Microvascular Damage After Coronary Artery Bypass Surgery: Assessment Using Dobutamine Stress Myocardial Contrast Echocardiography

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Abstract: *Background:* Although dobutamine stress myocardial contrast echocardiography (DSMCE) has been widely used for the prediction of myocardial functional recovery, dynamic changes that occur at the microcirculatory level during stress have been studied limitedly. The objective of the present study was to use low-dose DSMCE to assess microvascular damage and predict myocardial functional recovery in coronary artery disease (CAD) patients receiving coronary artery bypass grafting. *Methods:* Forty-six CAD patients were subjected to low-dose DSMCE, as well as echocardiography and coronary computed tomography angiography before revascularization, 1 year after coronary artery bypass grafting. Dynamic changes occurring at the microcirculatory level during stress were analyzed for the ability to predict functional recovery. Quantitative assessment of functional recovery was determined using myocardial blood flow (MBF) via receiver operating characteristic curve analyses. *Results:* Patients who failed to recover had fewer changes in MBF (ΔMBF) at rest and with stress compared with the segments showing functional recovery. Semiquantitative changes (enhanced or reduced) of the myocardial perfusion score (ΔMPS) and quantitative changes in ΔMBF of stress myocardial contrast echocardiography enhanced the specificity of resting MPS and the sensitivity of wall motion scores ($P < 0.05$) for the prediction of functional recovery. *Conclusions:* Specific stress ΔMBF more accurately reflected the extent of microvascular damage compared with wall motion scores and resting MPS. ΔMBF and ΔMPS under stress myocardial contrast echocardiography provided higher accuracy than wall motion scores and resting MPS in predicting functional recovery in CAD patients after revascularization.

Key Indexing Terms: Myocardial contrast echocardiography; Dobutamine stress echocardiography; Myocardial blood flow; Coronary microcirculation; Functional recovery. **[Am J Med Sci 2014;347(5): 387–392.]**

Myocardial viability in patients with decreased left ventricular function has important implications for both therapy and prognosis.[1] Myocardial contrast echocardiography (MCE) includes the assessment of microvascular integrity and myocardial blood flow (MBF) using continuous intravenous injections of microbubbles and quantification of acoustic intensity curves in the myocardium.[2–5] The combination of MCE and dobutamine stress echocardiography (DSE) has been recently used to detect the presence of residual myocardial viability in patients with coronary artery diseases (CAD). However, limited data exist on changes in myocardial perfusion of the heart during DSE.

In the present study, we hypothesized that functional damage during microvasculation in viable myocardium is more clinically relevant than resting myocardial perfusion and contractile reserve. Therefore, this study was designed to assess functional alterations in microvascular flow during stress using low-dose dobutamine stress myocardial contrast echocardiography (LD-DSMCE) combined with optimized MCE, resulting in better prognostic information for regional functional recovery. The cutoff parameters of MCE for the assessment of functional recovery are also discussed.

PATIENTS AND METHODS

Patients

Forty-six patients with CAD (29 men; mean age of 58 years; range, 50–67 years) were enrolled in the present study. All patients had indications for coronary artery bypass grafting (CABG) according to the current guidelines.[6] Inclusion criteria included: (1) unstable angina or previous myocardial infarction (acute myocardial infarction >6 weeks); (2) multivessel disease assessed via coronary angiography and (3) complete revascularization (CABG) after the identical surgical protocol. Exclusion criteria included: (1) cardiogenic shock; (2) malignant life-threatening diseases; (3) severe valvular disease; (4) concomitant cardiac surgery for another disease; (5) patients with obstructed grafts 1 year after CABG by 256-slice multislice computed tomography angiography (MSCTA) and (6) inadequate echocardiographic image quality. The current study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Harbin Medical University.

Study Protocol

All patients were assessed at baseline with a complete echocardiogram for regional wall motion score and global left ventricular function. MCE was performed both at rest and during LD-DSMCE to assess resting and stress myocardial perfusion and contractile reserve. All patients received CABG in our institution after the same surgical protocol. One year after CABG (postrevascularization), a resting echocardiogram and MSCTA were performed to reassess regional wall motion score and the effect of CABG. Patients who developed obstructed grafts were eliminated from further study.

Dobutamine Stress Echocardiography

Images were obtained using a standard commercial echocardiography system (IE33; Philips Ultrasound, Bothell, WA) and digitally stored for subsequent analyses. Parasternal long-axis and short-axis views, as well as 3 standard apical views (4-chamber, 2-chamber and 3-chamber) of the left

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ventricular, were acquired at rest and during the DSE study. The left ventricular was divided according to the 17-segment model of the American Society of Echocardiography.[7] A standard, low-dose dobutamine stress protocol was performed, whereby dobutamine infusion began at 5 μg/kg/min for 5 minutes, followed by 10 μg/kg/min for another 5 minutes.[8] Blood pressure and cardiac rhythms were monitored continuously before and during dobutamine infusion. Regional wall motion abnormalities (WMAs) were graded as follows: (1) normal; (2) hypokinesia; (3) akinesia and (4) dyskinesia. Wall motion score index was calculated as the sum of all WMAs divided by the number of segments. Ejection fraction was quantified using the bi-plane Simpson's method.[9] Potential for functional recovery was defined as a wall motion score (WMS) decrease by ≥1 during dobutamine administration. Alterations from dyskinesia to akinesia were not considered as an improvement in function.

