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Noninvasive assessment of myocardial bridging by coronary flow velocity reserve with transthoracic Doppler echocardiography: vasodilator vs. inotropic stimulation

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ABSTRACT

Background: To consider hemodynamic assessment of myocardial bridging (MB) adequate, it is believed that inotropic stimulation with dobutamine should be estimated because its dynamic nature depends on the degree of extravascular coronary compression. This study evaluated comparative assessment of hemodynamic relevance of MB using coronary flow velocity reserve (CFVR) measurements by transthoracic Doppler echocardiography (TTDE) with vasodilatative and inotropic challenges.

Methods: This prospective study included forty-four patients with angiographic evidence of isolated MB of the left anterior descending coronary artery (LAD) and systolic compression of ≥50% diameter stenosis. All patients were evaluated by exercise stress-echocardiography (ExSE) test for signs of myocardial ischemia, and CFVR of the distal segment of LAD during iv.infusion of adenosine (ADO:140 μg/kg/min) and iv.infusion of dobutamine (DOB:10-40 μg/kg/min), separately.

Results: Exercise-SE was positive for myocardial ischemia in 8/44 (18%) of patients. CFVR during ADO was significantly higher than CFVR during peak DOB (2.85 ± 0.68 *vs.* 2.44 ± 0.48, $p = 0.002$). CFVR during peak DOB was significantly lower in SE-positive group in comparison to SE-negative group (2.01 ± 0.16 *vs.* 2.54 ± 0.47, $p < 0.001$), but not for ADO (2.47 ± 0.51 *vs.* 2.89 ± 0.70, $p = 0.168$), respectively. Multivariable logistic analysis showed that CFVR peak DOB was the most significant predictor of functional significant MB (OR 0.011, 95%CI: 0.001–0.507, $p = 0.021$). Receiver-operating characteristic curves have shown that TTDE-CFVR obtained by high-dose of dobutamine infusion is better than those by adenosine regarding to functional status of MB (AUC 0.861, $p = 0.004$; AUC 0.674, $p = 0.179$, respectively).

Conclusions: Non-invasive CFVR measurement by TTDE during inotropic stimulation, in comparison to vasodilation, provides more reliable functional evaluation of MB.

1. Introduction

First described at the beginning of the XXth century [1], myocardial bridges (MBs) represent a congenital variation found in humans and some higher primates [2] defined by a segment of a major epicardial coronary artery, running intramurally through the myocardium beneath a muscle bridge [3–4], rendering the artery "tunneled". Located mainly in the medial segment of left anterior descending coronary artery (LAD), it is characterized by systolic compression of the overbridged arterial segment ("milking effect") [5–6] with a delay in early diastolic relaxation and a persistent lumen diameter reduction in

Abbreviations: ADO, Adenosine; AS, Area stenosis; BP, Blood pressure;; CAD, Coronary artery disease; CFVR, Coronary flow velocity reserve; CFV, Coronary flow velocity; Cx, Left circumflex coronary artery; DOB, Dobutamine; DS, Diameter stenosis; ExSE, Exercise stress-echocardiography; MB, Myocardial bridging; HR, Heart rate; LAD, Left anterior descending coronary artery; LV, Left ventricular; LVEF, Left ventricular ejection fraction; MLD, Minimal luminal diameter; PCI, Percutaneous coronary intervention; QCA, Quantitative coronary angiography; RCA, Right coronary artery; RPP, Rate-pressure product; TTDE, Transthoracic Doppler echocardiography; WMA, Wall-motion abnormalities.

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diastole, hindering hence its hemodynamics. Although MB is commonly considered a benign anatomic variation, it is well known that it may cause myocardial ischemia, arrhythmias, acute coronary syndrome and even sudden cardiac death [6–8]. The clinical, hemodynamic and prognostic significance of this anomaly is still unclear, as revascularization strategies did not produce the expected benefit due to higher incidence of complications, in particular in-stent restenosis [9–14]. Therefore, identifying an MB which can cause myocardial ischemia is essential in order to avoid unnecessary interventions.

