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Early changes in left atrial volume after acute myocardial infarction. Relation to invasive hemodynamics at rest and during exercise

Rine Bakkestrøm [b,*,1], Mads J. Andersen [a,2], Mads Ersbøll [a,3], John Bro-Jeppesen [a,4], Finn Gustafsson [a,5], Lars Køber [a,6], Christian Hassager [a,7], Jacob E. Møller [a,b,8]

[a] From the Heart Center, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Odense, Denmark
[b] Department of Cardiology, Odense University Hospital, Odense, Denmark

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ABSTRACT

Background: Dilatation of left atrium (LA) reflects chronic LA pressure or volume overload that possesses considerable prognostic information. Little is known regarding the interaction between LA remodeling after acute myocardial infarction (MI) and left atrial pressure at rest and during exercise. The objective was to assess changes in LA volume early after MI in patients with diastolic dysfunction and the relation to invasive hemodynamics and natriuretic peptides.

Methods: 62 patients with left ventricle ejection fraction (LVEF) ≥ 45%, diastolic E/e' > 8 and LA volume index >34 ml/m^2 within 48 h of MI were enrolled. After 1 and 4 months blood sampling, echocardiography and right heart catheterization were performed during exercise test.

Results: LA remodeling was considered in patients with a change from mild (35–41 ml/m^2), to severe (>48 ml/m^2) dilatation after 4 months (Found in 22 patients (35%)). Patients with LA remodeling were characterized by lower a' (1 month 8.9 ± 2.0 vs. 10.4 ± 2.5 cm/s, p = 0.002; 4 month 8.8 ± 2.0 vs. 10.4 ± 2.4 cm/s, p = 0.007) and higher MR-proANP (1 month 162 ± 64 vs. 120 ± 44 pg/l, p = 0.005; 4 months 175 ± 48 vs. 129 ± 56 pg/l, p = 0.002). With exercise, pulmonary artery pressure, right atrial pressure and pulmonary capillary wedge pressure increased markedly in all patients. There were however, no significant differences in filling pressure at rest or during exercise irrespective of whether LA remodeling occurred.

Conclusion: Contrary to our hypothesis early LA dilatation after MI was weakly associated with resting and exercise induced changes in LA pressure overload. The dilatation was however associated with lower e' and higher MR-proANP.

1. Introduction

The left atrium acts as a reservoir and conveys blood from the pulmonary vascular bed to the left ventricle. The maximal size of the left atrium is determined by multiple factors including severity of diastolic dysfunction with impaired relaxation and decreased left ventricular (LV) chamber compliance, exposing the atrium to increased filling pressure during diastole [1,2].

With persistent left atrial (LA) pressure overload, LA wall tension will be increased which is believed to cause stretching of the atrial myocardium and cause dilation of the LA. Thus LA volume is considered to reflect the duration and severity of increased left atrial pressure [1,3,4]. Furthermore, several previous studies have demonstrated that left atrial size is an important and independent predictor of prognosis in patients with heart failure, valve disease and ischemic heart disease with significantly higher mortality among patients with LA dilatation [5–9].

Following acute myocardial infarction (MI) it is well known that myocardial damage can cause dynamic changes in LV geometry and

* Corresponding author at: Department of Cardiology, Odense University Hospital, Sønder Boulevard 29, DK-5000 Odense C, Denmark.
E-mail address: Rine.Bakkestroem@rsyd.dk (R. Bakkestrøm).
[1] MD. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
[2] MD, PhD. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
[3] MD, PhD. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
[4] MD, PhD. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
[5] MD, PhD, DmSc. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
[6] MD, DmSc. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
[7] MD, DmSc. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
[8] MD, PhD, DmSc. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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LV compliance with infarct expansion and progressive dilatation of the LV (LV remodeling). Opposed to LV remodeling less is known about early changes in LA volume (LA remodeling) following AMI. Recent data have demonstrated that changes in LA maximal volume during the first months after MI assessed with echocardiography or cardiac magnetic resonance imaging are predictive of outcome [10,11]. Although these studies suggest that LA remodeling is associated with impaired renal function, hypertension and LV remodeling, the hemodynamic determinants of LA remodeling are unknown.

