Relationships Between Biomarkers and Left Ventricular Filling Pressures at Rest and During Exercise in Patients After Myocardial Infarction

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ABSTRACT

Background: Increased pulmonary capillary wedge pressure (PCWP) is an independent prognostic predictor after myocardial infarction (MI), but PCWP is difficult to assess noninvasively in subjects with preserved ejection fraction (EF). We hypothesized that biomarkers would provide information regarding PCWP at rest and during exercise in subjects with preserved EF after MI.

Methods and Results: Seventy-four subjects with EF >45% and recent MI underwent right heart catheterization at rest and during a symptom-limited semisupine cycle exercise test with simultaneous echocardiography. Plasma samples were collected at rest for assessment of midregional pro−A-type natriuretic peptide (MR-proANP), N-terminal pro−B-type natriuretic peptide (NT-proBNP), galectin-3 (Gal-3), copeptin, and midregional pro-adrenomedullin (MR-proADM). Plasma levels of MR-proANP and PCWP were associated at rest ($r = 0.33$; $P = .002$) and peak exercise ($r = 0.35$; $P = .002$) as well as with changes in PCWP ($r = 0.26$; $P = .03$). Plasma levels of NT-proBNP and PCWP were weakly associated at rest ($r = 0.23$; $P = .03$) and peak exercise ($r = 0.28$; $P = .02$) but not with changes in PCWP ($r = 0.20$; $P = .09$). In a multivariable analysis, plasma levels of MR-proANP remained associated with rest and exercise PCWP ($P < .01$), whereas NT-proBNP did not. Plasma levels of Gal-3, copeptin, and MR-proADM were not associated with PCWP at rest or peak exercise.

Conclusions: In subjects recovering from an acute MI with preserved EF, plasma levels of natriuretic peptides, particularly MR-proANP, are associated with filling pressures at rest and during exercise. (*J Cardiac Fail 2014;20:959−967*)

Key Words: Acute myocardial infarction, hemodynamics, exercise testing, biomarkers.

Increased filling pressures independently predict outcome after myocardial infarction (MI).[1,2] However, invasive hemodynamic testing is expensive and carries a risk of complications. When left ventricular (LV) ejection fraction (LVEF) is preserved (>45%), noninvasive demonstration of elevated filling pressure is particularly challenging. Recent recommendations suggest using the quotient of peak early mitral inflow velocity (E) and peak early diastolic tissue Doppler velocity in the mitral annulus (e′), which have shown modest association with invasive obtained filling pressure in most studies[3,4] though not all.[5] European guidelines suggest that filling pressures are increased when E/e′ is >15.[6] Accordingly studies have demonstrated that echocardiographic indices suggestive of increased LV filling pressure and pulmonary hypertension are associated with worse outcome after MI,[7−11] but ∼25% of subjects with preserved LVEF after MI have E/e′ values in the intermediate range,[8−15] where the association with filling pressure is less clear.[12,13]

Subjects with heart failure and preserved EF (HFpEF)[14] and post-MI subjects with preserved LVEF and diastolic

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dysfunction[13,15] are prone to elevation in pulmonary capillary wedge pressure (PCWP) during exercise in relation to limitations in LV diastolic reserve, but identifying these vulnerable subjects requires invasive assessment. The ability to noninvasively identify subjects with compromised resting or exercise hemodynamics has gained increasing interest owing to development of experimental therapies aiming at reducing LV filling pressures.[14,16]

Natriuretic peptides (N-terminal pro−B-type natriuretic peptide [NT-proBNP] and midregional pro−A-type natriuretic peptide [MR-proANP]) are released in response to increases in wall stress,[17,18] but little is known about these correlations with filling pressures during exercise. In addition, other candidate biomarkers have been related to filling pressures, including galectin-3, copeptin, and midregional pro-adrenomedullin (MR-proADM), but comparative data with directly measured filling pressures are lacking. We hypothesized that plasma concentrations of these biomarkers would identify subjects with increased filling pressures at rest or during exercise in post-MI subjects with preserved LVEF.

