Exercise Hemodynamics in Patients with and without Diastolic Dysfunction and Preserved Ejection Fraction after Myocardial Infarction

Andersen et al: Exercise Hemodynamics in MI with Preserved LVEF

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DOI: 10.1161/CIRCHEARTFAILURE.112.967919

Abstract

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

Methods and Results—Invasive hemodynamic exercise testing was performed in 46 patients with a recent MI and LVEF>45% and in 10 healthy volunteers. MI patients were enrolled prospectively and divided into those with diastolic dysfunction (MI+DD; left atrial volume index>34 ml/m² and diastolic E/e’ ratio>8; n=35) and those without diastolic dysfunction (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 (PCWP) >15 (14±4 mmHg), while none of the MI-DD (10±2mmHg) or controls (9±2mmHg) displayed PCWP elevation (p=0.03). During exercise, an abnormal rise in PCWP (>25mmHg) was observed in 94% of MI+DD (36±6mmHg) compared to 36% of MI-DD (24±6mmHg) and none of the controls (16±6 mmHg), p<0.001. Exercise right atrial pressure was highest in MI+DD followed by MI-DD and control (15±5 vs. 9±4 vs 7±5 mmHg, p<0.001), whereas no difference in cardiac index was found between groups.

Conclusions—In post-MI patients with preserved EF and LV diastolic dysfunction, cardiac output with exercise is maintained at the expense of substantially increased filling pressure. Diastolic dysfunction and loss of diastolic reserve may promote progression from stage B to stage C heart failure after myocardial infarction.

Key Words: diastolic dysfunction, exercise, myocardial infarction, heart failure
Myocardial infarction (MI) is associated with neurohormonal activation, microvascular dysfunction, and regional wall motion abnormalities which 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 HF is high. 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 to patients with no echocardiographic signs of elevated LV filling pressure. 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, though loss of diastolic function could accelerate the transition to symptomatic HF in patients with MI.

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 to MI patients without DD and to healthy controls.

**Methods**

**Patients and controls:** Forty six patients >50 years of age were prospectively enrolled 32 ± 16 days after documented MI. Patients in sinus rhythm were eligible if 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).\(^7\,^8\) Patients with obstructive pulmonary disease, moderate or severe left-sided valve disease, or those requiring additional revascularization were excluded. Ten healthy volunteers >40 years of age 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 was performed immediately at presentation. Patients presenting with non ST segment elevation MI (NSTEMI) 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.\(^8\,^9\) 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 number: 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 offline analysis using Philips Xcelera analysis software version 3.1 (Philips Healthcare, Best, the Netherlands). LV volumes and LVEF were assessed using Simpson’s 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 (WMS) were semiquantitatively assessed using a standard 16 segmental model in accordance with current guidelines. For Doppler recordings horizontal sweep was 75-100 cm/s and a mean of 3-5 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-F triple lumen Swan-Ganz thermistor and balloon-tipped catheter (Edwards Lifesciences, Irvine, California, USA). 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 (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 five minutes of rest. PCWP at rest and post exercise was measured at end-expiration. During exercise a mean PCWP was used. An average of three measurements of CO that did no differ more than 10% was used to calculate CO. Transmural filling pressure (pressure difference between LV diastolic pressure and pericardial pressure) was estimated as the difference between PCWP and RAP. Pulmonary vascular resistance index (PVRI) was calculated as: 80x(mean PAP-PCWP)/CI. Systemic vascular resistance index (SVRI) was calculated as: 80x(mean arterial pressure-RAP)/CI. Rate pressure product (RPP) was calculated as HR x Systolic BP. 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., the Netherlands). Workload started at 0 watt and increased by 25 watts every 2 minutes. Patients were encouraged to exercise until exhaustion (Borg>18).\textsuperscript{13} Brachial blood pressure was measured by sphygmomanometry at baseline and at every two minutes until maximum workload was reached and repeated after 5 minutes of rest. First measurement of CO was started after 20 sec of exercise and PCWP was measured after 90 sec of exercise on each level.

Based on previous studies of healthy controls we considered a PCWP at rest exceeding 15 mmHg and 25 mmHg during supine exercise to be abnormally increased.\textsuperscript{14-18}

**Statistical analysis:** Data are presented as mean ± SD or median (interquartile range, IQR) unless otherwise indicated. Between group differences were tested using analysis of variance (ANOVA), Chi square, or non-parametric 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. Due to 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 posthoc analyses of within and between group differences were adjusted with Bonferroni correction to adjust for multiple comparisons. A p value <0.05 was considered significant. Statistical analyses were performed using SAS version 9.2 (Cary, NC, USA).