In a clinical setting, coronary flow reserve measurements are useful in assessing the functional significance of coronary lesions and provide information that complements the functional assessment with all non-invasive techniques currently used [15]. Therefore, they can be helpful for making the decision about revascularization procedures in patients with coronary lesions when other evidence for reversible myocardial ischemia is insufficient [16]. Since MB is a dynamic, transient stenosis that depends on the degree of extravascular compression, several authors suggest that adequate hemodynamic assessment of MB should include inotropic stimulation with dobutamine [17–19]. Additionally, high doses of dobutamine infusion (>20 μg/kg/min) have been shown to induce the same effect on the microcirculation as well as adenosine, regardless of whether ischemia is present or not [20]. The evaluation of coronary flow velocity reserve (CFVR) by transthoracic Doppler echocardiography (TTDE) has been proven as a reliable diagnostic tool with a high feasibility to assess coronary flow of the LAD [21–24]. Previous studies included only patients with fixed (atherosclerotic) coronary stenoses, while there are no data about relation between stress-induced myocardial ischemia and both TTDE-CFVR during adenosine and dobutamine infusions in patients with isolated MB on the LAD. We hypothesized that non-invasive CFVR by TTDE during dobutamine infusion will have a better diagnostic power in the assessment of the functional significance of MB compared to CFVR during adenosine infusion.

Therefore, the aim of this study was to evaluate hemodynamic relevance of MB by non-invasive CFVR measurements with vasodilatative and inotropic challenge, in the context of exercise stress-induced myocardial ischemia.

2. Methods

2.1. Study population

The present study is a prospective, single-centre study conducted from January 2011 to June 2016 with the inclusion of symptomatic and asymptomatic patients with angiographic evidence of isolated MB on LAD and significant systolic compression of intramyocardial segment (≥50% diameter stenosis obtained by quantitative coronary angiography). Exclusion criteria were: (1) MB patients with angiographic non-significant systolic compression of the intramyocardial arterial segment; (2) patients aged ≤18 years old; (3) presence of atherosclerotic coronary artery disease (CAD) in other coronary segments of LAD or coronary arteries; (4) previous ST-elevation or non-ST-elevation myocardial infarction of anterior/anterolateral wall; (5) previous aorto-coronary by-pass grafting surgery; (6) congenital and acquired valvular heart disease; (7) left ventricular ejection fraction (LVEF) ≤40%; (8) LV hypertrophy; (9) cardiomyopathies; (10) atrial fibrillation; and (11) renal failure. All patients were evaluated for clinical symptoms defined as stable (typical or atypical) or unstable angina according to the current recommendations [25–26].

Resting two-dimensional echocardiography, treadmill-exercise stress-echocardiography (ExSE) and TTDE-CFVR evaluation during both adenosine and dobutamine infusions were performed in all patients. Antianginal drugs including long-acting nitrates, calcium-channel blockers and beta-blockers, as well as xanthine-containing foods or beverages, were discontinued 24–48 h before the examinations.

The study protocol was presented and approved by the Medical Ethical Committees of the Clinical Center of Serbia and the School of Medicine University of Belgrade's one (Belgrade, Serbia). Informed consent was obtained from all patients.

2.2. Stress echocardiography

After standard echocardiographic examination, all patients were evaluated with treadmill-ExSE according to maximal Bruce protocol, as previously described [27]. Echocardiographic studies were performed with digital ultrasound system (Acuson Sequoia C256, Siemens Medical Solutions USA, Inc., Mountain View, CA), with a 3V2C multifrequency transducer using second-harmonic technology. Briefly, all standard echocardiographic views were obtained in the left lateral decubitus position before and immediately after exercise. Echocardiographic images were interpreted and analyzed by a senior echocardiographer blinded for patients' clinical, angiographic, and functional status. For the purpose of this analysis, LV walls were divided into the 17-segment model and segmental wall motion was graded as follows: 1 = normal, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic [28]. To explore the interobserver variability in reading SE images, in all selected patients ExSE studies were separately analyzed by two independent senior observers. ExSE test was considered positive for myocardial ischemia when new or worsening of preexisting wall-motion abnormalities (WMA) was observed in at least two adjacent LV segments in the LAD territory and confirmed by both observers. Only stress-echocardiographic abnormalities were considered as positive tests. Neither the presence of a resting WMA, nor the presence of stress-induced angina or ischemic ECG changes was considered as positive test result.