Methods

Study Design and Patient Population

We enrolled 80 post-MI subjects with preserved LVEF (>45%) who all underwent right heart catheterization at rest and during symptom limited semisupine cycle exercise test with simultaneous echocardiography. Inclusion criteria were preserved LVEF and written informed consent. Subjects with permanent atrial fibrillation, known history of cardiomyopathy, more than mild valvular heart disease (more than mild stenosis or regurgitation), obstructive or restrictive pulmonary disease, or inability to perform exercise testing were excluded. The majority (70) of included subjects were post-MI patients with echocardiographic signs of diastolic dysfunction (MI + DD; E/e′ >8 and left atrial (LA) volume >32 mL/m^2, and 10 post-MI subjects had normal diastolic function as judged by echocardiography (MI−DD; E/e′ <8 and LA < 32 mL/m^2). Hemodynamic and echocardiographic data for these subjects has been previously published.[12,15] Subjects were studied on chronic medications in the fasted state. The subjects were stratified in a binary fashion with the use of peak exercise PCWP >25 mm Hg as cutoff for abnormal filling pressure with exercise.[14] The Ethics Committee in Hovedstaden Region approved the study, and written informed consent was obtained from every subject.

Invasive Hemodynamic Measurements

Right heart catheterization was performed with the use of a standard 7.5-F triple-lumen Swan-Ganz thermistor and balloon-tipped catheter (Edwards Lifesciences, Irvine, California). The catheter was introduced, guided by ultrasound, into the right internal jugular vein and advanced to the pulmonary artery. PCWP, right atrial pressure (RAP), systolic pulmonary arterial pressure (PAP), diastolic PAP, mean PAP, blood pressure (BP), and cardiac output (CO; thermodilution technique) were measured at rest, at each level of exercise until exhaustion, and after 5 minutes of rest. PCWP at rest and after exercise was measured at end-expiration. During exercise, mean PCWP was used. We considered resting PCWP >15 mm Hg and/or exercise PCWP >25 mm Hg to be abnormally increased.[14]

Exercise Protocol

Subjects performed a multistage symptom-limited semisupine cycle exercise test with the use of an Echo Cardiac Stress Table (Lode, the Netherlands). Workload started at 0 W and was increased by 25 W every 2 minutes. Subjects were encouraged to maintain a fixed pedaling speed of 60 rpm for the duration of the exercise. They were also encouraged to exercise until exhaustion (Borg >18).

Echocardiography

All subjects underwent resting echocardiographic examinations obtained according to current guidelines.[19,20] During exercise, 2-dimensional tissue Doppler images (TDI) and pulsed- (PW) and continuous-wave Doppler images were acquired in the apical 4-chamber view. All examinations were performed by an experienced echocardiographer using a Philips iE33 (Philips Healthcare, Best, the Netherlands) cardiac ultrasound system. Echocardiographic cine loops were obtained by recording a minimum of 3 consecutive heart cycles. Images were stored digitally for offline analysis with the use of Philips Xcelera analysis software version 3.1 (Philips Healthcare).

LV volumes and LVEF were assessed with the use of the Simpson biplane method of discs from the apical 4- and 2-chamber views at rest. LA volume was measured from the apical 4- and 2-chamber views with the use of the area-length method at rest. Volumes were indexed to body surface area (BSA) when appropriate. With the use of PW Doppler, E velocities were measured with the sample volume placed at the tips of mitral leaflets during diastole. With the use of TDI and PW Doppler with the sample volume placed in the septal and lateral mitral annulus, e′ velocities were measured and averaged.[4]

For Doppler recordings, horizontal sweep was of 75 or 100 mm/s and 3−5 consecutive beats were used and averaged. All analyses were performed blinded to hemodynamic and biomarker values.

Biomarkers

Plasma samples were collected at rest from the internal jugular vein after positioning of the Swan-Ganz catheter before exercise. Plasma and serum were collected in EDTA-primed glass tubes, centrifuged for 10 minutes at 3,000 rpm, and stored at −80°C until analysis. Samples underwent ≤2 freeze/thaw cycles before analysis. NT-proBNP was measured on the Modular E platform (Roche Diagnostics) with lower limit of detection (LOD) at 25 pg/mL and interassay coefficient of variations (CVs) of 12.6% at 29.2 pg/mL and 9.6% at 8.5 pg/mL.[21] Plasma concentrations of copeptin were measured on the automated Kryptor Plus platform (Thermo-Fischer, Waltham, Massachusetts). The interassay CVs were 18.3% for 1.4 pmol/L, 6.8% for 9.3 pmol/L, and <3% for concentrations >18 pmol/L.[22] The automated Kryptor Plus platform was also used to quantify the plasma levels of MR-proADM (LOD of 0.08 nmol/L and CV <20% for values >0.12 nmol/L) and MR-proANP (LOD of 6.0 pmol/L and CV 10%).[22−24] Galectin-3 was measured on a Vidas platform (Biomérieux, Ballerup, Denmark) with an LOD of 1.13 ng/mL and interassay CV <10.4%.[25]