**Results**

All patients were free of angina at 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 NSTEMI. All patients with MI-DD
presented with STEMI. Between MI+DD and MI-DD patients presenting with STEMI there was neither significant differences in the TIMI flow before (1.1 ± 1.4 vs. 1.5 ± 1.4, p=0.36) or after (2.8 ± 0.6 vs. 3.0 ± 0, p=0.11) intervention, nor significant differences in time from diagnostic ECG to first balloon inflation (103 (range 78-129) min vs. 94 (range 66-148) min, p=1). In the MI+DD group presenting with NSTEMI revascularization was performed within 72 hours (1 ± 1 day, range 0-3 days) after initial presentation. In the MI+DD 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 three 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 WMS (p=0.05) compared with MI-DD, higher NT-pro brain natriuretic peptide, LV mass, left atrial volume and E/e’ compared to 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 non-significant trend towards higher use of blood pressure lowering medication especially angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-receptor blockers (ARB) in MI+DD compared to MI-DD and controls.

**Resting hemodynamics:** At rest MI+DD had significant higher mean PAP (20±5 vs 17±2 vs 15±3 mmHg, p=0.004) and PCWP (14±4 vs. 10±2 vs 9±2 mmHg, p=0.002) compared 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 cardiac index (CI), RAP, mean arterial blood pressure, RPP, SVRI or PVRI between groups (Table 2). In MI+DD 10 patients (29%) had a resting PCWP of more than 15 mmHg. No MI-DD patients or controls had a resting PCWP of more than 15 mmHg.

**Exercise hemodynamics** In all cases, the exercise test was terminated due to 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 to 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 and Table 2). This increase was noted even at passive exercise (free-cycling with no resistance). During exercise mean PCWP increased to > 25 mmHg in all but two patients in MI+DD (94%). In contrast, only 4 patients in MI-DD and none of the controls displayed this pathologic 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). Transmural LV filling pressure (PCWP - RAP) was also significantly increased in MI+DD with peak exercise (20±5 vs 15±4 vs 9 ± 3 mmHg, 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, RPP, PVRI and SVRI there were no between-group differences at peak exercise (Table 2). Exclusion of patients with NSTEMI from analyses did not change any of the results.

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

Discussion

The present study demonstrates that in apparent low risk, MI patients with preserved LVEF and diastolic dysfunction on Doppler echocardiography, filling pressure with exercise increase substantially and significantly more than what is seen in comparable MI patients without diastolic dysfunction and in healthy controls. Despite severely increased filling pressure, cardiac output response to exertion was maintained. Thus, in MI patients with diastolic dysfunction 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 represent an early key step in the progression from a compensated, asymptomatic state (Stage B HF) to symptomatic HF (Stage C), and accordingly diastolic dysfunction in the post MI patient may represent 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 none or mild dyspnea on exertion; patients that normally would be considered to have a favorable prognosis. However, per protocol patients were selected and grouped based on presence or absence of LV diastolic dysfunction (dilated LA and an abnormal E/e’ ratio), which was based on 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.², ⁴, ¹⁹ 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 cardiac output. 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 pathologic. 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 ejection fraction (HFP EF).

We found in MI patients with diastolic dysfunction, 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. As LV volumes and stroke volume was 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 HFP EF. 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 due to preexisting diastolic dysfunction in the present population is however unclear. But the higher prevalence
of hypertension in the MI+DD group does suggest that preexisting diastolic dysfunction 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 suggestive of 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 due to pericardial constraint and thus impairs the ability to increase SV and CO.\textsuperscript{12} This is very similar to what has been reported in patients with HFpEF\textsuperscript{26, 27} where an increase in pulmonary pressures, RAP, and PCWP at the same magnitude as in the present study has been reported.

There are a number of important distinctions between the MI+DD subjects in the current study and HFpEF subjects enrolled in prior studies. HFpEF subjects by definition presented with symptoms of HF, in contrast to the current subjects were selected based on the echocardiography. Moreover, more widespread findings of inadequate cardiovascular reserve were noted in HFpEF patients, including blunted increases in cardiac output, contractility, arterial vasodilation and heart rate with exercise.\textsuperscript{14, 28-31} Thus it may be that development of other components of cardiovascular reserve limitation is what causes the development of symptomatic HF after myocardial infarction. As such, the present study may provide an important hemodynamic link between the substrate of diastolic dysfunction 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 heart failure. The importance of development of heart failure after MI has been emphasized by Torabi and associates in 896 patients with prior MI, where 84% of deaths during follow-up were preceded by symptoms of
heart failure. The current results also reinforce the point that resting invasive hemodynamic assessment is inadequate to determine the abnormalities in LV diastolic reserve. If resting analysis alone was used, more than 70% population would erroneously have been judged to be normal despite a severely abnormal response to exercise.