We hypothesized that LA remodeling occurs after MI and that differences in LA size reflect differences in the severity of atrial pressure overload and is associated with increased neurohormonal activation. We therefore performed serial determination of LA size in patients with a recent AMI and mild LA dilatation and assessed the association between LA size and central hemodynamics at rest and during exercise, and cardiac natriuretic peptides.

2. Methods

2.1. Patients

The present study is a prespecified substudy of the Sildenafil In Acute Myocardial Infarction (SIDAMI) trial [12]. In brief, males and non-pregnant females aged ≥50 with a recent documented MI were screened for participation at a single tertiary center (Copenhagen University Hospital Rigshospitalet). Patients were considered eligible if echocardiography performed within 48 h of the MI suggested diastolic dysfunction and left ventricular ejection fraction (LVEF) was ≥45% (n = 329). Diastolic dysfunction was defined as the ratio of the early diastolic peak mitral inflow velocity (E) to early mitral annulus diastolic velocity (e′) > 8 and LA volume index ≥34 ml/m^2.

Patients with permanent atrial fibrillation, known history of cardiomyopathy, moderate or severe left-sided valvular disease, obstructive or restrictive pulmonary disease, inability to perform exercise testing, those with inadequate acoustic windows, and patients requiring further revascularization or with residual coronary stenosis exceeding 50% were excluded (n = 31). Finally, 228 patients declined to participate, 2 withdrew consent, 1 was lost to follow-up and 5 were excluded due to incomplete data. Thus a total number of 62 patients completed this substudy. One month after admission spirometry, blood testing, comprehensive resting Doppler echocardiography, resting right heart catheterization, 6-minute walk test and symptom-limited supine cycle exercise test with simultaneous echocardiography and right heart catheterization were performed. Approximately 4 months (95 ± 16 days) after MI echocardiography, right heart catheterization and exercise test were repeated.

The ethics Committee for the Capital Region Copenhagen approved the trial protocol (ID: H-A-2009-023). All patients provided written informed consent, and the study was registered at ClinicalTrials.gov (ID: NCT 01046838).

2.2. Echocardiography

Resting and exercise echocardiography was 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). LV volumes and LVEF were assessed using the 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 biplane planimetry. Measurements were obtained in end systole prior to the mitral valve opening and the volume was indexed for body surface area [4]. According to the most recent guidelines on chamber quantification [13] the patients were divided according to LA volume index into mildly abnormal (35–41 ml/m^2), moderately abnormal (42–48 ml/m^2) and severely abnormal (>48 ml/m^2). Change in LA volume index was calculated as the change in LA volume index from first (performed at admission) to third (performed 4 months after AMI) echocardiography. Patients that experienced an increase in LA volume index from mild to severe dilatation were considered to have LA remodeling, which constitute an increase in LA volume index of at least 10 ml/m^2.

Mitral inflow was assessed in the apical 4-chamber view with the pulsed wave Doppler sample volume placed at the tips of the mitral valve leaflets during diastole. Mitral annular motion was assessed using pulsed wave tissue Doppler with the sample volume placed in the septal and lateral mitral annulus. Early (e') and late (a') diastolic velocities were recorded, the mean of the septal and lateral e' velocities was used for calculation of E/e'. Wall motion scores were assessed semiquantitatively using the standard 16 segmental model in accordance with current guidelines [13]. For Doppler recordings the average of 3 to 5 consecutive beats was measured using a horizontal sweep of 75 to 100 cm/s. The analyses were performed blinded to invasive measurements.