Myocardial Contrast Echocardiography

MCE was undertaken in 3 standard apical long-axis (apical 4-, 2- and 3-chamber) views and 3 parasternal short-axis views using a low-power technique at a mechanical index of 0.1. SonoVue (Bracco Research SA, Geneva, Switzerland) were applied using a slow bolus injection (1.0–1.5 mL per bolus) followed by a 5-mL saline flush,[10] which was repeated as necessary. Replenishment was observed after high mechanical index (1.7) microbubble destruction to assess myocardial perfusion.[11,12] Replenishment was visualized for >15 cardiac cycles. Identical views were acquired at stress. Before acquisition of stress loops, a contrast infusion was administered and dobutamine infusion was terminated.[13] Within 30 seconds, there was sufficient contrast enhancement, and stress contrast images were acquired using long-axis views (and short-axis views if of sufficient quality).[13] Image acquisition during stress was not different from acquisition at rest.[13] MCE images were digitally stored at baseline and following stress.

Assessment of MCE

Semiquantitative

A 4-point semiquantitative scoring system was used for the assessment of contrast intensity myocardial perfusion scores (MPS) as follows: (1) normal contrast intensity; (2) mild reduction; (3) moderate-to-severe reduction and (4) absent.[14] The potential for functional recovery using resting MCE was defined as MPS ≤2 points.[14] During stress, the potential for functional recovery was defined as changes (enhanced or reduced) in MPS (ΔMPS) ≥1 point.

Quantitative

MBF was quantified using Q-Lab 7.1 software (Philips Medical Systems, Best, The Netherlands). Regions of interest were tracked manually within the myocardium of each segment with careful exclusion of the epicardial and endocardial borders of the myocardium. The software package automatically calculated the mean acoustic intensity of each region of interest and generated time-intensity curves that were subsequently fitted to a monoexponential function: $y = A\ (1-e^{-\beta t})$, where y is the acoustic intensity at a sequence of images in time, A is the plateau acoustic intensity and β is the rate constant of rise in acoustic intensity and represents mean microbubble velocity.[15] An MBF index was calculated as the product of A multiplied by β.

Revascularization and Follow-up

One year after CABG, all patients in the study were examined using coronary MSCTA and echocardiography. A 256-multislice CT (Philips Brilliance iCT, The Netherlands) was performed for the evaluation of graft patency. The contrast agent used was Iopromide (370 mgI/mL; BAYER, Berlin, Germany). The patients with obstructed grafts were excluded. A segment with resting dysfunction was categorized as functional recovery if the WMS improved by 1 at 1 year after CABG.[16] A change from dyskinesia to akinesia was not considered as an improvement in function.[16]

Statistical Analyses

Continuous variables are expressed as mean ± standard deviation and categorical variables as proportions. Two-tailed paired and unpaired Student's *t* tests were used for comparisons of independent and dependent variables, respectively. The χ^2 and Fisher's exact tests were used for comparisons of proportions. Receiver operating characteristic (ROC) curve analyses were used to identify the critical cutoff value of ΔMBF for predicting regional myocardial functional recovery after CABG. All data analyses were performed using SPSS 13.0 for Windows (SPSS, Inc, Chicago, IL). Statistical significance was set at $P < 0.05$.

RESULTS

Study Group

Clinical and angiographic characteristics of the 46 patients who were selected for LD-DSMCE 1 week before CABG, and echocardiography and MSCTA 1 year (321 ± 50 days) after CABG, are summarized in Table 1. During the preoperative period, all patients had resting WMAs. CABG was performed with 3 to 5 grafts. There are a total of 782 segments in the 46 patients. Among the 782 segments, 380 had resting WMAs. Among the 380 resting WMAs, 368 segments were analyzed using WMS and MPS. Two hundred twenty segments of the 368 analyzed segments improved at follow-up.

Dobutamine Stress Echocardiography

All stress tests were performed without serious complications. Several patients had slight recurrent angina or clinical

TABLE 1. Patient demographics, risk factors and clinical features (n = 46)

Age (yr)	58.6 ± 8.3
Males, n (%)	29 (63.0)
Height (cm)	164.9 ± 8.2
Weight (kg)	70.2 ± 11.3
BMI (kg/m²)	25.8 ± 3.2
Hypertension (SBP/DBP >140/90 mm Hg), n (%)	28 (60.9)
Diabetes, n (%)	20 (43.5)
Hypercholesterolemia (cholesterol >5 mmol/L), n (%)	32 (69.6)
Smoker, n (%)	20 (43.5)
Family history (n)	18 (39.0)
Previous myocardial infarction (>6 wk), n (%)	16 (34.8)
Unstable angina	30 (65.2)
LVEF baseline (%)	0.38 ± 0.11
Rest WMSI	1.64 ± 0.58
No. grafts per patient	3.2

Data are represented as mean ± standard deviation or number (%) of patients.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; WMSI, wall motion score index.