**Limitations:** In many populations diastolic dysfunction 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 due to differences in body weight (BMI) and age is unclear. Assessment of PCWP may be challenging during exercise where the pressure tracings 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 approximately 10 years younger and had lower BMI 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 (i.e. BMI, Beta blockade, hypertension) was not done due to small sample size. Beta 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 to controls. Importantly, beta-blocker use and age were similar in MI+DD and MI-DD, arguing against the group difference in exercise hemodynamic being related to confounding effects of age or medication use alone.

**Conclusion and implications**

The present study demonstrate that in MI patients with preserved LVEF and diastolic dysfunction on Doppler echocardiography, filling pressures with exercise increase substantially and significantly more than in comparable MI patients without diastolic
dysfunction 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 cardiac output 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 heart failure and eventually death, and thus it may provide a novel target for therapy.

Sources of Funding

The study was supported by grants from the following Danish Foundations.

The Danish Council for Independent Research, Copenhagen; The Danish Heart Foundation, Copenhagen; Toyota Foundation, Copenhagen; Arvid Nielsen Foundation, Copenhagen; A and E Danielsens Foundation, Copenhagen; Lauritz Peter and wife foundation, Hillerød; Brd. Hartmann foundation, Herlufmagle; The capital region, Copenhagen; Lykfeldts Foundation, Hedehusene; S Jacobsen and Wife Foundation, Copenhagen; Karl G Andersen Foundation, Copenhagen; the Beckett Foundation, Copenhagen.

Disclosures

None.

References


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Table 1. Clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients with myocardial infarction (N = 35)</th>
<th>No diastolic dysfunction (n = 11)</th>
<th>Controls (N=10)</th>
<th>P value ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>61 ± 7*</td>
<td>57 ± 10*</td>
<td>46 ± 5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male (%)</td>
<td>30 (86)</td>
<td>10 (91)</td>
<td>7 (70)</td>
<td>0.27</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29 ± 4*</td>
<td>26 ± 3</td>
<td>25 ± 3</td>
<td>0.03</td>
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<td>BSA, m²</td>
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<td>2.1 ± 0.2</td>
<td>2.0 ± 0.3</td>
<td>0.23</td>
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<tr>
<td>Current smokers (%)</td>
<td>10 (29)</td>
<td>4 (27)</td>
<td>3 (30)</td>
<td>0.84</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>20 (57)†</td>
<td>2 (18)</td>
<td>NR</td>
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<tr>
<td>Diabetes (%)</td>
<td>4 (11)</td>
<td>0 (0)</td>
<td>NR</td>
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<tr>
<td>Drug Therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>3 (9)</td>
<td>0 (0)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>β-Blockers (%)</td>
<td>32 (91)</td>
<td>10 (91)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>ACEI/ARB (%)</td>
<td>14 (40)</td>
<td>1 (9)</td>
<td>NR</td>
<td></td>
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<td>CA²⁺ blockers (%)</td>
<td>9 (26)</td>
<td>0 (0)</td>
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<td>Statins</td>
<td>35 (100)</td>
<td>40 (101)</td>
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<td>STEMI (%)</td>
<td>28 (80)</td>
<td>11 (100)</td>
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<td></td>
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<tr>
<td>RCA Culprit (%)</td>
<td>14 (40)</td>
<td>7 (64)</td>
<td>NR</td>
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<tr>
<td>LCX Culprit (%)</td>
<td>9 (26)</td>
<td>1 (9)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>LAD Culprit (%)</td>
<td>12 (34)</td>
<td>3 (27)</td>
<td>NR</td>
<td></td>
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<tr>
<td>Nt-Pro-BNP, pg/L (median)</td>
<td>585 (390-973) *†</td>
<td>194 (103-267) *</td>
<td>50 (50-77)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Max TnT, μg/L (median)</td>
<td>2.70 (1.06-8.44)</td>
<td>1.03 (0.5 – 1.78)</td>
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<tr>
<td>WMS</td>
<td>1.31 ± 0.21†</td>
<td>1.18 ± 0.12</td>
<td>NR</td>
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<tr>
<td>FEV1 (l/min)</td>
<td>3.2 ± 0.7</td>
<td>3.4 ± 0.9</td>
<td>3.5 ± 0.8</td>
<td>0.40</td>
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<tr>
<td>FEV1 % of expected</td>
<td>94 ± 16</td>
<td>94 ± 13</td>
<td>93 ± 16</td>
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<tr>
<td>LV mass index, g/m²</td>
<td>90 ± 18*†</td>
<td>72 ± 14</td>
<td>64 ± 20</td>
<td>&lt;0.0001</td>
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<td>LVEF, %</td>
<td>54 ± 6*</td>
<td>56 ± 6*</td>
<td>65 ± 6</td>
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<td>Left atrial volume index ml/m²</td>
<td>44 ± 11*†</td>
<td>27 ± 8</td>
<td>30 ± 7</td>
<td>&lt;0.0001</td>
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<td>TAPSE, mm</td>
<td>2.6 ± 0.4</td>
<td>2.4 ± 0.4</td>
<td>2.7 ± 0.4</td>
<td>0.46</td>
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<td>E/A ratio</td>
<td>1.1 ± 0.4*</td>
<td>1 ± 0.2*</td>
<td>1.5 ± 0.3</td>
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<tr>
<td>E/e'average</td>
<td>10.8 ± 2.7*†</td>
<td>6.8 ± 1.6</td>
<td>7.5 ± 1.2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are presented as mean ±SD, n (%) unless otherwise indicated. For between-group comparisons: *p<0.05 versus controls; †p<0.05 versus MI - DD.
A, late transmitral filling velocity; ACEI, angiotensin-converting enzyme inhibitors; ANOVA, analysis of variance; ARB, angiotensin-receptor blockers; BMI, body mass index; BSA, body surface area; E, transmitral early filling velocity; e’, tissue Doppler early velocity; FEV1, forced expiratory volume; LAD, left anterior descendent coronary artery; LCX, left circumflex coronary artery; LV, left ventricular; LVEF, left ventricular ejection fraction; NR, not relevant; NT-ProBNP, N-terminal pro-brain natriuretic peptide; RCA, right coronary artery; TAPSE, tricuspid annular plane systolic excursion; TnT, Troponin-T; STEMI, ST-elevation myocardial infarction; WMS, wall motion scores.
Table 2. Exercise induced changes in invasive hemodynamics and LV volumes from rest to peak exercise