2.3. Evaluation of coronary flow velocity reserve by transthoracic Doppler echocardiography

Transthoracic CFVR assessment during both adenosine and dobutamine infusions were performed using the same ultrasound unit, as previously described [29–30]. Baseline and maximal (peak) diastolic coronary flow velocity (CFV) was measured in the distal segment of LAD at baseline, during iv. infusion of adenosine (140 μg/kg/min), and each dose of dobutamine, starting at a dosage of 10 μg/kg/min, and increasing by 10 μg/kg/min every 3 min, to the maximal dosage of 40 μg/kg/min. All measurements represented an average of 3 cardiac cycles. CFVR was calculated as the ratio of peak diastolic CFV (after adenosine or dobutamine stimulation) and baseline CFV.

Dobutamine infusion was considered hemodynamically adequate if one of the two conditions were satisfied: (1) increase in heart rate (HR) of at least 50 bpm from baseline HR (delta HR), or (2) increase in HR of at least 75% of the maximum age-predicted HR [31]. In case of inadequate increase in HR, in the absence of ischemia or other side effects, a bolus of atropine 0.5 mg was injected during the last minute of the test and repeated up to a maximal dose of 2 mg if necessary.

Heart rate, blood pressure (BP) and 12-lead ECG were monitored continuously and recorded under baseline conditions, during adenosine and each dose of dobutamine infusion. Rate-pressure product (RPP) was calculated as HR multiplied by systolic BP.

All studies were recorded on VHS tapes and echocardiographic images and clips were stored on magneto-optical discs for off-line analysis. At each time point, three optimal diastolic flow profiles were measured and the results averaged. Peak diastolic CFV measurements were done off-line by using the integrated software package of the ultrasound system, by a senior investigator who was blinded for the patient's clinical status.

2.4. Quantitative coronary angiography

We performed a detailed frame-by-frame quantitative coronary angiography (QCA) analysis of the interpolated reference diameter, minimal luminal diameter (MLD), percent diameter stenosis (DS), and area stenosis (AS) at the most severe site of the MB [32], during cardiac cycle at following time points: at end systole (peak of T wave), early- (end of T wave), mid- (beginning of P wave) and end-diastole (beginning of QRS complex). All angiographic images were obtained at least 1 min after intracoronary injection of 200 μg of nitroglycerin and analyzed by dedicated system for QCA (Siemens Quantcor QCA). The images were analyzed off-line by a senior investigator blinded for the patients' clinical, functional, and echocardiographic status.

2.5. Statistical analysis

All data were entered into a specially created database and then processed in the statistical program IBM Statistical Package for the Social Sciences version 18.0 (SPSS Inc., Chicago, Illinois). Continuous variables are expressed as mean ± SD and categorical variables are reported as count with percentages. Categorical variables were compared using a Chi-squared or Fischer's exact test, depending on group size. For ExSE-images analysis, interobserver agreement was tested using kappa coefficient. Normal distribution of continuous variables was confirmed by the Kolmogorov–Smirnov test. Student's *t*-test (pair or unpaired, as required) or one-way analysis of variance (ANOVA) followed by the post-hoc Tukey HSD test were used to compare data between two or more groups. Differences in systemic and coronary hemodynamic parameters between baseline and during both adenosine and dobutamine infusions were tested using ANOVA for repeated measures with Bonferroni correction for multiple pairwaise comparison. All tests were considered two-sided. Relation between demographic, clinical, echocardiographic, angiographic, systemic and coronary hemodynamic parameters was analyzed by Pearson's correlation coefficient. A $p < 0.05$ was considered statistically significant.

The Bland-Altman method was used for assessing the limits of agreement between CFVRs measured by the two methods [33]. Univariable logistic regression analysis was used to evaluate the relation between various demographic, clinical, angiographic and coronary hemodynamic parameters and detecting stress-induced myocardial ischemia. To select covariates independently associated with stress-induced ischemia in MB-patients, significant univariable predictors were reassessed by several models of multivariable logistic regression analyses using forward and bootstrap methods, with values for inclusion and elimination set at $p \leq 0.05$.

Receiver operating characteristic (ROC) curves with the 95% confidence intervals (CI) were used to estimate diagnostic accuracy of non-invasive CFVR after adenosine and peak dobutamine infusions for discrimination of MB-patients with and without stress-induced myocardial ischemia.