2.3. 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, 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) were measured at each level of exercise until exhaustion and after 5 min of rest. PCWP at rest and post exercise was measured at end-expiration. During exercise PCWP was averaged over 10 s. CO was measured using thermodilution as the average of 3 measurements with <10% variance. CO was indexed to body surface area as cardiac index (CI). At rest and at peak exercise a central venous blood sample was drawn from the pulmonary artery and analyzed for lactate concentration, mixed venous oxygen saturation and pH.

2.4. Excercise protocol

All patients performed a multistage symptom-limited semi-supine cycle ergometer exercise test using an Echo Cardiac Stress Table (Lode B.V., The Netherlands). Workload started at 0 W and increased by 25 W every 2 min. Patients were encouraged to exercise until exhaustion (Borg > 18) [14]. Brachial blood pressure was measured by sphygomanometry at baseline and at every 2 min until maximum workload was reached and repeated after 5 min of rest.

2.5. Biomarkers

Plasma samples were collected at rest from the internal jugular vein after positioning of the Swan-Ganz catheter prior to exercise. Plasma and serum were collected in EDTA primed glass tubes, immediately centrifuged for 10 min at 3000 rpm and stored at −80 °C until analysis. NT-proBNP (N-terminal pro brain natriuretic peptide) was measured on the Modular E platform (Roche Diagnostics) with lower limit of detection (LOD) at 25 pg/ml and interassay coefficient of variation (CV) of 12.6% at 29.2 pg/ml and 9.6% at 8.5 pg/ml [15]. The automated Kryptor Plus platform was also used to quantify the plasma levels of MR-proANP (mid regional pro atrial natriuretic peptide) (LOD of the assay is 6.0 pmol/l and CV 10%) [16]. Estimated glomerular filtration rate was calculated according to the Modification of Diet in Renal Disease formula [17].

2.6. Statistical analysis

Data are presented as mean ± standard deviation or median (interquartile range) unless otherwise indicated. Normally distributed within-individual changes from baseline to follow-up were evaluated using the paired *t* test. For non-Gaussian distributed variables non-parametric rank sum test was used. Association between change in LA volume index and clinical, echocardiographic and invasive measurements were assessed with linear regression. Residuals were tested for homogeneity of variation based on visual inspection of residual and QQ plots and Shapiro Wilks test. A probability value <0.05 was considered significant. Statistical analyses were performed using SPSS Statistics version 21 (IBM, NY).

3. Results

Sixty-two patients with fully revascularized recent AMI were enrolled. Patients were characterized by mildly to moderately increased E/e'-ratio (11.1 ± 2.6), mildly dilated left atrium (38 ± 6 ml/m^2) and preserved LVEF (56 ± 7%) on echocardiography performed within 48 h of admission. Majority of patients (90%) were males, the mean age was 62 ± 8 years, and 30 patients (48%) had a history of hypertension, Table 1. Fifty-three patients (86%) were diagnosed with ST-segment elevation AMI (STEMI). The culprit lesion was located in the left anterior descending in 24 (39%), in the left circumflex in 18 (29%) and in right coronary artery in 20 (32%). All STEMI patients underwent primary percutaneous coronary intervention (PCI) with stent insertion, Table 1.

3.1. Changes in left atrial size

At enrollment 54 patients (85%) had a mildly dilated LA and only 3 (5%) had severe dilatation, Fig. 1. During follow-up LA volume increased significantly from 38 ± 6 ml/m^2 to 44 ± 10 ml/m^2 after 1 month and 48 ± 11 ml/m^2 after 4 months in the total study population. In 22 patients (35%) a change in LA volume index from mild to severe dilatation was seen and these patients were considered to have LA remodeling, Fig. 1. Compared to patients without LA remodeling, patients with LA remodeling were comparable with respect to clinical characteristics and echocardiographic parameters at admission, Table 1. At 1 month follow-up a' was significantly lower in patients with LA remodeling which also was found after 4 months, Tables 2 and 3. After 4 months patients with LA remodeling had larger left ventricular end diastolic volume (LVEDV) compared to patients