<table>
<thead>
<tr>
<th></th>
<th>Myocardial infarction and diastolic dysfunction (N = 35)</th>
<th>Myocardial infarction and no diastolic dysfunction (n = 11)</th>
<th>Controls (N=10)</th>
<th>P Value Overall group ANOVA</th>
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<tbody>
<tr>
<td></td>
<td>Rest Max exercise</td>
<td>Rest Max exercise</td>
<td>Rest Max exercise</td>
<td>Rest Max exercise</td>
</tr>
<tr>
<td>HR</td>
<td>63 ± 11</td>
<td>128 ± 14</td>
<td>60 ± 7</td>
<td>136±17</td>
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<tr>
<td>Systolic BP, mmHg</td>
<td>132 ± 20</td>
<td>185 ± 29</td>
<td>132 ± 14</td>
<td>185±15</td>
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<tr>
<td>Diastolic BP, mmHg</td>
<td>76 ± 12</td>
<td>94 ± 16</td>
<td>74 ± 10</td>
<td>100±9</td>
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<tr>
<td>RPP, mmHg/min</td>
<td>8346 ± 2061</td>
<td>23561 ± 4372</td>
<td>7966 ± 1665</td>
<td>26521±6156</td>
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<tr>
<td>MAP, mmHg</td>
<td>89 ± 13</td>
<td>117 ± 17</td>
<td>88 ± 10</td>
<td>121±11</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>2.8 ± 0.7</td>
<td>8.1 ± 1.4*</td>
<td>2.6 ±0.4</td>
<td>8.7±1.3</td>
</tr>
<tr>
<td>RAP, mmHg</td>
<td>7 ± 3</td>
<td>15 ± 5*</td>
<td>6 ±3</td>
<td>9±4</td>
</tr>
<tr>
<td>sPAP, mmHg</td>
<td>27 ± 6*</td>
<td>63 ± 12*†</td>
<td>23±2</td>
<td>43±15</td>
</tr>
<tr>
<td>dPAP, mmHg</td>
<td>16 ± 4*</td>
<td>39 ± 7*†</td>
<td>13±2</td>
<td>27±7</td>
</tr>
<tr>
<td>mPAP, mmHg</td>
<td>20 ± 5*</td>
<td>50 ± 9*†</td>
<td>17±2</td>
<td>37±5</td>
</tr>
<tr>
<td>PCWP, mmHg</td>
<td>14 ± 4*†</td>
<td>36 ± 6*†</td>
<td>10±2</td>
<td>24±6*</td>
</tr>
<tr>
<td>TMP, mmHg</td>
<td>7 ± 4*</td>
<td>20 ± 5*†</td>
<td>4 ± 2</td>
<td>15±4*</td>
</tr>
<tr>
<td>METS</td>
<td>1</td>
<td>6.4 ± 1.4</td>
<td>1</td>
<td>7.8±2.3</td>
</tr>
<tr>
<td>pH, mixed venous</td>
<td>7.40±0.02</td>
<td>7.26±0.07</td>
<td>7.40±0.02</td>
<td>7.22±0.04</td>
</tr>
<tr>
<td>SVO₂, %</td>
<td>68.7±6.8</td>
<td>41.8±13.6</td>
<td>72.6±2.2</td>
<td>38.5±12.3</td>
</tr>
<tr>
<td>Lactate, mmol/l</td>
<td>0.9 ± 0.4</td>
<td>8.3 ± 3.1</td>
<td>1.0±0.4</td>
<td>10.0±2.5</td>
</tr>
<tr>
<td>SVRI, dynes m⁻²/sec cm⁻⁵</td>
<td>2459±733</td>
<td>1008±192</td>
<td>2580±660</td>
<td>1054±238</td>
</tr>
<tr>
<td>PVRI, dynes m⁻²/sec cm⁻⁵</td>
<td>203 ± 78</td>
<td>143 ± 67</td>
<td>211±51</td>
<td>125±53</td>
</tr>
<tr>
<td>LVEDV Indexed ml/m²</td>
<td>64 ± 12</td>
<td>63 ± 11†</td>
<td>55 ± 12</td>
<td>50±8</td>
</tr>
<tr>
<td>LVESV Indexed ml/m²</td>
<td>30 ± 8*</td>
<td>25 ± 7*†</td>
<td>24 ± 7</td>
<td>19±4</td>
</tr>
<tr>
<td>OS, mmHg/m²/ml</td>
<td>0.22 ± 0.10</td>
<td>0.59 ± 0.15*</td>
<td>0.20 ± 0.06</td>
<td>0.48±0.14*</td>
</tr>
</tbody>
</table>

