link between the substrate of DD after MI and the development of HF.

The study indicates that abnormal LV filling on Doppler echocardiography early after MI is associated with abnormal diastolic reserve with risk of intermittent congestion and thus greater vulnerability to progress to symptomatic HF. The importance of development of HF after MI has been emphasized by Torabi et al20 in 896 patients with prior MI, where 84% of deaths during follow-up were preceded by symptoms of HF. The current results also reinforce the point that resting invasive hemodynamic assessment is inadequate to determine the abnormalities in LV diastolic reserve.14,27 If resting analysis alone was used, >70% of the population would erroneously have been judged to be normal, despite a severely abnormal response to exercise.

Limitations
In many populations, DD has been associated with reduced exercise capacity. Although we found a trend toward a lower exercise capacity in patients with MI+DD, this was not statistically significant. Whether the lack of significance is a result of a type II error with a low number of controls and an outlier with low exercise capacity in this group or because of differences in body weight (body mass index) and age is unclear. Assessment of PCWP may be challenging during exercise where the pressure trabecular may be significantly affected by respiration, and it may be difficult to determine end-expiration accurately. To account for this, we used mean PCWP rather than end-expiratory PCWP, which would have yielded even higher PCWP. The healthy controls were ~10 years younger and had lower body mass index than the patient groups, and it is possible that some of the observed hemodynamic differences could be related to this. We did adjust for age in a multivariate model but additional adjustment (ie, body mass index, β-blockade, hypertension) was not done because of the small sample size. β-Adrenergic blocking agents (prescribed in >90% of MI+DD and MI−DD) have negative inotropic and lusitropic effects that might have contributed to the observed rise in LV filling pressures compared with controls. It is important to note that β-blocker use and age were similar in MI+DD and MI−DD, arguing against the group difference in exercise hemodynamics being related to confounding effects of age or medication use alone.

Conclusion and Implications
The present study demonstrates that in MI patients with preserved LVEF and DD on Doppler echocardiography, filling pressures with exercise increase substantially and significantly more than in comparable MI patients without DD and healthy controls. Thus abnormal LV filling on Doppler echocardiography at rest identifies a group of patients who are only able to obtain a sufficient increase in CO during exercise at the expense of elevated filling pressures. Abnormal LV filling is an early morphological expression that identifies patients at increased risk of developing HF and eventually death and, thus, may provide a novel target for therapy.

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Disclosures
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Exercise Hemodynamics in MI With Preserved LVEF

Several studies have demonstrated that normal left ventricular (LV) filling pattern is only seen in one third of patients in the acute phase of myocardial infarction. When LV filling is severely abnormal, survival is poor and the risk of developing heart failure is high. However, most patients do not present with severely abnormal LV filling pattern, and patients with less severe diastolic dysfunction often display only minor evidence of myocardial damage, with preserved LV systolic function. The cause and hemodynamic consequences of abnormal LV filling in these patients are poorly understood, and abnormalities may only be apparent during increased circulatory demands, such as exercise. The present study demonstrates that in patients with a recent myocardial infarction, with preserved LV ejection fraction and diastolic dysfunction on Doppler echocardiography, filling pressures with exercise increase substantially and significantly more than in comparable myocardial infarction patients without baseline diastolic dysfunction or in healthy controls. Thus, abnormal LV filling on Doppler echocardiography at rest identifies a group of patients who are only able to obtain a sufficient increase in cardiac output during exercise at the expense of elevated filling pressures. Abnormal LV filling is an early morphological expression that may identify patients at increased risk of developing heart failure.
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