Data are presented as mean ±SD. For between-group comparisons: *p<0.05 versus controls; †p<0.05 versus Mi - DD. All variables changed significantly (p<0.001) within group with exercise from rest to maximal exercise except for RAP in the control group (p=0.83) and LVEDV in the Mi+DD group (p=0.5).

ANOVA analysis of variance analysis; BP, blood pressure; CI, cardiac index; HR, heart rate; LVEDV, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; MAP, mean artery pressure; METS, metabolic equivalent; OS, Diastolic operating stiffness; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVRI, pulmonary vascular resistance index; RAP, right atrial pressure; RPP, rate pressure product (HR x Systolic BP); SVO₂, mixed venous oxygen saturation; SVRI, systemic vascular resistance index; TMP, LV trans-mural filling pressure.
Figure Legends

Figure 1. Changes in (A) pulmonary capillary wedge pressure (PCWP) and (B) right atrial pressure (RAP) with exercise. Sub max = 4 METS. Error bars represent SD.

* p<0.05 MI + DD versus controls. † p<0.05 MI + DD versus Group B. ¶ p<0.05 MI - DD versus controls.

‡ p<0.05 for within group changes.

Figure 2. Changes in (A) cardiac index (CI) and (B) transmural filling pressure with exercise.

Sub max = 4 METS. Error bars represent SD.

* p<0.05 MI + DD versus Controls. † p<0.05 MI + DD versus MI - DD. ¶ p<0.05 MI - DD versus controls. ‡ p<0.05 for within group changes.
Figure A: Mixed model between groups p<0.0001

Figure B: Mixed model between groups p<0.0001
Exercise Hemodynamics in Patients with and without Diastolic Dysfunction and Preserved Ejection Fraction after Myocardial Infarction

Mads J. Andersen, Mads Ersbøll, John Bro-Jeppesen, Finn Gustafsson, Christian Hassager, Lars Køber, Barry A. Borlaug, Søren Boesgaard, Jesper Kjærgaard and Jacob E. Møller

Circ Heart Fail. published online June 15, 2012;
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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